PREDICTION OF HUMAN SYSTEMIC, BIOLOGICALLY RELEVANT PHARMACOKINETIC (PK) PROPERTIES BASED ON QUANTITATIVE STRUCTURE PHARMACOKINETIC RELATIONSHIPS (QSPKR) AND INTERSPECIES PHARMACOKINETIC ALLOMETRIC SCALING (PK-AS)

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PREDICTION OF HUMAN SYSTEMIC, BIOLOGICALLY RELEVANT PHARMACOKINETIC (PK) PROPERTIES BASED ON QUANTITATIVE STRUCTURE PHARMACOKINETIC RELATIONSHIPS (QSPKR) AND INTERSPECIES PHARMACOKINETIC ALLOMETRIC SCALING (PK-AS)

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADME</td>
<td>Absorption, distribution, metabolism and elimination</td>
</tr>
<tr>
<td>AS</td>
<td>Allometric scaling</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>β-ARL</td>
<td>Beta-adrenergic receptor ligand</td>
</tr>
<tr>
<td>β-LA</td>
<td>Beta-lactam antibiotic</td>
</tr>
<tr>
<td>B: P</td>
<td>Blood-to-plasma ratio</td>
</tr>
<tr>
<td>BW</td>
<td>Body weight</td>
</tr>
<tr>
<td>CL_{extrahep}</td>
<td>Extra-hepatic clearance</td>
</tr>
<tr>
<td>CL_{hep}</td>
<td>Hepatic clearance</td>
</tr>
<tr>
<td>CL_{int}</td>
<td>Intrinsic hepatic clearance</td>
</tr>
<tr>
<td>CL_{int_{in-vitro}}</td>
<td><em>In-vitro</em> intrinsic clearance (hepatic)</td>
</tr>
<tr>
<td>CL_{int_{in-vivo}}</td>
<td><em>In-vivo</em> intrinsic clearance (hepatic)</td>
</tr>
<tr>
<td>clogP</td>
<td>Calculated logarithm of octanol-water partition coefficient</td>
</tr>
<tr>
<td>CL_{nonren}</td>
<td>Non-renal clearance</td>
</tr>
<tr>
<td>CL_{nonren_{blood}}</td>
<td>Non-renal blood clearance</td>
</tr>
<tr>
<td>CL_{nonren_u}</td>
<td>Unbound non-renal clearance</td>
</tr>
<tr>
<td>CL_{ren}</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>CL_{ren_u}</td>
<td>Unbound renal clearance</td>
</tr>
<tr>
<td>CL_{tot}</td>
<td>Total clearance</td>
</tr>
<tr>
<td>CL_{tot/F_{oral}}</td>
<td>Apparent total clearance</td>
</tr>
<tr>
<td>CL_{tot_u}</td>
<td>Unbound total clearance</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac Output</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol ortho-methyl transferase</td>
</tr>
<tr>
<td>ER_{hep}</td>
<td>Hepatic extraction ratio</td>
</tr>
</tbody>
</table>
\( f_e \) fraction of dose excreted unchanged in urine after intravenous administration

\( F_{oral} \) Oral bioavailability

\( f_u \) fraction unbound in plasma

\( \text{GFR} \) Glomerular filtration rate

\( \text{GPCR} \) G-protein coupled receptors

\( Q_{\text{hep}} \) Hepatic blood flow

\( \text{HBA} \) Hydrogen bond donors

\( \text{HBD} \) Hydrogen bond acceptors

\( \text{HER} \) High hepatic extraction ratio

\( \text{IER} \) Intermediate hepatic extraction ratio

\( \text{IV} \) Intravenous administration

\( \text{IVIVE} \) *In-vitro-in-vivo* extrapolation

\( \text{KW} \) Kidney weight

\( \text{LBF} \) Liver blood flow

\( \text{LER} \) Low extraction ratio

\( \log (D) \) logarithm of octanol-buffer pH distribution coefficient

\( \log (D)_{7.4} \) logarithm of octanol-buffer pH (7.4) distribution coefficient

\( \log (P) \) logarithm of octanol-water partition coefficient

\( \text{MPE} \) Mean prediction error

\( \text{MIC} \) Minimum Inhibitory concentration

\( \text{M-3-G} \) Morphine-3-glucuronide

\( \text{M-6-G} \) Morphine-6-glucuronide

\( \text{MLLR} \) Multiple log-linear regression

\( \text{MW} \) Molecular weight

\( \text{MV} \) Molar volume

\( \text{nRot} \) Number of rotatable bonds

\( \text{PD} \) Pharmacodynamics

\( \text{P-gp} \) P-glycoprotein

\( \text{PK} \) Pharmacokinetics

\( \text{PPB} \) Plasma protein binding
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>Polar surface area</td>
</tr>
<tr>
<td>QSAR</td>
<td>Quantitative structure-activity relationship</td>
</tr>
<tr>
<td>QSPKR</td>
<td>Quantitative structure pharmacokinetic relationship</td>
</tr>
<tr>
<td>RRA</td>
<td>Relative receptor affinity</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>RBF</td>
<td>Renal blood flow</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root mean squared error</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>Half-life</td>
</tr>
<tr>
<td>$V_d$</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>$V_{d\beta}$</td>
<td>Terminal phase volume of distribution</td>
</tr>
<tr>
<td>$V_{dc}$</td>
<td>Volume of distribution of central compartment</td>
</tr>
<tr>
<td>$V_{ds}$</td>
<td>Volume of distribution at steady-state</td>
</tr>
<tr>
<td>$V_{ds} / F_{oral}$</td>
<td>Apparent volume of distribution at steady-state</td>
</tr>
<tr>
<td>$V_{ds} u$</td>
<td>Unbound volume of distribution at steady-state</td>
</tr>
</tbody>
</table>

List of symbols:

- $\beta$ Beta
- $\delta$ delta
- $\kappa$ kappa
- $\mu$ Mu
- $\gamma$ RBC partition coefficient
- $K_i$ Receptor affinity constant
Abstract

PREDICTION OF HUMAN SYSTEMIC, BIOLOGICALLY RELEVANT PHARMACOKINETIC (PK) PROPERTIES BASED ON QUANTITATIVE STRUCTURE PHARMACOKINETIC RELATIONSHIPS (QSPKR) AND INTERSPECIES SCALING (PK-AS)

by

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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ASSOCIATE PROFESSOR, DEPARTMENT OF PHARMACEUTICS

This research developed validated QSPKR and PK-AS models for predicting human systemic PK properties of three, preselected, pharmacological classes of drugs, namely opioids, β-adrenergic receptor ligands (β-ARL) and β-lactam antibiotics (β-LAs) using pertinent human and animal systemic PK properties ($f_{uu}$, $CL_{tot}$, $V_{dss}$, $f_{c}$) and their biologically relevant unbound counterparts from the published literature, followed by an assessment of the effect of different
molecular descriptors on these PK properties and on the PK-AS slopes for \( \text{CL}_{\text{tot}} \) and \( \text{Vd}_{\text{ss}} \) from two species (rat and dog).

Lipophilicity (\( \log (D)_{7.4} \)) and molecular weight (MW) were found to be the most statistically significant and biologically plausible, molecular properties affecting the biologically relevant, systemic PK properties:

For compounds with \( \log (D)_{7.4} > -2.0 \) and \( \text{MW} < 350 \text{ D} \) (e.g., most opioids and \( \beta \)-ARL), increased \( \log (D)_{7.4} \) resulted in decreased \( \text{fu} \) and increased \( \text{Vd}_{\text{ss}} \), \( \text{CL}_{\text{tot}} \) and \( \text{CL}_{\text{nonren}} \), indicating the prevalence of hydrophobic interactions with biological membrane/proteins. As result, the final QSPKR models using \( \log (D)_{7.4} \) provided acceptable predictions for \( \text{fu} \), \( \text{Vd}_{\text{ss}} \), \( \text{CL}_{\text{tot}} \) and \( \text{CL}_{\text{nonren}} \). For both the datasets, inclusion of drugs undergoing extrahepatic clearance worsened the QSPKR predictions.

For compounds with \( \log (D)_{7.4} < -2.0 \) and \( \text{MW} > 350 \text{ D} \) (e.g., \( \beta \)-LA), increased MW (leading to more hydrogen bond donors/acceptors) resulted in a decrease in \( \text{fu} \), likely indicating hydrogen bonding interactions with plasma proteins. In general, it was more difficult to predict PK parameters for \( \beta \)-LAs, as their \( \text{Vd}_{\text{ss}} \) approached plasma volume and \( \text{CL}_{\text{ren}} \) and \( \text{CL}_{\text{nonren}} \) were low - as a result of their high hydrophilicity and large MW, requiring specific drug transporters for distribution and excretion.

The PK-AS analysis showed that animal body size accounted for most of the observed variability (\( r^2 > 0.80 \)) in systemic PK variables, with single species methods, particularly those using dog, gave the best predictions. The \( \text{fu} \) correction of PK variables improved goodness of fit and predictability of human PK. There were no apparent effects of molecular properties on the predictions. \( \text{CL}_{\text{ren}} \), \( \text{CL}_{\text{ren}} \), \( \text{CL}_{\text{nonren}} \), and \( \text{CL}_{\text{nonren}} \) were the most difficult variables to predict,
possibly due to the associated interspecies differences in the metabolism, renal and hepatobiliary drug transporters.
CHAPTER 1. INTRODUCTION

1. Introduction

1.1. Background and Significance

The majority of chemical drug candidates entering clinical testing for safety and efficacy ultimately fail to reach the market place, among other things due to the lack of better understanding of their absorption, distribution, metabolism, and excretion (ADME) properties in early drug development. The overall process of drug development is extremely time consuming and expensive, making early screening of drug candidates imperative. Thus, the early in-silico prediction of human pharmacokinetic (PK) properties for new drug candidates has become an important step in drug discovery. For this, a variety of experimental approaches such as inter-species pharmacokinetic allometric scaling (PK-AS), physiologically based PK modeling and in-vitro-in-vivo extrapolation (IVIVE) are used. On the other hand, there are in-silico approaches such as quantitative structure pharmacokinetic relationships (QSPKR), which can be used in the early drug discovery process as screening tools to eliminate chemicals likely lacking drug-like properties. The aim of this research is to develop mathematical/statistical ("in-silico") models for predicting human PK of existing opioid, β-adrenergic receptor ligand (β-ARL) and β-lactam antibiotic (β-LA) drugs using methods such as QSPKR modeling and interspecies allometric PK scaling (PK-AS). These models may then be generalized to assist during the drug
discovery process in the rational selection of new compounds as likely “druggable” chemical entities with more favorable human PK properties.

1.2. Quantitative-structure pharmacokinetic relationships

In the past, Hansch and co-workers\textsuperscript{10} studied relationships between the physicochemical properties and the \textit{in-vitro} activity at the receptor for homologous series of compounds and innovated the field of quantitative structure activity relationship (QSAR), but this was limited to biological activity of chemicals. However, lack of ultimate therapeutic activity may not always be due to inadequate drug-receptor interaction, but can be due to inappropriate concentrations and/or concentration-time course of drug at the receptor. Structure-related properties of a chemical can be determined by experimental or computational means more efficiently than its PK properties using \textit{in vitro} or \textit{in vivo} approaches; a statistically validated QSPKR model is capable of predicting the PK properties of a new chemical within a homologous series as compared to the time-consuming and labor-intensive processes of chemical synthesis and biological evaluation. If applied judiciously, QSPKR may save substantial amounts of time, money, and human resources. Various computational techniques are used to calculate molecular descriptors for a compound\textsuperscript{11} and to predict human PK properties using \textit{in-silico} QSPKR models.\textsuperscript{8, 12-16} QSPKR attempts to correlate chemical structure attributes with PK properties and to build models using statistical approaches. PK properties (which characterize ADME) are typical for a certain type of drug molecule similarly as are their aqueous solubility, melting point, electronic charge, pK\textsubscript{a}, lipophilicity, etc. The fundamental assumption of QSPKR is that variations in the PK parameters of a series of chemicals are dependent on variations in their structural, physical, and/or chemical
Recently, ‘Lipinski’s Rule of Five’\textsuperscript{17} described the importance of molecular properties in ADME: He based his conclusions on a \textit{in-vitro} GI solubility and GI permeability studies for 2245 compounds in United States Adopted Name (USAN) database, which includes names of compounds entering Phase II clinical testing. The rule states that a compound is likely to have poor pral absorption if molecular weight (MW) is more than 500 D, clog P> 5, there are more than 5 hydrogen bond donors (HBD) and more than 10 hydrogen bond acceptors (HBA). However, the molecular properties in the “Rule of Five” are not independent; increase in MW often leads to addition of more carbons and halogens, leading to higher clogP or additions of more hetero atoms, leading to higher hydrogen (H) bonding capacity. Higher H-bonding can result in a decrease in GI permeability and higher clogP can lead to lower GI solubility. The rule is based on compounds in the Pfizer pipeline which did not reach the market due to unfavorable physicochemical or PK-PD properties, does not consider \textit{in-vivo} PK data and substrates for active transporters can be an exception to this rule.

Most of the QSPKR studies in the literature are either on homologous series of compounds, resulting from systematic variation in the structure of the compounds or on datasets which have heterogenous compounds, from different structural and pharmacological classes predicted primary PK variables such as $f_{aa}$, $CL_{tot}$ and $V_{ds}$\textsuperscript{16, 18-27} The use of homologous series results in a narrow range of molecular properties, which makes identification of important molecular properties difficult, and the widespread use of MLLR/univariate regression on the heterogenous datasets may neglect major interaction amongst the molecular properties. Studies carrying out discriminatory/trend analysis have divided the QSPKR databases into different categories such as charge/ionization state,
therapeutic area or into different ranges of MW bins.\textsuperscript{16, 21, 22} Such discriminatory analyses make it easier to assess in a qualitative fashion how changes in the physicochemical properties will impact the ADME properties in a particular physicochemical space, which is not possible using multivariate modeling methods.

Obach et al\textsuperscript{16} carried out a trend analysis on a database of 670 drugs (median MW: 342 D (range 3-1816 D), median log(D)\textsubscript{7.4}: 0.42, median nRot: 5, median HBA: 6 and median HBD: 2), administered by I.V. route, they divided the dataset by ionization state into acid (n =159), base (n=271), neutral (n = 173) and zwitterionic drugs (n = 67). The median values for these molecular descriptors were well below “Lipinski’s Rule of Five”. It was found that acids showed lower median values volume of distribution at steady state (Vd\textsubscript{ss}) than bases, with neutrals and zwitterions in between. Bases generally showed greater values for total body clearance (CL\textsubscript{tot}) than acids, neutrals or zwitterions.

Gleeson \textsuperscript{21} generated rules of thumb for a set of molecular properties based on clogP, MW and ionization state using a huge GSK database on rat in-vivo PK studies. The dataset was biased towards more lipophilic and high MW compounds. He found that molecules had more favorable systemic PK properties if MW was less than 400 D and clogP less than 4, while they were classified as less favorable if one or more of the parameters was found to be above the cut-offs. Bases showed higher Vd\textsubscript{ss}, followed by neutrals and zwitterions, while acids showed the lowest Vd\textsubscript{ss}. Acids showed mean CL\textsubscript{tot} considerably lower than neutral and zwitterions, which in turn was lower than bases. As MW increased, Vd\textsubscript{ss} increased, PPB increased, while there was no relationship between CL\textsubscript{tot} and MW. However, there was a relationship between clogP and CL\textsubscript{tot}, as the clog P increased; there was an increase in CL\textsubscript{tot}. 4
Varma et al\textsuperscript{22} analyzed the effect of physicochemical properties on renal clearance (CL\textsubscript{ren}) for a dataset of 370 drugs and found that lipophilicity showed a negative relationship, while polar descriptors like HBA, HBD showed a positive relationship with CL\textsubscript{ren}. Analysis of net tubularly secreted or net reabsorbed subsets revealed that ionized compounds show a greater probability of net secretion, fewer tendencies to be reabsorbed and likely interactions with renal uptake drug transporters. Van de Waterbeemd et al\textsuperscript{20} studied the effect of log (D)\textsubscript{7.4} on oral absorption, brain uptake and various PK properties. It was found that increasing log (D), increased oral absorption, plasma protein binding (PPB) and volume of distribution (Vd), however, an increase in log (D)\textsubscript{7.4} makes a molecule also more vulnerable to CYP450 metabolism, leading to higher clearance (CL\textsubscript{tot}).

In general, all these studies showed that lipophilicity determines partitioning and distribution processes, including cell membrane permeability, PPB, affinity for drug metabolizing enzymes, whereas the charge type governs ion-pair interactions with plasma proteins, lipids and drug metabolizing enzymes.

Testa et al\textsuperscript{28} reviewed a number of QSPKR studies and examined the relationship of lipophilicity with different PK processes like membrane permeation, absorption, PPB, distribution and CL\textsubscript{ren}. Amongst all the PK processes, relationship between metabolism and lipophilicity was more complex, since biotransformation involves both low energy (enzyme binding) and high energy (catalysis) processes and lipophilicity can only be related to low energy processes. Testa et al\textsuperscript{28} described lipophilicity as a net result of intermolecular forces involving solute and the two phases between which it partitions and is based on its factorization into number of parameters like hydrophobicity (\(\pi\)), H-bond donor acidity, H-bond acceptor basicity, hydrophobic and dispersion forces.
Veber et al\textsuperscript{29} studied the effect of molecular properties on rat PK properties of 1100 compounds in a GSK database and found that the Lipinski’s MW cut-off of 500 D does not significantly differentiate compounds with poor oral bioavailability ($F_{\text{oral}}$) from the compounds with acceptable $F_{\text{oral}}$ values. His observations suggest that compounds which have 10 or fewer nRot and 12 or fewer HBD/HBA will have a high probability of good $F_{\text{oral}}$.

Some QSPKR studies predict apparent clearance ($\text{CL}_{\text{tot}}/F_{\text{oral}}$) and volume of distribution ($V_{\text{ss}}/F_{\text{oral}}$) since they used the PK data after oral administration.\textsuperscript{26, 30, 31} These studies showed that lipophilicity was an important determinant for PPB, $\text{CL}_{\text{tot}}/F_{\text{oral}}$ and $V_{\text{ss}}/F_{\text{oral}}$. Involvement of a complex phenomenon like oral bioavailability ($F_{\text{oral}}$) can make these predictions difficult even more compared to systemic ADME due to confounding effects of incomplete absorption, first-pass effect or interspecies differences in absorption.

This research concentrates only on intravenous (I.V.) PK studies for three classes of drugs (opioids, $\beta$-ARLs and $\beta$-LAs), each dataset has drugs that are structural analogs, act on a common pharmacological target and, at the same time, show considerable diversity in their physicochemical and PK properties. Initially, QSPKR analysis was done for individual datasets, followed by a trend analysis on the pooled dataset where all the the three datasets were pooled together. Construction of such QSPKR models not only requires sufficient information available in literature and reliable computational tools, but also databases whose elements have been compiled with critical evaluation of drug design, sampling methods, bioanalytical and PK analysis methods. The final dataset compiled after critical evaluation of literature in this research contained 146 drugs (38 opioids, 48 $\beta$-ARLs and 60 $\beta$-LAs) with a wide range of molecular properties; median $\log(P)$: 1.2 (-6.1 to 7.2), median $\log(D)$\textsubscript{4,7}: -0.95 (-7.3-3.7), median MW: 365 D (199-672), median: nRot: 7 (1-15), median HBD: 3 (0-7)
and median HBA: 6 (0-17). This database has a relatively small number of compounds and median values for clog(P), MW, HBD and HBAs are well below Lipinski’s ‘Rule of Five’ and median nRot values below the Veber\textsuperscript{29} cut-off for permeable compounds, however, it contains information about compounds which have been approved by FDA or which were/are used in clinical settings. Table 1.1 gives a comparison of the dataset in this research with the datasets in the published literature.

In this approach, it is assumed that only unbound drug is available for distribution, excretion and metabolism. Thus, QSPKR models were built for the unbound PK properties. The term $f_u$ indicates the fraction of drug in plasma which is not bound to plasma proteins (e.g., albumin, alpha-acid glycoprotein) and, thus, is available for distribution, elimination and interaction with the target drug receptors. Highly plasma protein bound drugs are likely to have small $V_{dss}$ and $CL_{tot}$ values even though their “true $V_{dss}$” may be high (indicating wide distribution of unbound drug) and “true $CL_{tot}$” may be high (indicating high hepatic/renal extraction of unbound drug).

In addition to considering binding to plasma proteins, the fraction of drug in whole blood that is bound to red blood cells (RBC) can also be important. The value for red cell partition coefficient ($\gamma$) can be estimated using the blood-to-plasma ratio (B:P) (Table 1.2); and $\gamma$ assesses the fraction in blood that is bound to RBC and other cellular components after correction with PPB.

In addition, for the physiological assessment of the extent of tissue distribution, $V_{dss}$ should be corrected for PPB to obtain the unbound volume of distribution at steady state ($V_{dss}^{u}$) in order to compare with physiological spaces (plasma volume, blood volume, extracellular and intracellular spaces, total body water and body weight (BW)).
CL_{tot} is the volume of plasma completely cleared of the drug per unit time. It reflects the sum of all individual elimination pathways, i.e., CL_{ren} and non-renal clearance (CL_{nonren}).

CL_{ren} measures the contribution of renal elimination. Since only unbound drug can be removed by renal glomerular filtration, CL_{ren} should be corrected for PPB to obtain unbound renal clearance (CL_{ren}^{u}) (Table 1.2). Physiological comparison of CL_{ren}^{u} to glomerular filtration rate (GFR) allows identification of net renal tubular secretion or reabsorption.

Non-renal clearance (CL_{nonren}) measures the contribution of all elimination pathways other than renal. It is usually assumed to be due to hepatic metabolism/biliary excretion (CL_{hep}). However, it can be also due to extra-hepatic clearance (CL_{extrahep}) in blood/other tissues.

Usually, plasma drug concentrations are used for estimating PK properties. However, the body organs are perfused by blood, not plasma alone. Thus, blood clearance (CL_{nonren}^{blood}) may be more physiologically relevant than plasma clearance, especially for hepatic clearance, where, clearance is compared to liver blood flow (LBF: 20 ml/min/kg\(^{32}\)) in humans. If CL_{nonren}^{blood} exceeds the LBF, there is evidence of extra-hepatic metabolism. Thus, blood clearance was related to plasma clearance by B:P, and CL_{nonren}^{blood} was estimated accordingly (Table 1.2).\(^{33}\)

Intrinsic clearance (CL_{int}) is the intrinsic ability of the liver to remove the drug in absence of any blood flow restrictions. \(\text{CL}_{\text{int}}^{in-vivo}\) can be estimated using the well-stirred model, assuming CL_{nonren}^{blood} as the hepatic clearance (Table 1.2).\(^{26}\) The hepatic extraction ratio (ER_{hep}) is the intrinsic ability of the liver to extract the drug from blood, i.e., ratio of the arterio-venous concentration difference relative to the arterial concentration (including both
hepatic artery and portal vein). Hepatic blood flow ($Q_{hep}$), $f_u$ and $CL_{int}$ determine the hepatic extraction ratio ($ER_{hep}$).

Based on the above, the QSPKR study was carried out on the biologically relevant PK properties such as unbound volume of distribution at steady state ($V_{dss\ u}$), unbound total clearance ($CL_{tot\ u}$), renal clearance ($CL_{ren}$), unbound renal clearance ($CL_{ren\ u}$), non-renal clearance ($CL_{nonren}$), unbound non-renal clearance ($CL_{nonren\ u}$), in-vivo intrinsic clearance ($CL_{int\ in-vivo}$) and hepatic extraction ratio ($ER_{hep}$). The effect of physicochemical properties such as $pK_a$, MW, molar volume (MV), polar surface area (PSA), dipole moment, energy, clogP, % ionized at pH 7.4 and two dimensional molecular descriptors like HBD, HBA, nRot was studied on the PK variables. Distribution coefficient, Log (D), is the correct descriptor for ionizable systems and is at physiologically relevant pH. The distribution coefficient is the ratio of the sum of the concentrations of all forms of the compound (ionized plus un-ionized) in each of the two phases, 1-octanol and buffer (pH 7.4). Thus, log (D)$_{7.4}$ was used. The % ionized at pH 6.3 allowed us to study if the ionization of compounds changed in urine (urinary pH: 6.3). These molecular properties were included based on the biological plausibility and their widespread use in the literature.
Table 1.1. Comparison of the Database in the Present QSPKR Study with the Databases in the Published QSPKR Studies

<table>
<thead>
<tr>
<th></th>
<th>Published Literature</th>
<th>Present QSPKR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database</td>
<td>Random – Contained chemically and pharmacologically diverse compounds</td>
<td>Three pharmacological classes</td>
</tr>
<tr>
<td></td>
<td>Homologous series – Databases which consisted of compounds which were a result of systematic structural variations.</td>
<td></td>
</tr>
<tr>
<td>PK variables</td>
<td>- In-vitro/in-vivo PK variables in humans and animals.</td>
<td>- In-vitro/in-vivo PK variables in humans.</td>
</tr>
<tr>
<td></td>
<td>- Systemic as well as non-systemic (oral) data.</td>
<td>- Systemic PK variables corrected for PPB, thus, QSPKR study was biologically relevant.</td>
</tr>
<tr>
<td></td>
<td>- Exposure metrics – AUC, $t^{1/2}$, MRT, $CL_{tot}/F_{oral}$, $Vd_{ss}/F_{oral}$, $CL_{tot}$, $Vd_{ss}$</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1.2. Estimation of *In-vitro* and *In-vivo* PK Variables

<table>
<thead>
<tr>
<th><em>In-vitro/In-vivo</em> systemic PK variable</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC partitioning coefficient</td>
<td>[ \gamma = \frac{(B : P) - (1 - H)}{H \cdot f_u} ] where H=hematocrit was assumed to be 0.46</td>
</tr>
<tr>
<td>( V_{d_{ss}} )</td>
<td>[ V_{d_{ss}} = V_d \cdot \left( 1 + \frac{k_{12}}{k_{21}} \right) ]</td>
</tr>
<tr>
<td>( V_{d_{ss}} )</td>
<td>[ V_{d_{ss}} = CL_{int} \cdot \frac{\alpha \cdot \beta}{\alpha^2 + \beta^2} ]</td>
</tr>
<tr>
<td>(assuming two compartment model)</td>
<td></td>
</tr>
<tr>
<td>( V_{d_{ss}}^u )</td>
<td>[ V_{d_{ss}}^u = V_{d_{ss}}^u ]</td>
</tr>
<tr>
<td>( CL_{tot}^u )</td>
<td>[ CL_{tot}^u = CL_{tot}/f_u ]</td>
</tr>
<tr>
<td>( CL_{rem} )</td>
<td>[ CL_{rem} = CL_{tot} \cdot f_e ]</td>
</tr>
<tr>
<td>( CL_{rem}^u )</td>
<td>[ CL_{rem}^u = CL_{rem}/f_u ]</td>
</tr>
<tr>
<td>( CL_{nonren} )</td>
<td>[ CL_{nonren} = CL_{int} \cdot CL_{rem} ]</td>
</tr>
<tr>
<td>( CL_{nonren}^{blood} )</td>
<td>[ CL_{nonren}^{blood} = CL_{nonren} \cdot (B:P) ] where ( CL_{nonren}^{blood} ) was assumed to be hepatic clearance (CLhep)</td>
</tr>
<tr>
<td>( CL_{int}^{in-vivo} )</td>
<td>[ CL_{int}^{in-vivo} = \frac{(Q_{hep} \cdot CL_{hep})}{(f_u/B:P) \cdot (Q_{hep} \cdot CL_{hep})} ] where ( Q_{hep} ) is the liver blood flow (assumed to be 20 ml/min/kg in humans)</td>
</tr>
<tr>
<td>( ER_{hep}^1 )</td>
<td>[ ER_{hep}^1 = \frac{CL_{nonren}^{blood}}{Q_{hep}} ] (assuming that liver is the only organ responsible for metabolism for ( CL_{nonren} ))</td>
</tr>
<tr>
<td>( ER_{hep}^2 )</td>
<td>[ ER_{hep}^2 = 1 - F_{oral} ] (assuming that there is complete dissolution and permeation and estimated from oral PK data)</td>
</tr>
</tbody>
</table>
Limitations of QSPKR modeling:

- Sometimes, molecular descriptors used in QSPKR studies are collinear, which may cause redundancy in the information. PK properties like volume of distribution, clearance, protein binding are also interdependent, as they may depend on common factors. This can be addressed by using statistical techniques like partial least square analysis or artificial neural networks.

- There are some descriptors like log (P) which are easily interpreted, but topological descriptors like molecular connectivities are difficult to interpret mechanistically.

- An increase in number of molecular descriptors may lead to increase in statistical fit, but, there is always a chance of overfitting of data.

- Available softwares packages provide a plethora of molecular descriptors, and appropriate selection of variables can be a limitation. To solve this, complex algorithms like genetic algorithms can be used. However, this increases the cost of the study.

- Considerable bias in the available PK data like influence of age, smoking, disease states, etc. on the PK and lack of systemic PK studies within homologous series of drugs. Thus, QSPKR relies upon quality of the in-vivo PK data obtained.

- QSPKR models as predictive tools work better only when the compounds in the training dataset have same structural backbone and wide range of physicochemical properties.

- QSPKR models are based on a set of compounds with a certain range of physicochemical properties/structure attributes. Thus, it is more difficult, if not impossible, to predict PK of a compound which lies outside that space.
1.3. Interspecies PK allometric scaling (PK-AS):

In preclinical drug development, animal PK studies are carried out in at least two species (rat, dog and/or monkey) to support toxicity studies. The animal PK studies aid in identifying sources of variability such as elimination pathways (renal and/or hepatic), metabolic pathways, etc. In conjunction with toxicity and biological activity information, PK studies can be further used to predict dosing regimen. Once the human concentration response (i.e., dose-exposure) can be predicted, the challenge is to predict human systemic PK. Allometric Scaling (AS) is one of the most widely used approaches in predicting human PK parameters (CL\textsubscript{tot}, V\textsubscript{dss}, t\textsubscript{1/2}) from the available \textit{in-vivo} PK data in animal species.\textsuperscript{3, 34, 35}

Allometric Scaling (AS) is the study of body size and its physiological consequences. It is based on the relationship between organ size, perfusion and body weight (BW), which can be explained by the equation:

\[ Y = a(BW)^b, \]

where Y is the parameter of interest (e.g., PK property like CL\textsubscript{tot}, V\textsubscript{dss}, etc.) and a and b are the intercept and exponent (coefficient) of the allometric equation, respectively. For instance, an increase in body mass will cause reduction in the metabolic rate per unit mass, which, in turn, will influence the turn-over rate at the cellular level. Oxygen consumption also varies amongst animal species based on BW. Relative oxygen consumption increases as the BW decreases. This leads to increase in oxygen supply, and hence increased cardiac output. As a result, blood flow to 1 gm tissue will be 100 times greater in a mouse than in the elephant. It has shown that metabolic rate of an organism is proportional to the 0.75\textsuperscript{th} power of the BW.\textsuperscript{36} It was also found that liver weight and LBF in all species scales well with BW (r > 0.99) and LBF was found to be directly proportional to liver weight.\textsuperscript{37} Blood
volume in terrestrial mammals scales with an exponent of 0.99 and skeletal mass with an exponent of 1.09. Volume of distribution is proportional with the BW across different species and the exponent is found to be close to 1.0.\textsuperscript{38}

In the past few years, extensive research has been carried out to improve the accuracy of AS. Various modifications include maximum life span potential or brain weight correction\textsuperscript{39}, rule of exponents\textsuperscript{40} and \textit{in-vitro} correction\textsuperscript{41}. Additionally, several quantitative methodologies using mechanistic correction factors based on liver blood flow\textsuperscript{42} and glomerular filtration rate\textsuperscript{4} have been employed. Also, based on the mechanism of elimination of drugs, correction factors have been suggested for renally secreted\textsuperscript{43} and biliary excreted drugs.\textsuperscript{44}

Prediction methodologies in the literature concentrate on more than one species because it is believed that high correlation amongst the PK parameters among three species is an indication of achieving better prediction of human PK. However, Boxenbaum showed that human antipyrine CL\textsubscript{tot} was poorly predicted despite high $r^2$ values and use of multiple species.\textsuperscript{37} Similar observations have been made by Ward et al\textsuperscript{13} for a database of 103 marketed compounds. Ward et al\textsuperscript{13} also was found that allometric scaling approaches using two species were less successful at predicting CL\textsubscript{tot} than LBF method in an individual species. In the past, scaling from monkey LBF method was proven to the accurate methodology when 124 compound dataset of structurally and pharmacologically diverse compounds was studied.\textsuperscript{45} A high $r^2$ (> 0.90) does not guarantee that all data points will be close to the regression line. Thus, the extrapolation from this regression line based on limited number of species might have a considerable amount of uncertainty associated with it. Therefore, $r^2$ alone does not offer a good measure for predictive ability of the allometric
relationship. Power functions can create substantial errors in the data fitting and log-log transformations of the data visually minimize the deviations from the regression line. Thus, in this research, the predictive ability of the various allometric methods was assessed using % MPE for bias and % RMSE for imprecision. Predictive performance was also assessed using the number of compounds in the pre-selected fold error ranges of 0.5-2.0-fold.

Intrinsic interspecies differences in drug disposition make the human PK prediction difficult, especially when active transport or extrahepatic metabolism is involved. Drug transporters play a key role in various ADME processes and can show remarkable interspecies differences. For drugs with high ER hep, LBF method or simple allometry may improve prediction, since LBF correlates well with BW. However, for the drugs, where clearance is not limited by LBF, but by hepatic CYP450 enzymes, allometry can be less predictive. Hepatic enzyme activity and expression can vary across species. Thus, Lave et al suggested a method of combining AS and IVIVE to improve the human predictions. Jolivette et al hypothesized that understanding of molecular properties for inliers or outliers for each species would increase the accuracy of the interspecies predictions. It was found that human extrapolation from rat and dog is more likely to accurately predict human CL tot for molecules that are relatively small and hydrophilic compared to larger, more lipophilic compounds.

Jolivette et al also found that rat CL tot will not be predictive of human for molecules that have clog(P) value more than 0, and that molecules with high CL tot in rat but with clog(P) more than 3 will not have high CL tot in humans. A qualitative analysis of 102 compounds (57 metabolized by liver - 29 low clearance, 17 intermediate clearance, 11 high clearance and 33 excreted by kidneys and 11 eliminated by renal as well as by metabolism)
by Tang et al. revealed the application of two potential rules for predicting the occurrence of large vertical allometry/overprediction in prediction of systemic $\text{CL}_{\text{tot}}$, ratio of unbound fraction of drug in plasma ($f_u$) between rats and humans greater than 5; and $\text{clogP}$ greater than 2. It was concluded that metabolic elimination could also serve as an additional indicator for expecting large vertical allometry.

Most of the interspecies scaling studies in the literature are performed on heterogenous datasets, which have compounds from different structural and pharmacological classes, and they also predict typical primary PK variables like $f_u$, $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$ or $\text{CL}_{\text{tot}}/F$ and $\text{Vd}_{\text{ss}}/F$. Mcginnity found that $F_{\text{oral}}$ estimated from oral rat PK studies was lower than the observed human absorption for most drugs, even when solubility and permeability were not the limiting factors, suggesting that the dog may be more representative of human for compounds absorbed via transcellular pathways.

Feng et al. found that scaling unbound $\text{CL}_{\text{tot}}$ across animal species improved the prediction of eight Parke-Davis compounds and 26 drugs from the literature. All these drugs were small molecules eliminated hepatically, renally or both. It was found that in general, human $\text{CL}_{\text{tot}}^u$ was predicted more accurately and average error decreased. For drugs with significant variation in PPB across species, human prediction improved after PPB correction and overestimation only occurred for drugs which were mainly eliminated by metabolism.

Hosea et al. conducted a retrospective analysis using 50 proprietary compounds for which oral single dose human PK data was available. It was found that the use of single species lead to more accurate predictions than using multiple species and use of unbound concentrations resulted in accurate predictions.
Using oral data may have add confounding factors such as interspecies differences in first pass gut metabolism and absorption to the predictions and hence this study used only I.V. data and inter-species scaling was done for biologically relevant systemic unbound PK parameters like $\text{CL}_{\text{tot}}^u$ and $\text{Vd}_{\text{ss}}^u$ for the three datasets (opioids, $\beta$-ARLs and $\beta$-LAs). Several predictions methods such as one-species-BW method, two-species allometry were used for predicting human $\text{CL}_{\text{tot}}$, $\text{Vd}_{\text{ss}}$, $\text{CL}_{\text{tot}}^u$ and $\text{Vd}_{\text{ss}}^u$ and LBF method was used for $\text{CL}_{\text{tot}}$, $\text{CL}_{\text{nonren}}$, $\text{CL}_{\text{tot}}^u$ and $\text{CL}_{\text{nonren}}^u$ and GFR ratio method for $\text{CL}_{\text{ren}}$ and $\text{CL}_{\text{ren}}^u$ using rat and dog PK data.

Assumptions:

Overall, AS is based on the assumption that there are anatomical, physiological and biochemical similarities among animals, and they can be described by using mathematical models. AS can be done using various methods like one species-BW scaling, LBF method, etc. with or without consideration of PPB. Each method has its own assumptions:

<table>
<thead>
<tr>
<th>Method</th>
<th>Assumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>For $\text{CL}_{\text{tot}}$</td>
<td></td>
</tr>
<tr>
<td>One species-BW scaling without $f_u$ correction</td>
<td>There are no qualitative interspecies differences in PPB, metabolic pathways and intrinsic clearance.</td>
</tr>
<tr>
<td>One species-BW scaling with $f_u$ correction</td>
<td>There are no interspecies differences in metabolic pathways and intrinsic clearance.</td>
</tr>
<tr>
<td>LBF method without $f_u$ correction</td>
<td>Clearance is primarily by hepatic route and that blood: plasma ratio is constant across the species. There are no interspecies differences in plasma protein binding.</td>
</tr>
<tr>
<td>Method</td>
<td>Assumption</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>LBF method with $f_u$ correction</td>
<td>Clearance is primarily by hepatic route and that B:P ratio is constant across the species.</td>
</tr>
<tr>
<td>GFR ratio method without $f_u$ correction</td>
<td>Clearance is primarily by renal route and there are no interspecies differences in plasma protein binding and assumes no active tubular transport.</td>
</tr>
<tr>
<td>GFR ratio method with $f_u$ correction</td>
<td>Clearance is primarily by renal route and assumes no active tubular transport.</td>
</tr>
</tbody>
</table>

For $V_d_{ss}$

| One species-BW scaling without $f_u$ correction | There are no interspecies differences in plasma protein binding and tissue binding. |
| One species-BW scaling with $f_u$ correction   | There are no interspecies differences in tissue binding. |

**Limitations:**

- AS is empirical in nature
- AS for clearance does not take into consideration species differences in the metabolic pathways that may have significant impact on the extrapolation from the preclinical data.
- For accurate prediction, a certain range of body weights have to be used. Often, the species with lowest body weight has substantial leverage effect on the prediction.
- AS ignores genetic polymorphisms in human drug metabolizing enzymes and other sources of variability by providing average (“typical”) values of clearance.
- AS is more powerful tool for retrospective analysis than for prospective dose predictions. For first time in human dose studies, AS may give prediction intervals so wide that they are of limited use and thus, it is difficult to determine which drugs would fail a priori.
• It is difficult to predict human PK for drugs undergoing biliary excretion, extra-hepatic metabolism and tubular transport processes in kidneys using AS.

1.4. Overview

This dissertation is organized to address the prediction of human PK using QSPKR and interspecies scaling for datasets of drugs belonging to three different pharmacological classes of drugs: Opioids, β-ARLs and β-LAs. Chapter 2 states the individual hypothesis and the specific aims that will be addressed in the succeeding chapters. The dissertation can be divided into two parts:

**Part I** describes the QSPKR study. It contains Chapter 3-6. Chapter 3 consists of a brief introduction on QSPKR and describes the overall methods use in the QSPKR study followed by Chapter IV, V and VI, which describe the results of QSPKR study on opioids, β-ARLs and β-LAs, respectively. Each chapter consists of a brief introduction, description of model building, evaluation and validation followed by a discussion section.

**Part II** describes the Interspecies Scaling. It contains Chapter 7-10. Chapter 7 consists of a brief introduction on interspecies scaling and describes the overall methods used in the study followed by Chapter 8, 9 and 10 which describe interspecies scaling study on opioids, β-ARLs and β-LAs, respectively. Each chapter consists of a brief introduction, results followed by discussion section.

Chapter 11 describes the comparative analysis of molecular and PK properties of opioids, β-ARLs and β-LAs. Chapter 12 pools all the three datasets and discusses the pooled data analysis. Chapter 13 summarizes the overall conclusions from each chapter as it relates to the original hypotheses.
2. Research hypothesis

Using available information for the three pharmacological classes of drugs, namely opioids, β-ARLs and β-LAs:

- **Hypothesis I:** Molecular properties can be used to quantitatively predict systemic human PK; however, the molecular properties responsible for the biologically relevant PK properties differ by class of drugs.

  For this hypothesis:
  
  o Literature was reviewed to collect pertinent, valid systemic PK properties in humans.
  o Biologically relevant PK variables were estimated.
  o Effect of different molecular descriptors was assessed on various PK properties.
  o QSPKR models were developed and validated for biologically relevant PK properties for individual dataset and trend analysis was done for the pooled dataset.

- **Hypothesis II:** Human PK can be successfully allometrically scaled from rat and dog PK; however, the allometric scaling coefficient depends on the molecular properties drug properties.

  For this hypothesis:
  
  o Literature was reviewed to collect pertinent, valid systemic PK properties of opioids, β-ARLs and β-LAs in different species and relevant PK variables were estimated.
PK properties of opioids were compared and assessed for differences across species.

Different allometric methods were evaluated for explaining these interspecies differences.

Different prediction methods were evaluated to predict human PK properties from animal PK.

Effect of molecular properties on allometric coefficients/predictions errors was studies.
CHAPTER 3. Quantitative-Structure Pharmacokinetic Relationships (QSPKR)

3. Quantitative-Structure Pharmacokinetic Relationships (QSPKR)

3.1. Introduction:

Selection of an appropriate dataset, particularly the range and distribution of the structural attributes is critical for the success of any QSPKR study. It is a prerequisite that the data on physicochemical and biological properties are available for a sufficient number of analogs belonging to the same class of compounds. Opioids, β-β-ARLs and β-LAs were selected as the drug classes for this study because they are structural analogs, based on their pharmacological target and, at the same time, showed considerable diversity in physicochemical and PK properties. In-addition, published data on the in-vivo PK properties were available for a sufficient number of representatives of these classes of drugs. Furthermore, since no obvious PK nonlinearities were found for most of these drugs after I.V. administration, making it simple to compare PK properties for the different compounds. Thus, the objective of the present study was to develop QSPKR models which describe and predict human PK for opioids, β-ARLs and β-LAs.
3.2. Specific aims

- Review the literature to collect pertinent, valid systemic PK properties in humans and animals.
- Estimate biologically relevant PK variables.
- Assess the effect of different molecular descriptors on various PK properties.
- Develop and validate QSPKR models for biologically relevant PK properties.

3.3. Methods I

3.3.1. Collection of PK variables

The biomedical literature was searched for original research and review articles on PK and PD properties of 38 opioids (34 agonists/partial agonists and 4 antagonists), 48 β-ARLs (43 antagonists and 5 agonists) and 60 β-lactam antibiotics in humans. The search was further narrowed down to PK studies, urinary excretion studies (if available) in healthy humans after intravenous (I.V.) administration. In the literature, many articles focus on hepatic or renal dysfunction population and in such cases, data from the healthy control population was used. If necessary, I.V. PK data were obtained from absolute oral bioavailability (F_oral) studies. F_oral data were obtained from PK studies done after oral administration in healthy population. Values for f_u in plasma was obtained from in-vitro PPB studies, using therapeutically relevant concentration ranges. B:P ratio was obtained from ex-vivo or in-vitro studies on whole blood and plasma from healthy humans. RBC partitioning (γ) was calculated from f_u and B: P information (Table 1.1). Receptor affinities (K_i) at the µ-receptors for opioids were obtained from different in-vitro receptor binding studies on rat tissue homogenates and
were normalized using receptor affinity of a prototypical opioid like morphine to give relative receptor affinity (RRA). For β-ARLs, $K_i$ values were obtained from *in-vitro* receptor binding studies in human $\beta_{1,2,3}$ receptors.

*In-vivo* PK variables like $CL_{tot}$, $Vd_{ss}$, and fraction excreted unchanged ($f_{ce}$) in urine after I.V. administration for each drug were compiled after critical evaluation of study design, dosing regimen, sampling schedule, assay procedures and PK analysis methods. Of all the PK variables, the way of reporting varied widely for volume of distribution ($Vd$), *i.e.*, pseudo-steady state $Vd$ ($Vd_p$), central compartment $Vd$ ($Vd_{cc}$) or $Vd_{ss}$. The papers which report $Vd_{ss}$ were selected preferentially. Alternatively, $Vd_{cc}$ and micro-constants or macro-rate constants were used to calculate $Vd_{ss}$ (Table 1.2).61 If PK properties were not reported but concentration-time profiles were provided, then the concentration-time profile was read electronically, and $Vd_{ss}$ and $CL_{tot}$ were estimated using non-compartmental analysis.33

If the studies did not report BW-corrected PK properties, then the PK properties were corrected for BW using the mean value of BW of the subjects used in the study. In case, BW was not mentioned, a BW of 70 kg was assumed for humans.32 Since the PK properties were compiled from separate research articles, the data obtained were variable in terms of number of subjects, types of study subject, doses, sample collection intervals, methods of sample analysis and PK-PD analysis methods reported. The final PK parameters were the means of PK parameters obtained from different studies. The tabulation of the final PK studies is given in Appendix I (a-c).
3.3.2. Computation of molecular properties

Physicochemical properties like pKₐ, molecular weight (MW), molar volume (MV), calculated logP (clogP), % ionized at pH 6.3 and pH 7.4 and two dimensional molecular descriptors like number of hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), and number of rotatable bonds (nRot) were computed using ACD-solubility/DB 12.01. The chemical structures were drawn for each drug, and final energy minimization was conducted using Sybyl software V7.3 (Tripos, Inc., Louis, MO) to get molecular descriptors like polar surface area (PSA), energy and dipole moment. Log (P) is not an accurate determinant of lipophilicity for ionizable compounds because it correctly describes the partition coefficient of only neutral (uncharged) molecules. Since the majority of drugs are ionizable, log (P) is not an appropriate predictor of a compound's behavior in the changing pH environments of the body. The distribution coefficient, Log (D), is the correct descriptor for ionizable systems and is at physiologically relevant pH. The distribution coefficient is the ratio of the sum of the concentrations of all forms of the compound (ionized plus un-ionized) in each of the two phases, 1-octanol and buffer (pH 7.4). Thus, log(D)₇.₄ was obtained from ACD-solubility/DB 12.01. % ionized at pH 6.3 was also calculated which allowed us to study if the ionization of compounds changed in urine (since average urinary pH is 6.3).

3.3.3. Estimation of biologically relevant variables

Biologically relevant variables such as Vdₜ ot capacity, CLtot, CLren, CLren, CLnonren, CLnonren, CLint, Vdss, CLtot, CLren, CLnonren, CLnonren, and ERhep were estimated using the formulae in Table 1.2.
3.3.4. PK classification of drugs

For each class of drugs, molecular descriptors, primary in-vivo PK variables like CL\textsubscript{tot}, Vd\textsubscript{ss}, CL\textsubscript{ren}, f\textsubscript{u}, in-vitro variables like f\textsubscript{u} and estimated unbound parameters (CL\textsubscript{tot}\textsuperscript{u}, Vd\textsubscript{ss}\textsuperscript{u}, CL\textsubscript{nonren}\textsuperscript{u}, CL\textsubscript{ren}\textsuperscript{u}) for each compound were compared across all the drugs. The distribution of the molecular descriptors and PK variables was studied using means, medians, quartile ranges and standard deviations calculated across all the drugs to assess considered differences between compounds. The drugs in each class were further categorized using the criteria in Table 3.1.

Table 3.1. PK Classification of Drugs

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Based on plasma protein binding (PPB)</strong></td>
<td></td>
</tr>
<tr>
<td>High PPB</td>
<td>f\textsubscript{u} &lt; 20%</td>
</tr>
<tr>
<td>Intermediate PPB</td>
<td>20% &lt; f\textsubscript{u} &lt; 80%</td>
</tr>
<tr>
<td>Low PPB</td>
<td>f\textsubscript{u} &gt; 80%</td>
</tr>
<tr>
<td><strong>Based on route of elimination</strong></td>
<td></td>
</tr>
<tr>
<td>Highly metabolized drug and major route of metabolism is hepatic (assuming no extra-hepatic metabolism)</td>
<td>f\textsubscript{e} &lt; 20%</td>
</tr>
<tr>
<td><strong>Based on hepatic extraction ratio</strong></td>
<td></td>
</tr>
<tr>
<td>Low extraction ratio (LER)</td>
<td>ER\textsubscript{hep} &lt; 0.3</td>
</tr>
<tr>
<td>Intermediate extraction ratio (IER)</td>
<td>0.3 &lt; ER\textsubscript{hep} &lt; 0.7</td>
</tr>
<tr>
<td>High extraction ratio (HER)</td>
<td>ER\textsubscript{hep} &gt; 0.7</td>
</tr>
<tr>
<td><strong>Based on extrahepatic metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Drug undergoes extra-hepatic metabolism</td>
<td>CL\textsubscript{nonren}\textsubscript{blood} \geq Q\textsubscript{hep}</td>
</tr>
<tr>
<td>High F\textsubscript{oral} when high ER\textsubscript{hep} \textsuperscript{l}</td>
<td></td>
</tr>
<tr>
<td><strong>Based on the renal handling</strong></td>
<td></td>
</tr>
<tr>
<td>Drug undergoes net tubular reabsorption</td>
<td>CL\textsubscript{ren}\textsuperscript{u} &lt; GFR</td>
</tr>
</tbody>
</table>
### Classification Criteria

<table>
<thead>
<tr>
<th>Based on plasma protein binding (PPB)</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>High PPB</td>
<td>$f_u &lt; 20%$</td>
</tr>
<tr>
<td>Intermediate PPB</td>
<td>$20% &lt; f_u &lt; 80%$</td>
</tr>
<tr>
<td>Low PPB</td>
<td>$f_u &gt; 80%$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Based on route of elimination</th>
<th>Where $GFR$ is the glomerular filtration rate (120 ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug undergoes net glomerular filtration</td>
<td>$\text{CL}_{\text{ren}}^u = GFR$</td>
</tr>
<tr>
<td>Drug undergoes net tubular secretion</td>
<td>$\text{CL}_{\text{ren}}^u &gt; GFR$</td>
</tr>
</tbody>
</table>

#### 3.4. Methods II – Statistical Analysis

**3.4.1. Descriptive statistics**

**3.4.1.1. Covariate screening – Molecular descriptors**

Covariate screening: Correlation matrices amongst molecular descriptors were constructed to assess for collinearity. If two descriptors were collinear, i.e. $r \geq 0.8$, only one of them was used in the final univariate/multivariate analysis.

**3.4.1.2. Correlation analysis – PK variables**

Correlation analysis: If the PK variable showed skewed distribution, then the PK variable was log transformed. Correlation matrices amongst PK variables were constructed to assess collinearity.

**3.4.2. QSPKR Model Building and Evaluation**

For opioids and $\beta$-ARLs, analyses were performed on two data sets: complete and reduced dataset (excluding opioids/$\beta$-ARLs known/suspected to undergo extra-hepatic metabolism). Univariate linear regression of all PK variables vs. each molecular descriptors was
performed. Relationships which showed p<0.05 and $r^2 \geq 0.30$ were used further to build a final QSPKR model by multiple linear regression (JMP 8.0, SAS, Cary, NC). PK variables (except $f_c$ and $f_u$) were log-transformed. Final QSPKR models were obtained from and evaluated on two datasets: complete and reduced (excluding opioids/β-ARLs known/suspected to undergo extrahepatic, nonrenal elimination, e.g., ester hydrolysis). Goodness of fit for the final QSPKR models was assessed by $r^2$ (p<0.05), and their predictive performance was cross-validated in SAS 9.2 using the leave-one-out method (see below).

### 3.4.3. Cross-validation

Cross-validation was done using leave-out-one method in SAS 9.2. This method leaves a single observation from the original sample as the validation data, and the remaining observations are treated as the training data. This is repeated such that each observation in the sample is used exactly once as the validation data. For each model, the excluded observation is predicted, and the cross-validated explained variance ($q^2$) is computed using the following formula:

$$q^2 = 1 - \frac{\sum (predicted - observed)^2}{\sum (observed - mean)^2}$$

A model with a $q^2 \geq 0.40$ was considered acceptable.
CHAPTER 4. QSPKR OF OPIOIDS

4. Opioids

4.1. Background

Opioids are first-line agents for the treatment of moderate to severe pain. They are generally used in anesthetic procedures (in combination with general anesthetics). They are highly effective and inexpensive and can be given by multiple routes of administration. However, there are some limitations as they can cause potentially life-threatening respiratory depression, gastrointestinal disturbances like constipation, CNS side effects like nausea, dizziness, and they have the potential to cause drug dependence. These drugs exert their pharmacological actions through interaction with three types of G-protein coupled receptors (GPCR), mu (μ₁, μ₂), kappa (κ₁, κ₂, κ₃) and delta (δ₁, δ₂), which bind to endogenous ligands like endorphins, dynorphin and enkephalines, respectively (Figure 4.1). Figure 4.2 shows the common structural backbone of most of the opioids and structure of a prototypical opioid, morphine, and its important binding groups for the analgesic activity.63 Depending on the activity at the receptors, opioids are categorized into agonists, partial agonists and antagonists. Opioid agonists and antagonists are structurally similar, have similar molecular weights; however, there are considerable differences in their potency and PK properties. Table 4.1 shows the therapeutic I.V. doses of some opioids. There is a difference of more than 55000-fold difference in the therapeutic doses, indicating that
there are some opioids like sufentanil and remifentanil which are very potent (0.001 mg/kg), while there are opioids like dezocine which are least potent (5 mg/kg). Some of these differences are due to variability in the affinity to and intrinsic activity at the opioid (µ-) receptors, i.e., their PD properties; however, differences in their physicochemical and PK properties may be of importance as well. To account for these differences, effect of the physicochemical properties on the PK-PD properties was studied. The PK-PD properties in humans were compared across different opioids and later on, the study was extended to comparison of PK of opioids across different animal species. This helped in understanding the similarities and dissimilarities in the PK of opioids across different animal species. In-vivo PK data from preclinical studies are an important tool in drug discovery in understanding PK parameters as well as predicting human PK. However, often it is difficult to extrapolate PK from animals to humans because of the inherent differences in the physiology and metabolic pathways between animals and humans. Different allometric methods were used to explain these differences in opioids. Thus, objective of this meta-analysis was to evaluate potential use of molecular properties to predict in-vivo human PK properties like total and unbound $CL_{tot}$, $V_d_{ss}$, $CL_{ren}$ and in-vitro PK properties like PPB and $\gamma$ and to use interspecies scaling to predict human PK.
Opioid receptors

μ receptor

- Supraspinal and spinal analgesia (µ₁)
- Euphoria (µ₁)
- Urinary retention (µ₁)
- Respiratory depression and spinal analgesia (µ₂)
- Physical dependence (µ₂)
- Constipation (µ₂)
- Miosis

κ receptor

- Analgesia (κ₁, κ₂, κ₃)
- Dysphoria (κ₂, κ₃)
- Diuresis
- Sedation

δ receptor

- Analgesia (δ₁, δ₂)
- Respiratory depression
- Constipation

β-Endorphin
Endomorphins

Dynorphin A

Enkephalins

Figure 4.1. Opioid Receptors and its Pharmacological Actions
Figure 4.2. Common Structural Backbone and Important Functional Groups of Opioids
Table 4.1. Therapeutic doses for different opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (I.V.) [mg/kg]</th>
<th>Dose (I.V.) [µmoles]</th>
<th>AUC [µmoles/ml*min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>M3G</td>
<td>0.40</td>
<td>56.3</td>
<td>3.496E-01</td>
</tr>
<tr>
<td>M6G</td>
<td>0.01</td>
<td>2.0</td>
<td>1.618E-02</td>
</tr>
<tr>
<td>Oxy-morphine</td>
<td>0.01</td>
<td>1.7</td>
<td>1.185E-02</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.02</td>
<td>5.3</td>
<td>3.502E-03</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.14</td>
<td>35.0</td>
<td>1.919E-02</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>0.07</td>
<td>15.9</td>
<td>2.013E-02</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.57</td>
<td>133.6</td>
<td>1.480E-01</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0.54</td>
<td>143.5</td>
<td>2.898E-01</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>0.14</td>
<td>28.0</td>
<td>1.605E-02</td>
</tr>
<tr>
<td>Heroin</td>
<td>4.71</td>
<td>893.3</td>
<td>6.429E-02</td>
</tr>
<tr>
<td>Ketobemidone</td>
<td>0.14</td>
<td>39.6</td>
<td>4.640E-02</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>0.01</td>
<td>3.9</td>
<td>3.535E-03</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>0.001</td>
<td>0.1</td>
<td>4.203E-05</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.01</td>
<td>3.1</td>
<td>1.449E-03</td>
</tr>
<tr>
<td>Meperidine</td>
<td>1.07</td>
<td>303.2</td>
<td>4.323E-01</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.14</td>
<td>32.3</td>
<td>1.710E-01</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>0.43</td>
<td>105.1</td>
<td>7.740E-02</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.01</td>
<td>2.4</td>
<td>9.282E-03</td>
</tr>
<tr>
<td>Tildine</td>
<td>0.60</td>
<td>153.6</td>
<td>1.425E-01</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.001</td>
<td>0.3</td>
<td>3.424E-04</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.0001</td>
<td>0.026</td>
<td>2.653E-05</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.004</td>
<td>0.6</td>
<td>4.550E-04</td>
</tr>
<tr>
<td>Meptazinol</td>
<td>0.35</td>
<td>105.0</td>
<td>6.028E-02</td>
</tr>
<tr>
<td>Dezocine</td>
<td>5.00</td>
<td>1426.5</td>
<td>5.420E-01</td>
</tr>
<tr>
<td>Piracetamide</td>
<td>0.20</td>
<td>32.5</td>
<td>6.201E-02</td>
</tr>
<tr>
<td>Dextropoxyphene</td>
<td>3.43</td>
<td>707.0</td>
<td>7.537E-01</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>0.01</td>
<td>2.9</td>
<td>8.754E-04</td>
</tr>
<tr>
<td>Methylnaltrexone</td>
<td>0.30</td>
<td>59.0</td>
<td>3.779E-02</td>
</tr>
<tr>
<td>Naloxone</td>
<td>0.004</td>
<td>0.8</td>
<td>3.908E-04</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>0.01</td>
<td>2.9</td>
<td>2.811E-03</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0001</td>
<td>0.03</td>
<td>2.653E-05</td>
</tr>
<tr>
<td>Maximum</td>
<td>5.00</td>
<td>1426.48</td>
<td>7.537E-01</td>
</tr>
<tr>
<td>Mean</td>
<td>0.61</td>
<td>143.18</td>
<td>0.11</td>
</tr>
<tr>
<td>-fold range</td>
<td>35000</td>
<td>55140</td>
<td>28409</td>
</tr>
</tbody>
</table>

n 30  30  30

4.2. Results

4.2.1. Comparison of Molecular Descriptors and PK Variables of Opioids

Opioids (34 agonists/partial agonists and four antagonists) showed considerable diverse physicochemical and 2D molecular properties (Table 4.2). They are small molecules with molecular weights ranging from 230-500 Dalton. Morphine is a prototypical opioid and, out
of 38 opioids in the dataset, 17 opioids were found to have the typical morphine scaffold. Two active metabolites of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are acidic and most polar in nature. Most of the opioids were found to have 2 pK\textsubscript{a}s, pK\textsubscript{a1} due to the basic group (-NH\textsubscript{2} group) and pK\textsubscript{a2} due to weakly acidic group (-OH group) and act as zwitterions in certain range of pH. % Ionized showed large differences, remifentanil showed the least (9%) while dezocine showed the most (100%) % ionized at pH 7.4. Descriptive statistics (Table 4.3) showed that for all the molecular descriptors (except log(D)\textsubscript{7.4}), the mean value is greater than the median value, and the distribution is skewed towards the right. High standard deviations indicate a considerable variation in molecular descriptors across the opioids. The predefined acceptance criterion for collinearity was r ≥ 0.80, but none of the descriptors were found to be collinear.

The final mean PK variables obtained from different studies are shown in Table 4.4, and the estimated PK variables are shown in Table 4.5. Descriptive statistics (Table 4.6) showed that for most PK variables (except f\textsubscript{u} and γ), the mean value is greater than the median value. For most of the PK variables, distribution was found to be skewed. High standard deviations show that PK variables show considerable variation across the opioids. Thus, for subsequent analyses, the PK variables (except f\textsubscript{u} and γ) were log-transformed. Some of the PK variables were strongly correlated with each other (Table 4.7).

Based on the criteria outlined in Table 3.1, opioids were classified into different categories as shown in Table 4.8. In this dataset, opioids varied in their PPB from 8 % to 96 %. Hydromorphone showed the highest f\textsubscript{u} and buprenorphine showed the lowest f\textsubscript{u}. The γ value depends on f\textsubscript{u} in plasma, since only unbound drug in plasma can partition into RBCs. Table 4.5 shows that remifentanil has the highest γ indicating that the f\textsubscript{u} is low due to high
PPB. On the other hand, nalbuphine has a low $\gamma$ due to low PPB. M6G has negligible $f_u$. For drugs with $\gamma > 1.0$, CL_{tot} exceeds CL_{nonren}^{blood} and for drugs with $\gamma < 1.0$, CL_{nonren}^{blood} exceeds CL_{tot}. The extent of distribution varied (more than 100-fold) across the opioids. Polar compounds like morphine glucuronides showed the lowest Vd_{ss}, while more lipophilic ones like dextropropoxyphene, fentanyl, sufentanil, etc. showed high Vd_{ss} values. CL_{tot}^{u} varied across the opioids (more than 300-fold). High PPB tends to lower CL_{tot} values. CL_{tot} value for remifentanil was found to be exceeding LBF, while heroin and nicomorphine showed CL_{tot} exceeding cardiac output (CO- 86 ml/min/kg) in humans, indicating extra-hepatic metabolism/ester hydrolysis in blood and other body tissues. Meperidine is also an ester and is likely to undergo hydrolysis in blood and other tissues by non-specific esterases. Mirfentanil and dextromethorphan also had CL_{tot} values exceeding cardiac output, indicating extrahepatic/nonrenal clearance in blood and other body tissues. All of the opioids (except glucuronides and methylnaltrexone) were found to be highly metabolized ($f_e < 20\%$). Compounds like morphine glucuronides, and oxymorphone are low ER drugs while several have CL_{nonren} approaching or exceeding LBF, indicating that they are high ER drugs. M6G, hydromorphone, oxycodone, tramadol, heroin, and sufentanil showed CL_{ren}^{u} less than GFR (GFR $\sim$ 1.7 ml/min/kg$^{32}$), indicating that they are mainly tubularly reabsorbed. On the other hand, M3G, piritramide and naltrexone showed CL_{ren}^{u} equal to GFR, indicating that they are excreted by net glomerular filtration in kidneys. Morphine, codeine, nalbuphine, butorphanol, meperidine, fentanyl and nalmefene showed CL_{ren}^{u} exceeding GFR, indicating that they undergo net tubular secretion. Morphine glucuronides and nalbuphine were found to have low BP ratio due to low $\gamma$, while alfentanil showed low BP ratio due to high PPB. BP ratio more than 1.0 indicated high PPB (e.g., butorphanol) or high $\gamma$ (e.g. hydromorphone,
morphine). $\text{CL}_{\text{nonren}}^{\text{blood}}$ values for morphine, nalbuphine, butorphanol, tilidine and naltrexone were higher than LBF. In addition, drugs such as morphine, codeine and hydromorphone, had high $F_{\text{oral}}$ values (Table 4.4) although they had high apparent ER$_{\text{hep}}$, indicating that they undergo extrahepatic clearance. Thus, the major clearance mechanism for these opioids is hepatic and extrahepatic metabolism/clearance, and the ER$_{\text{hep}}$ estimates probably overestimate their hepatic extraction. M6G has estimated ER$_{\text{hep}}$\textsuperscript{1} of 6%, so we would expect a high bioavailability. However, studies showed that $F_{\text{oral}}$ is only 11%, indicating that there maybe issues in gastrointestinal solubility/permeability.
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drug</th>
<th>MW [D]</th>
<th>clogP</th>
<th>pH7.4</th>
<th>Pκa2</th>
<th>log (D) at pH 7.4</th>
<th>% Ionized at pH 7.4</th>
<th>Molar volume (cm³/mol)</th>
<th>nRot</th>
<th>HBA</th>
<th>HBD</th>
<th>PSA (Å²)</th>
<th>Dipole moment (Debye)</th>
<th>Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M3G</td>
<td>461</td>
<td>-1.56</td>
<td>2.8</td>
<td>-4.11</td>
<td>12</td>
<td>280</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td></td>
<td></td>
<td>232</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>M6G</td>
<td>461</td>
<td>0.69</td>
<td>2.8</td>
<td>-1.93</td>
<td>25</td>
<td>280</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td></td>
<td></td>
<td>248</td>
<td>98</td>
</tr>
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<td>3</td>
<td>Dihydrocodeine</td>
<td>301</td>
<td>0.61</td>
<td>8.4</td>
<td>14.2</td>
<td>-0.52</td>
<td>93</td>
<td>229</td>
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<td>1</td>
<td>72</td>
<td>116</td>
<td>79</td>
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<tr>
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<td>Morphine</td>
<td>285</td>
<td>0.87</td>
<td>8.3</td>
<td>9.5</td>
<td>0.04</td>
<td>82</td>
<td>198</td>
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<td>4</td>
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<td>79</td>
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Table 4.6. Descriptive Statistics for PK variables of Opioids

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## Table 4.7. Correlation Matrix for PK Variables of Opioids

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4.2.2. QSPKR analysis, model building and evaluation

The QSPKR analysis was done on two datasets, complete and reduced (after exclusion of drugs known/suspected of undergoing extra-hepatic metabolism), assuming that the same physicochemical properties responsible for hepatic metabolism/renal excretion may not be responsible for a drug’s tendency to be hydrolysed by non-specific esterases/amidases in tissues/blood. The results of univariate regression between PK parameters and molecular descriptors for complete dataset and reduced dataset are shown in Table 4.9 and Table 4.10. The relationships which showed $r^2 \geq 0.30$ and $p < 0.05$ were further used to build final multivariate QSPKR model by using log-linear and multiple log-linear regressions (MLLR). The final models from the QSPKR analysis are summarized in Table 4.11. *In-vitro* PK variables such as $f_u$ and $\gamma$ are strongly dependent on log $\log(D)_{7.4}$ (Table 4.9). PK variables, $\text{Vd}_{ss}^u$, $\text{CL}_{tot}^u$, $\text{CL}_{nonren}^u$ and $\text{CL}_{nonren}^u$, did show a significant relationship with log $\log(D)_{7.4}$. Molar volume (MV) and log $\log(D)_{7.4}$ combined showed a significant effect on $f_u$ (Figures 4.3-4.4). Secondary to $f_u$, $\text{CL}_{ren}$ decreased with MV and log $\log(D)_{7.4}$ (Table 4.9, Figure 4.7). $\text{CL}_{ren}$ is strongly related with log $\log(D)_{7.4}$; however, $\text{CL}_{ren}^u$ is not affected by log $\log(D)_{7.4}$ (Table 4.9, Figure 4.10). PPB increased strongly with log $\log(D)_{7.4}$, as did $\text{Vd}_{ss}^u$ and $\text{CL}_{tot}^u$ (Table 4.9, Figures 4.3, 4.9, 4.12). As a result of these offsetting effects, $\text{Vd}_{ss}$ and $\text{CL}_{tot}$ were not affected by log $\log(D)_{7.4}$ (Figures 4.5-4.6). Log $\log(D)_{7.4}$ accounted for 52 % variability in the $\text{ER}_{hep}$ for the complete dataset ($n = 11$, slope = 0.11) and 84 % variability for reduced dataset ($n = 7$, slope = 0.12), although the regression was governed by extreme cases; polar morphine glucuronides with very low $\text{ER}_{hep}$ and highly lipophilic sufentanil and pentazocine with very high $\text{ER}_{hep}$. 

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Univariate analysis showed a significant effect of HBA, HBD and PSA on $\text{CL}_{\text{nonren}}$, $\text{CL}_{\text{nonren}}^u$, and $\text{Vd}_{\text{ss}}^u$; however, the regression is leveraged by the extreme values for morphine glucuronides and, hence, these results were extremely sensitive to the inclusion of M3G and M6G. Log (D)$_{7.4}$, ranging from -4.1 to 3.7, was the sole most important molecular property, affecting most of the biologically relevant PK variables of opioids. The slopes for all PK variables, remained similar across the analyses for the complete and reduced datasets, indicating that the effect of molecular descriptors on these parameters was similar; however, exclusion of the drugs undergoing extra-hepatic metabolism lead to improvement in $r^2$, $q^2$ and a decrease in p-value and prediction errors (Table 4.9-4.11, Figures 4.13-4.20). Overall, the final QSPKR models developed provided acceptable predictions ($q^2 \geq 0.40$) for $f_u$, $\text{Vd}_{\text{ss}}^u$, $\text{CL}_{\text{nonren}}^u$, and $\text{CL}_{\text{ren}}$ (Table 4.11). For $\text{CL}_{\text{nonren}}^u$, the predictive ability improved after exclusion of drugs undergoing extra-hepatic, nonrenal elimination, indicating the importance of nonrenal clearance mechanisms (hepatic vs. extra-hepatic) on QSPKR clearance predictions.
Univariate effects of log(D)\textsubscript{pH\,7.4} and Molar Volume (MV) on \( f_u \). * Note: Opioids are numbered as per table 5

Figure 4.3. \( f_u \) vs. MV (Opioids)  

Figure 4.4. \( f_u \) vs. log (D)\textsubscript{pH\,7.4} (Opioids)
Univariate Effect of $\log(D)_{7.4}$- Complete dataset (Note: Opioids are numbered as per Table 4.4)

Figure 4.5. $V_{dss}$ vs $\log(D)_{7.4}$ (Opioids)

Figure 4.6. $CL_{tot}$ vs $\log(D)_{7.4}$ (Opioids)

Figure 4.7. $CL_{ren}$ vs $\log(D)_{7.4}$ (Opioids)

Figure 4.8. $CL_{nonren}$ vs $\log(D)_{7.4}$ (Opioids)
Figure 4.9. $\text{CL}_{\text{tot}}^u$ vs log(D)$_{7.4}$ (Opioids)

Figure 4.10. $\text{CL}_{\text{ren}}^u$ vs log(D)$_{7.4}$ (Opioids)

Figure 4.11. $\text{CL}_{\text{nonren}}^u$ vs log(D)$_{7.4}$ (Opioids)

Figure 4.12. $V_{dss}^u$ vs log(D)$_{7.4}$ (Opioids)
Table 4.9. Log-linear Regression between Molecular Descriptors and PK Variables for Complete Dataset

<p>|          | ( f_u ) | ( \gamma ) | ( \text{Log} (V_d) ) (L/kg) | ( \text{Log} (CL_{tot}) ) (ml/min/kg) | ( \text{Log} (CL_{ren}) ) (ml/min/kg) | ( \text{Log} (CL_{nonren}) ) (ml/min/kg) | ( \text{Log} (CL_{tot}^{u}) ) (ml/min/kg) | ( \text{Log} (CL_{ren}^{u}) ) (ml/min/kg) | ( \text{Log} (CL_{nonren}^{u}) ) (ml/min/kg) | ( \text{Log} (V_d^{u}) ) (L/kg) | ( \text{Log} (CL_{int}) ) (ml/min/kg) |
|----------|-----------|-------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| MW       | ( n = 29 ) | ( r^2 = 0.05 ) | ( n = 18 ) | ( r^2 = 0.002 ) | ( n = 36 ) | ( r^2 = 0.22 ) | ( n = 37 ) | ( r^2 = 0.009 ) | ( n = 21 ) | ( r^2 = 0.05 ) | ( n = 29 ) | ( r^2 = 0.19 ) | ( n = 21 ) | ( r^2 = 0.003 ) | ( n = 29 ) | ( r^2 = 0.05 ) | ( n = 18 ) | ( r^2 = 0.11 ) | ( n = 18 ) | ( r^2 = 0.02 ) | ( n = 28 ) | ( r^2 = 0.24 ) |
| Slope = -0.002 | (N.S.) | Slope = -0.004 | (N.S.) | Slope = -0.007 | (N.S.) | Slope = -0.004 | (N.S.) | Slope = 0.0005 | (N.S.) | Slope = -0.001 | (N.S.) | Slope = -0.003 | (N.S.) | Slope = -0.002 | (N.S.) | Slope = -0.008 | (N.S.) | Slope = -0.004 | (N.S.) | Slope = -0.005 | (N.S.) | Slope = -0.004 | (N.S.) |
| n = 29 | r = 0.42 | n = 18 | r = 0.35 | n = 36 | r = 0.07 | n = 37 | r = 0.22 | n = 21 | r = 0.35 | n = 29 | r = 0.31 | n = 21 | r = 0.19 | n = 21 | r = 0.006 | n = 29 | r = 0.02 | n = 18 | r = 0.07 | n = 18 | r = 0.02 | n = 28 | r = 0.08 |
| Slope = -0.13 | (p &lt; 0.05) | n = 29 | r = 0.47 | n = 18 | r = 0.04 | n = 37 | r = 0.12 | n = 36 | r = 0.01 | n = 21 | r = 0.52 | n = 21 | r = 0.02 | n = 29 | r = 0.20 | n = 28 | r = 0.03 | n = 18 | r = 0.13 | n = 18 | r = 0.02 | n = 27 | r = 0.08 |
| n = 21 | r = 0.73 | n = 28 | r = 0.49 | Slope = 0.30 | (p &lt; 0.05) | Slope = 0.46 | (p &lt; 0.05) |
| nRot | ( n = 29 ) | ( r^2 = 0.23 ) | ( n = 18 ) | ( r^2 = 0.23 ) | ( n = 37 ) | ( r^2 = 0.11 ) | ( n = 37 ) | ( r^2 = 0.05 ) | ( n = 21 ) | ( r^2 = 0.19 ) | ( n = 21 ) | ( r^2 = 0.05 ) | ( n = 29 ) | ( r^2 = 0.02 ) | ( n = 29 ) | ( r^2 = 0.02 ) | ( n = 18 ) | ( r^2 = 0.02 ) | ( n = 28 ) | ( r^2 = 0.02 ) | ( n = 10 ) | ( r^2 = 0.02 ) |
| n = 21 | r = 0.12 | n = 18 | r = 0.08 | n = 37 | r = 0.05 | n = 37 | r = 0.19 | n = 21 | r = 0.35 | n = 29 | r = 0.20 | n = 21 | r = 0.19 | n = 21 | r = 0.05 | n = 29 | r = 0.02 | n = 18 | r = 0.07 | n = 18 | r = 0.02 | n = 28 | r = 0.08 |
| Slope = -0.06 | (p &lt; 0.05) | n = 29 | r = 0.08 | n = 18 | r = 0.20 | n = 37 | r = 0.06 | n = 37 | r = 0.01 | n = 21 | r = 0.38 | n = 21 | r = 0.01 | n = 29 | r = 0.18 | n = 28 | r = 0.18 | n = 10 | r = 0.28 | n = 10 | r = 0.28 | n = 10 | r = 0.28 |
| Slope = -0.77 | (N.S.) | Slope = -0.12 | (N.S.) | Slope = -0.05 | (N.S.) | n = 29 | r = 0.35 | n = 21 | r = 0.006 | n = 29 | r = 0.02 | n = 29 | r = 0.05 | n = 21 | r = 0.001 | n = 29 | r = 0.002 | n = 18 | r = 0.02 | n = 28 | r = 0.18 | n = 10 | r = 0.28 |
| Slope = -0.15 | (p &lt; 0.05) | n = 29 | r = 0.08 | n = 37 | r = 0.01 | n = 37 | r = 0.11 | n = 21 | r = 0.37 | n = 29 | r = 0.001 | n = 21 | r = 0.001 | n = 18 | r = 0.002 | n = 28 | r = 0.02 | n = 10 | r = 0.02 | n = 10 | r = 0.02 |
| HBA | ( n = 29 ) | ( r^2 = 0.08 ) | ( n = 18 ) | ( r^2 = 0.38 ) | ( n = 37 ) | ( r^2 = 0.06 ) | ( n = 37 ) | ( r^2 = 0.01 ) | ( n = 21 ) | ( r^2 = 0.37 ) | ( n = 29 ) | ( r^2 = 0.01 ) | ( n = 29 ) | ( r^2 = 0.02 ) | ( n = 29 ) | ( r^2 = 0.05 ) | ( n = 18 ) | ( r^2 = 0.18 ) | ( n = 18 ) | ( r^2 = 0.02 ) | ( n = 28 ) | ( r^2 = 0.08 ) |
| Slope = 0.04 | (N.S.) | Slope = -0.12 | (N.S.) | Slope = -0.05 | (N.S.) | n = 29 | r = 0.35 | n = 21 | r = 0.006 | n = 29 | r = 0.02 | n = 29 | r = 0.05 | n = 21 | r = 0.001 | n = 29 | r = 0.002 | n = 18 | r = 0.02 | n = 28 | r = 0.18 | n = 10 | r = 0.28 |
| HBD | ( n = 29 ) | ( r^2 = 0.01 ) | ( n = 18 ) | ( r^2 = 0.08 ) | ( n = 37 ) | ( r^2 = 0.06 ) | ( n = 37 ) | ( r^2 = 0.01 ) | ( n = 21 ) | ( r^2 = 0.37 ) | ( n = 29 ) | ( r^2 = 0.01 ) | ( n = 29 ) | ( r^2 = 0.02 ) | ( n = 29 ) | ( r^2 = 0.05 ) | ( n = 18 ) | ( r^2 = 0.18 ) | ( n = 18 ) | ( r^2 = 0.02 ) | ( n = 28 ) | ( r^2 = 0.08 ) |</p>
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*Criteria of selection for model building: $r^2 \geq 0.30$ and $p<0.05$*
Univariate Effect of log(D) - Reduced Dataset (Note: Opioids are numbered as per Table 4.4.)

Figure 4.13. Vdss vs log(D)7.4 (Opioids)

Figure 4.14. CLtot vs log(D)7.4 (Opioids)

Figure 4.15. CLren vs log(D)7.4 (Opioids)

Figure 4.16. CLnonren vs log(D)7.4 (Opioids)
Figure 4.17. $CL_{tot} \text{ u vs log}(D)_{7.4}$ (Opioids)

Figure 4.18. $CL_{ren} \text{ u vs log}(D)_{7.4}$ (Opioids)

Figure 4.19. $CL_{nonren} \text{ u vs log}(D)_{7.4}$ (Opioids)

Figure 4.20. $V_{dss} \text{ u vs log}(D)_{7.4}$ (Opioids)
Table 4.10. Log-linear Regression between Molecular Descriptors and PK Variables for Reduced Dataset

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*Criteria of selection for model building: r^2 ≥ 0.30 and p<0.05*
Table 4.11. Final, Multivariate QSPKR Models for Opioids

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<th>PK Variable</th>
<th>Dataset</th>
<th>n</th>
<th>Property</th>
<th>Dataset</th>
<th>n</th>
<th>Property</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>No. of compounds in 0.5-2.0 fold error range</th>
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<td>Slope   r²  q²   % MPE   % RMSE</td>
<td>r²   q²   % MPE   % RMSE</td>
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<td>$f_u$</td>
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<td>log(D)</td>
<td></td>
<td></td>
<td></td>
<td>-0.13 0.42 -    -     -</td>
<td>0.67 0.61 40 152</td>
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<td>log(D)</td>
<td>MV</td>
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<td>0.74 0.66 47 181</td>
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<td></td>
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<td>-0.004 0.50 -    -     -</td>
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<td>$\log(V_{d,u}')$</td>
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<td></td>
<td>0.30 0.49 0.47 36 111</td>
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<tr>
<td></td>
<td>Reduced</td>
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<td></td>
<td></td>
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<td>0.30 0.51 0.47 26 80</td>
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<td>log(D)</td>
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<td>log(D)</td>
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<td>0.34 0.73 0.66 -35 173</td>
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<tr>
<td>$\log(CL_{ren})$</td>
<td>Complete</td>
<td>21</td>
<td>MV</td>
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4.2.3. Discussion

Opioid agonists and antagonists are structurally similar and have similar molecular weights; however, there are considerable differences in their PK-PD properties. The Vd_{ss} varies (more than 1000-fold) across the opioids. Vd_{ss}^u values were found to be greater than body weight, indicating high tissue sequestration; on the other hand, this was counteracted by high PPB that lead to lower Vd_{ss} values. CL_{nonren} indicates both high- and low- hepatic ER, latter due to low CL_{int} and/or high PPB e.g., Alfentanil is a low ER drug due to high PPB while oxymorphone is a low ER drug due to its low CL_{int}. For the majority of opioids, the clearance is due to non-renal elimination, i.e., hepatic and extra-hepatic clearance. Literature evidence indicates that remifentanil and heroin are esters undergoing hydrolysis by non-specific esterases in blood and tissues, explaining extra-hepatic clearance.\textsuperscript{64, 65} Meperidine is also an ester and may undergo hydrolysis by non-specific esterases in blood and tissues. Heroin, mirtfantanil, nicomorphine and dextromethorphan showed CL_{tot} values exceeding cardiac output (86 ml/min/kg) while morphine, nalbuphine, butorphanol, tilidine, naltrexone showed CL_{nonren} exceeding LBF as well; thus, it was concluded that, they may undergo extra-hepatic clearance. In-addition, drugs like morphine, codeine and hydromorphone, showed high F_{oral} values although they have very high apparent ER_{hep} values, indicating that at least part of their nonrenal clearance is extra-hepatic.

Overall, opioids showed large diversity in their physicochemical (>10,000-fold), PK (100-1000-fold) and PD (13,000- fold) properties. Some of these differences were due to variability in the affinity to and intrinsic activity at the opioid (µ-) receptors\textsuperscript{66}, i.e., their pharmacodynamic (PD) properties; however, differences in their physicochemical and PK
properties may be of importance as well. To account for the differences, the effects of the physicochemical properties on the PK-PD properties were studied. Lipophilicity (log (D)_{7.4}) was found to be the primary determinant of PK properties, since it governs the transport of the drug across several biological membranes. As the log (D)_{7.4} increased, there was a significant decrease in f_u since the drugs bind to the plasma proteins by hydrophobic interactions. This finding is consistent with protein binding of various barbiturates in the rats^{67}, penicillins in humans^{68} and β-blockers and anti-arrhythmic drugs in humans^{19,69}. Laznicek et al^{70} studied plasma protein binding–lipophilicity relationship of some organic acids and found a sigmoidal relation between f_u and log (D)_{7.4}. The same data was analyzed using linear regression which showed a significant relation (slope = -18.7, r^2 = 0.62). Obach et al^{16} using an asset of 554 drugs suggested that increasing log (D)_{7.4} increased PPB because of hydrophobic forces interaction with albumin and α-acid glycoprotein. In addition to plasma protein binding, it is essential to consider binding to blood components like RBCs. Lipophilic drugs penetrate the RBCs by dissolving into the lipid bilayer membrane. Hence, a significant relation was found between γ and log (D)_{7.4}. Similar results were found for γ of barbiturate series in rats^{67} and for β-blockers in humans^{19}. High PPB decreased Vd_{ss} for highly plasma protein bound drugs. After correction for PPB, it was observed that Vd_{ss}^u significantly increased with log (D)_{7.4}. This showed that there are two opposing forces acting on Vd_{ss}; offset each other, indicating, as log (D)_{7.4} increases, sequestration in tissues increase. A similar relationship was seen for Vd_{ss}^u for a series of sulfonamides in rats (n = 6, slope = 0.20 units, r^2 = 0.69)^{71} and β-blockers in human (n = 13, slope = 0.33 units, r^2 = 0.71)^{19}; with slopes similar to the slopes obtained in the present study on opioids (n = 28, slope = 0.37 units, r^2 = 0.59). Obach et al^{16} studied PK in humans for a diverse data set of 670 drugs (159
acids, 267 bases, 173 neutrals and 68 zwitterions) and found that there was an upward trend for $V_{d_{ss}}^u$ with increasing lipophilicity for bases, neutrals and zwitterions and it was found that bases had greater CL$_{tot}$ values than acids, neutrals or zwitterions. As the log (D)$_{7.4}$ increased, there was a significant decrease in CL$_{ren}$. This can be due to increase in passive reabsorption with increase in log (D)$_{7.4}$, thus preventing renal excretion. A similar trend was also observed between CL$_{ren}$ and log (D)$_{7.4}$ for a set of 391 compounds and β-blockers in human. In this data set, a significant relation was found between log (D)$_{7.4}$ and PPB. However, when CL$_{ren}$ was corrected for PPB, the relation between CL$_{ren}^u$ and log (D)$_{7.4}$ was insignificant. This might suggest that as the PPB increased, less amount of drug was available for glomerular filtration. In this dataset, there are many opioids which have CL$_{ren}^u$ values exceeding GFR, indicating that they undergo tubular secretion. This showed that the effect of lipophilicity was stronger on the drugs which are highly plasma protein bound and undergo filtration. CL$_{ren}$ decreased with molar volume, indicating that renal tubular reabsorption may also be limited by molecular size. This dataset was biased towards more lipophilic, hepatically metabolized compounds. Thus, for some drugs, especially with high log (D)$_{7.4}$, $f_c$ and/or CL$_{ren}$ may have been poorly estimated. Overall, PPB influenced CL$_{tot}$ and $V_{d_{ss}}$ because only free drug is available for elimination and distribution. The use unbound counterparts of CL$_{tot}$ and $V_{d_{ss}}$ removed the confounding impact of plasma protein binding and hence lead to significant relationships with higher $r^2$ values.

Generally, increased lipophilicity favors partitioning into the liver. When the drugs undergoing extra-hepatic clearance were excluded, as log (D)$_{7.4}$ increased, CL$_{nonren}$ and CL$_{nonren}^u$ increased, which in turn, lead to increase in ER$_{hep}$. This was consistent with the results obtained for a set of 12 β-blockers in human wherein it was found that there was a
significant increase in \( CL_{\text{nonren}} \) with increase in \( \log (D)_{7.4} \).\textsuperscript{19} In-addition, \( CL_{\text{tot}} \) is the combination of \( CL_{\text{ren}} \) and \( CL_{\text{nonren}} \). There were two opposing effects; \( CL_{\text{ren}} \) decreasing with \( \log (D)_{7.4} \) and \( CL_{\text{nonren}} \) increasing with \( \log (D)_{7.4} \), which may offset each other. \( CL_{\text{nonren}} \) is governed by \( f_u \) and/or \( CL_{\text{int}} \). \( CL_{\text{int}} \) increased significantly with \( \log (D)_{7.4} \), and \( f_u \) decreased with \( \log (D)_{7.4} \); however, there was a significant relationship between \( CL_{\text{nonren}} \) and \( \log (D)_{7.4} \) and \( CL_{\text{nonren}} \) and \( \log (D)_{7.4} \) indicating dominance of \( CL_{\text{int}} \) over \( CL_{\text{nonren}} \) for most opioids. Irrespective of the dataset, the slopes remained similar indicating that the effect of \( \log (D)_{7.4} \) on the PK parameters was similar; however, exclusion of drugs undergoing extra-hepatic metabolism lead to improvement in \( r^2 \), \( q^2 \) and decrease in p-value indicating robustness of the analysis towards exclusion of outliers (Table 4.11).

Although \( \log (D)_{7.4} \) can be effectively used in describing and predicting ADME properties, it is often seen that the transit of the drug in the body involves movement of drug across multiple biological membranes which are composed of phospholipids bi-layers as well as interaction with transporters, enzymes or receptors in order to elicit pharmacological action involving hydrophilic interactions is a result of an interplay amongst different molecular descriptors.\textsuperscript{15, 26, 73} Thus, in addition to \( \log (D)_{7.4} \), other molecular descriptors like HBA, HBD, PSA, dipole moment, MV, and nRot were used to build a QSPKR model for opioids. Log–linear regression between the molecular descriptors and PK properties showed that as the PSA, HBA and HBD increased; there was a significant decrease in \( CL_{\text{nonren}} \), \( CL_{\text{nonren}} \) and \( CL_{\text{ren}} \) and \( CL_{\text{int}} \); however, the regression was leveraged by the extreme values for polar morphine glucuronides and, hence, these results were extremely sensitive to the inclusion of M3G and M6G. Overall, for this study, \( \log (D)_{7.4} \) was found to be the most important molecular descriptor in the prediction of systemic PK variables of opioids,
reflecting its role in the transfer across biological membranes during distribution and elimination. None of the molecular descriptors showed any significant relation with RRA at µ-receptor, the most plausible reason being that affinity at the µ-receptor depends on how an opioid molecule orients itself in the space at the receptor with the corresponding amino acid residues of the binding pocket rather than its physicochemical properties. Overall, as indicated by the $q^2$ values, the QSPKR models developed provide useful predictions of relevant systemic PK properties of opioids in humans.
5. \(\beta\)-adrenergic receptor ligands (\(\beta\)-ARLs)

5.1. Background

In both their chemical structures and biologically activities, \(\beta\)-ARLs constitute an extremely varied group of drugs who clinically utility includes treating life threatening conditions such as acute anxiety, angina pectoris, asthma, cardiac arrhythmias and hypertension. Most of these varied drugs exert their therapeutic effects through interaction with adrenoceptors, G-protein coupled receptors, \(\beta_1\), \(\beta_2\) and \(\beta_3\) receptors, which bind neurotransmitters such as norepinephrine and epinephrine (Figure 5.1).\textsuperscript{74-76} Figure 5.2 and 5.3 depict common structural backbone and structure activity relation (SAR) for \(\beta\)-agonist and \(\beta\)-antagonist, respectively.\textsuperscript{63}
Figure 5.1. β-Adrenergic Receptors and their Pharmacological actions.

Figure 5.2. Common Structural Backbone and Important Functional Groups of β-agonist
Figure 5.3. Common Structural Backbone and Important Functional Groups of β-Antagonist
5.2. Results

5.2.1. Comparison of Molecular Descriptors and PK of β-ARLs in humans

The Table 5.1 shows a dataset of a 48 β-adrenergic agonist/antagonist (43 antagonists/partial antagonists and five agonists) with considerable diverse physicochemical and 2D molecular properties. β-ARLs are small molecules with molecular weights ranging from 225-510 Dalton. Depending on the selectivity at the α and β-receptors, the compounds can be classified into β₁-agonist/antagonist, β₂-agonist/antagonist and mixed α, β- blocker. Most of the β-ARLs have 2 pKₐ s, pKₐ₁ due to a basic group (-NH₂ group) and pKₐ₂ due to a weakly acidic group (-OH group) and act as zwitterions in certain range of pH. There are large differences (>1-billion-fold) in the lipophilicity as shown by log (D)₇.₄. The majority of the β-ARLs are ionized at pH 7.4 with dacetyl metipranolol (100%) showing the highest % ionized and flestolol showing the lowest (82%). Descriptive statistics (Table 5.2) showed that for all the molecular descriptors (except nRot), the mean value is greater than the median value and the distribution is skewed towards the right. High standard deviations indicate a considerable variation in molecular descriptors across the opioids. The predefined acceptance criterion for colinearity was \( r \geq 0.80 \). Molar volume and molecular weight showed strong correlation (\( r = 0.8915 \)) and thus, molar volume and not molecular weight, was selected for subsequent analysis.

The final mean PK variables obtained from different studies are shown in Table 5.3 and the biologically relevant PK variables are shown in Table 5.4. Descriptive statistics (Table 5.5) showed that for most PK variables (except \( f_\text{u} \) and \( \gamma \)), the mean value is greater than the median value. For most of the opioids, distribution was found to be skewed. High standard
deviations show that PK variables show considerable variation across the opioids. Thus, for subsequent analyses, the PK variables (except \( f_u \) and \( \gamma \)) were log transformed. Some of the PK variables were strongly correlated with each other (Table 5.6). Based on the criteria in Table 3.1, opioids were classified into different PK categories as shown in Table 5.7. In this dataset, they vary in their PPB from 1 % to 98 %. Sotalol shows the highest \( f_u \) (99%), and nebivolol shows the lowest \( f_u \) (1.9%). Propranolol has the highest \( \gamma \) indicating that the \( f_u \) is low due to high PPB. On the other hand, Sotalol has a low \( \gamma \) due to low PPB. There is considerable diversity in the PK properties amongst the \( \beta \)-ARLs. The \( V_{ds} \) varies (by more than 50-fold) across the \( \beta \)-ARLs. \( V_{ds}^u \) values are greater than BW, indicating high tissue sequestration. High PPB lowers \( V_{ds} \) values. Relatively polar compounds such as \( \beta \)-adrenergic agonists and some antagonists like xamoterol show low \( V_{ds} \), while more lipophilic ones like bopindolol, nebivolol, dilevolol, etc. show high \( V_{ds} \). \( CL_{tot}^u \) varies across the \( \beta \)-ARLs (more than 150-fold). High PPB lowers \( CL_{tot} \) values. For the majority of \( \beta \)-ARLs, clearance is due to non-rerenal elimination i.e. hepatic and extra-hepatic metabolism. Compounds like xamoterol, atenolol, sotalol, albuterol, terbutaline are low clearance drugs (\( CL_{nonren} \) less than 30% of the LBF) while several have \( CL_{nonren} \) approaching or exceeding LBF indicating that they are high clearance drugs. Some of the \( \beta \)-adrenergic antagonists have \( CL_{tot} \) values exceeding CO, indicating blood or tissue metabolism (e.g. esmolol, flestolol). \( CL_{nonren} \) indicates both high- and low- \( ER_{hep} \) drug; latter due to the low \( CL_{int} \) and/or high PPB, e.g., xamoterol, terbutaline–low \( ER_{hep} \) due to low intrinsic clearance. Out of 48 \( \beta \)-ARLs, on which data were available to determine the \( f_c \), 19 were found to be highly metabolized (\( f_c < 20\% \)). Hydrophilic \( \beta \)-blockers like sotalol and \( \beta \)-agonists like albuterol show high \( f_c \) values while lipophilic drugs like bevantolol show \( f_c < 20\% \). Talinolol, though a
lipophilic drug, has a $f_e$ value of 50%, since it is a known P-glycoprotein (P-gp) substrate\textsuperscript{77} and undergoes P-gp mediated renal tubular secretion. Lipophilic β-ARLs, such as labetalol, deacetyl metipranolol, propranolol, bufuralol tertatolol, betaxolol, penbutolol have $CL_{\text{ren}}$\textsuperscript{u} values less than GFR, indicating that they undergo net reabsorption. Sotalol has $CL_{\text{ren}}$\textsuperscript{u} value equal to GFR indicating it is excreted by net glomerular filtration. Rest all β-ARLs have $CL_{\text{ren}}$\textsuperscript{u} values greater than GFR indicating net tubular secretion. $CL_{\text{nonren}}$\textsuperscript{blood} values for β-ARLs like epanolol, landiolol, dilevolol, fenoterol nafetalol is higher than the LBF. Landiolol\textsuperscript{78, 79}, esmolol\textsuperscript{80} and flestolol\textsuperscript{81} are esters and undergo hydrolysis by non-specific esterases in blood and tissue. For the remaining compounds, the exact mechanism is not known but based on high $CL_{\text{nonren}}$\textsuperscript{blood} values, it can be concluded that these drugs undergo extra-hepatic clearance. Epanolol is an amide and may undergo hydrolysis by non-specific amidases in blood and tissues and shows $CL_{\text{tot}}$ exceeding LBF. Landiolol, dilevalol and labetalol showed $CL_{\text{nonren}}$ exceeding LBF, thus, it was concluded that, they undergo extra-hepatic metabolism. In-addition, fenoterol, a β-agonist, shows $CL_{\text{tot}}$ exceeding LBF and it is suspected of undergoing extra-hepatic metabolism by catechol o-methyl transferases (COMT) in blood and tissues.

On the PD side, β-ARLs also show large differences (100,000 fold) in the affinities at $\beta_1$, $\beta_2$ and $\beta_3$-receptors.\textsuperscript{82}
Table 5.1. Molecular Properties of β-ARLs (ordered by log (D)_{pH 7.4})

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<th>MW</th>
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<th>pK_{A2}</th>
<th>log (D) at pH 7.4</th>
<th>% Ionized at pH 7.4</th>
<th>nRot</th>
<th>HBA</th>
<th>HBD</th>
<th>MV [cm$^3$/mol]</th>
<th>PSA [Å$^2$]</th>
<th>Energy [Kcal/mol]</th>
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Table 5.2. Molecular Descriptor Correlations and Distributions for β-ARLs

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Correlation matrix

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Table 5.6. Correlation Matrix for PK Variables of β-ARLs

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<th>CL_{ren} (ml/min/kg)</th>
<th>CL_{nonren} (ml/min/kg)</th>
<th>CL_{tot} (ml/min/kg)</th>
<th>CL_{ren} (ml/min/kg)</th>
<th>CL_{nonren} (ml/min/kg)</th>
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<td>-0.4558</td>
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5.2.2. QSPKR Analysis, Model Building and Evaluation

Similar to data analysis for opioids, the QSPKR analysis was done on two datasets, complete and reduced (after exclusion of drugs known/suspected of undergoing extra-hepatic metabolism). The results of univariate regression between PK variables and molecular descriptors for the complete dataset and reduced dataset are shown in Table 5.8 and Table 5.9, respectively. The relationships which showed $r^2 \geq 0.30$ and $p < 0.05$ were further used to build final multivariate model by using log-linear and MLLR. The final models from the QSPKR analysis are summarized in Table 5.10. *In-vitro* PK variables like $\gamma$ and $f_u$ are strongly dependent on log $(D)_{7.4}$ with log log $(D)_{7.4}$ accounting for more than 60 % variability. Biologically relevant PK variables like $V_{dss}$, $CL_{tot}$ and $CL_{nonren}$ (Figure 5.9, 5.11-5.12) did show a significant increase with log $(D)_{7.4}$, with log $(D)_{7.4}$ accounting for more than 30 % variability. As a result of these offsetting effects, $V_{dss}$ and $CL_{tot}$ were not affected by log $(D)_{7.4}$ (Figures.5.5-5.6). $CL_{ren}$ significantly decreased and $CL_{nonren}$ increased with log $(D)_{7.4}$, however, the relationships did not meet the pre-specified criteria of $r^2 \geq 0.30$ to build final log-linear model. Secondary to $f_u$, $CL_{ren}$ decreased with log $(D)$ (Figure 5.7). Log $(D)$ accounted for 50 % variability in the ER$_{hep}^1$, although the regression was governed by extreme cases; polar $\beta$-ARLs like sotalol and atenolol with very low ER$_{hep}$ and highly lipophilic carvedilol with very high ER$_{hep}$.

Univariate analysis showed a significant effect of HBA, HBD and PSA on $CL_{ren}$ and $f_u$ ($r^2 = 0.10-0.20$, $p < 0.05$) and HBD on $CL_{nonren}$ ($r^2 = 0.28$, $p < 0.05$). Log $(D)_{7.4}$, ranging from -2.9 to 3.1, was the sole most important molecular property, affecting most of the biologically...
relevant PK variables of β-ARLs. The slopes for all PK variables vs. log (D)\(^7.4\), remained similar across the complete and reduced dataset indicating that the effect of molecular descriptors on these variables was similar; however, exclusion of the drugs undergoing extra-hepatic clearance lead to improvement in \(r^2\), \(q^2\) and decrease in p-value and prediction errors (Table 5.9, Figures 5.13-5.21). Overall, the final QSPKR models developed provided acceptable predictions (\(q^2 \geq 0.40\)) for \(f_{hu}\), \(Vd_{ssu}\), \(CL_{nonren\:u}\) and \(CL_{ren}\) (Table 5.10). For \(CL_{nonren\:u}\), the predictive ability improved after exclusion of drugs undergoing extra-hepatic, nonrenal elimination, indicating the importance of nonrenal clearance mechanisms (hepatic vs. extra-hepatic) on QSPKR clearance predictions.
Table 5.8. Log-linear Regression between Molecular Descriptors and PK variables for Complete Dataset of β-ARLs

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<th>Molecular descriptor</th>
<th>$f_a$</th>
<th>$\gamma$</th>
<th>Log ($V_{dss}$) (L/kg)</th>
<th>Log (CL$_{tot}$) (ml/min/kg)</th>
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<th>Log (CL$_{nonren}$) (ml/min/kg)</th>
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<th>Log (CL$_{tot}$) (ml/min/kg)</th>
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<tr>
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<td>Slope = -0.00003 (N.S.)</td>
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<td>Slope = 0.0007 (N.S.)</td>
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<td>Slope = 0.002 (N.S.)</td>
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<td>Slope = 0.22 (p &lt; 0.05)</td>
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<td>n = 34 $r^2 = 0.0003$</td>
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<td>$\gamma$</td>
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<td>Log $(\text{CL}_{tot})$ (ml/min/kg)</td>
<td>Log $(\text{CL}_{ren})$ (ml/min/kg)</td>
<td>Log $(\text{CL}_{nonren})$ (ml/min/kg)</td>
<td>Log $(\text{CL}_{tot}^u)$ (ml/min/kg)</td>
<td>Log $(\text{CL}_{ren}^u)$ (ml/min/kg)</td>
<td>Log $(\text{CL}_{nonren}^u)$ (ml/min/kg)</td>
<td>Log $(\text{Vd}_{oa}^u)$ (L/kg)</td>
</tr>
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<td>Dipole moment</td>
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<td>r$^2$ = 0.003</td>
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Slope = 0.03 (p < 0.05)
Slope = 0.002 (p < 0.05)
Slope = 0.005 (p < 0.05)
Slope = 0.004 (N.S.)
Slope = -0.002 (N.S.)
Slope = 0.0003 (N.S.)
Slope = -0.0005 (N.S.)
Slope = 0.000001 (N.S.)
Slope = -0.000001 (N.S.)
Univariate Effect of log(D) on β-ARLs - Complete dataset (Note: β-ARLs are numbered as per Table 5.1)

Figure 5.4. $f_u$ vs. log (D)$_{7.4}$ (β-ARLs)  
Figure 5.5. Vd$_{ss}$ vs. log (D)$_{7.4}$ (β-ARLs)  
Figure 5.6. CL$_{tot}$ vs. log (D)$_{7.4}$ (β-ARLs)
Figure 5.7. $\text{CL}_\text{ren}$ vs. log (D)$_{7.4}$ ($\beta$-ARLs)

Figure 5.8. $\text{CL}_\text{nonren}$ vs. log (D)$_{7.4}$ ($\beta$-ARLs)
Figure 5.9. $\text{CL}_{\text{tot}}$ vs. $\log (D)_{7.4}$ ($\beta$-ARLs)

Figure 5.10. $\text{CL}_{\text{ren}}$ vs. $\log (D)_{7.4}$ ($\beta$-ARLs)

Figure 5.11. $\text{CL}_{\text{nonren}}$ vs. $\log (D)_{7.4}$ ($\beta$-ARLs)

Figure 5.12. $\text{Vd}_{ss}$ vs. $\log (D)_{7.4}$ ($\beta$-ARLs)
Table 5.9. Log-linear Regression between Molecular Descriptors and PK Variables for Reduced Dataset of β-ARLs

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<tr>
<th>Molecular descriptor</th>
<th>$f_u$</th>
<th>$\gamma$</th>
<th>log (Vd&lt;sub&gt;u&lt;/sub&gt;) (L/kg)</th>
<th>log (CL&lt;sub&gt;tot&lt;/sub&gt;) (ml/min/kg)</th>
<th>log (CL&lt;sub&gt;ren&lt;/sub&gt;) (ml/min/kg)</th>
<th>log (CL&lt;sub&gt;nonren&lt;/sub&gt;) (ml/min/kg)</th>
<th>log (CL&lt;sub&gt;tot u&lt;/sub&gt;) (ml/min/kg)</th>
<th>log (CL&lt;sub&gt;ren u&lt;/sub&gt;) (ml/min/kg)</th>
<th>log (CL&lt;sub&gt;nonren u&lt;/sub&gt;) (ml/min/kg)</th>
<th>log (Vd&lt;sub&gt;u&lt;/sub&gt;) (L/kg)</th>
<th>log (CL&lt;sub&gt;tot u&lt;/sub&gt;) (ml/min/kg)</th>
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<td>Slope = 0.003</td>
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<td>(N.S.)</td>
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<td>(p &lt; 0.05)</td>
<td>(N.S.)</td>
<td>(p &lt; 0.05)</td>
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<td>(p &lt; 0.05)</td>
<td>(N.S.)</td>
<td>(p &lt; 0.05)</td>
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<td>(N.S.)</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
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<td>(\gamma)</td>
<td>(\log (V_{dss})) (L/kg)</td>
<td>(\log (CL_{tot})) (ml/min/kg)</td>
<td>(\log (CL_{ren})) (ml/min/kg)</td>
<td>(\log (CL_{nonren})) (ml/min/kg)</td>
<td>(\log (CL_{tot}^u)) (ml/min/kg)</td>
<td>(\log (CL_{ren}^u)) (ml/min/kg)</td>
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<tr>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.003) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{r}^2 = 0.006) (N.S.)</td>
<td>(\text{Slope } = -0.002) (N.S.)</td>
<td>(\text{Slope } = -0.002) (N.S.)</td>
</tr>
</tbody>
</table>
Univariate Effect of log(D) on β-ARLs - Reduced dataset

Figure 5.13. $f_u$ vs. log (D) $\gamma_{7.4}$ (β-ARLs)

Figure 5.14. Vdss vs. log (D) $\gamma_{7.4}$ (β-ARLs)

Figure 5.15. CLtot vs. log (D) $\gamma_{7.4}$ (β-ARLs)
Figure 5.16. CL_{ren} vs. log (D) at pH 7.4 (β-ARLs)

Figure 5.17. CL_{nonren} vs. log (D) at pH 7.4 (β-ARLs)
**Figure 5.18.** $\text{CL}_\text{tot}^\beta$ vs. $\log (D)$ at pH 7.4 ($\beta$-ARLs)

**Figure 5.19.** $\text{CL}_\text{ren}^\beta$ vs. $\log (D)$ at pH 7.4 ($\beta$-ARLs)

**Figure 5.20.** $\text{CL}_\text{nonren}^\beta$ vs. $\log (D)$ at pH 7.4 ($\beta$-ARLs)

**Figure 5.21.** $V_{\text{dss}}^\beta$ vs. $\log (D)$ at pH 7.4 ($\beta$-ARLs)
Table 5.10. QSPKR models for β-ARLs

<table>
<thead>
<tr>
<th>PK variable</th>
<th>Dataset</th>
<th>n</th>
<th>Property</th>
<th>Slope</th>
<th>( r^2 )</th>
<th>( q^2 )</th>
<th>% MPE</th>
<th>% RMSE</th>
<th>Slope</th>
<th>( r^2 )</th>
<th>( q^2 )</th>
<th>% MPE</th>
<th>% RMSE</th>
<th>No. of compounds in the 0.5-2.0 error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_u )</td>
<td>Complete</td>
<td>34</td>
<td>log(D)</td>
<td>-0.23</td>
<td>0.63</td>
<td>0.59</td>
<td>54</td>
<td>299</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>79 %</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>30</td>
<td>log(D)</td>
<td>-0.22</td>
<td>0.64</td>
<td>0.60</td>
<td>51</td>
<td>317</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>83 %</td>
</tr>
<tr>
<td>( \log(V_{du}) )</td>
<td>Complete</td>
<td>34</td>
<td>log(D)</td>
<td>0.45</td>
<td>0.75</td>
<td>0.70</td>
<td>15</td>
<td>143</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>71 %</td>
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<td></td>
<td>Reduced</td>
<td>30</td>
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<td>0.77</td>
<td>0.89</td>
<td>-5</td>
<td>57</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60 %</td>
</tr>
<tr>
<td>( \log(\text{CL}_{\text{tot}}) )</td>
<td>Complete</td>
<td>34</td>
<td>log(D)</td>
<td>0.41</td>
<td>0.54</td>
<td>0.49</td>
<td>15</td>
<td>46</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>29 %</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>30</td>
<td>log(D)</td>
<td>0.42</td>
<td>0.66</td>
<td>0.61</td>
<td>12</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47 %</td>
</tr>
<tr>
<td>( \log(\text{CL}_{\text{nonren}}) )</td>
<td>Complete</td>
<td>29</td>
<td>log(D)</td>
<td>0.51</td>
<td>0.43</td>
<td>0.35</td>
<td>27</td>
<td>120</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>34 %</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>26</td>
<td>log(D)</td>
<td>0.52</td>
<td>0.51</td>
<td>0.43</td>
<td>14</td>
<td>101</td>
<td>0.34</td>
<td>0.63</td>
<td>0.54</td>
<td>-14</td>
<td>126</td>
<td>46 %</td>
</tr>
</tbody>
</table>

HBD
5.2.3. Discussion

β-ARLs are structurally similar and have similar molecular weights; however, there are considerable differences in their PK-PD properties. The Vdss varies (more than 2000-fold) across the β-ARLs. Vdss values were found to be greater than BW, indicating high tissue sequestration; on the other hand, this was counteracted by high PPB that lead to lower Vdss values. For the majority of β-ARLs, clearance is due to non-renal elimination, i.e., hepatic and extra-hepatic metabolism.

To account for the differences in the PK-PD properties of β-ARLs, the effect of the physicochemical properties on the PK-PD properties was studied. Log (D)7.4 was found to be the primary determinant of biologically relevant PK properties like CLtot, CLnonren and Vdss for β-ARLs. As the log (D)7.4 increased, there was a significant decrease in fu since the drugs bind to the plasma proteins by hydrophobic interactions. This finding is consistent with protein binding of various barbiturates in the rats,67 penicillins in humans68 and anti-arrhythmic drugs in humans.19, 69 Obach et al16 using a set of 554 drugs suggested that increasing log (D)7.4 increased PPB because of hydrophobic forces interaction with albumin and α-acid glycoprotein. In addition to PPB, a significant relation was found between γ and log (D)7.4. Similar results were found for γ of barbiturate series in rats.67 PPB decreased Vdss for highly plasma protein bound drugs. After correction for PPB, it was observed that Vdss significantly increased with log (D)7.4. This showed that these two opposing forces acting on Vdss: offset each other. A similar relationship was seen for Vdss for a series of sulfonamides in rats (n = 6, slope = 0.20, r2 = 0.69)71 and β-blockers in human (n = 13, slope = 0.33, r2 = 0.71).19 van de Waterbeemd et al20 studied the effect of log (D)7.4 on ten β-
adrenergic antagonists and found that $V_{dss}^u$ increased with log $(D)_{7.4}$ indicating that compound’s ability to interact with the lipid core of the membrane as well as the ability of the basic nitrogen to interact with the ionized groups. Obach et al\textsuperscript{16} studied PK in humans for a diverse data set of 670 drugs (159 acids, 267 bases, 173 neutrals and 68 zwitterions) and found that there was $V_{dss}^u$ increased with lipophilicity for bases, neutrals and zwitterions and it was found that bases had greater $CL_{tot}$ values than acids, neutrals or zwitterions. As the log $(D)_{7.4}$ increased, there was a significant decrease in $CL_{ren}$. Similar trend was also observed between $CL_{ren}$ and log $(D)_{7.4}$ for a set of 391 compounds and $\beta$-blockers in humans.\textsuperscript{19, 72} However, when $CL_{ren}$ was corrected for PPB, the relation between $CL_{ren}^u$ and log $(D)_{7.4}$ was insignificant. For a set of ten $\beta$-adrenergic antagonists, van de Waterbeemd et al\textsuperscript{20} showed $CL_{ren}^u$ was approximately constant with log $(D)_{7.4}$. This may suggest that as the PPB increased, less amount of drug was available for glomerular filtration. In this dataset, there are many $\beta$-ARLs which have $CL_{ren}^u$ values exceeding GFR which indicating that they may undergo net tubular secretion. This showed that the effect of log $(D)_{7.4}$ was stronger on the drugs which are highly plasma protein bound and undergo filtration. The amount excreted in the urine declines with log $(D)_{7.4}$ due to increased importance of metabolic clearance, making the estimates for $f_U$ less accurate. Hinderling et al\textsuperscript{19} studied the effect of lipophilicity on PK of 14 $\beta$-blockers and found that there was a significant relation between \textit{in-vitro} parameters like $f_u$ and $\gamma$ and log $(D)$ and a significant effect of log $(D)$ on $V_{dss}^u$, $CL_{ren}$ and $CL_{nonren}$. Yamada et al\textsuperscript{31} predicted therapeutic doses for 18 $\beta$-blockers based on QSPKRA and it was found that there was a significant relation between PK parameters like $f_u$, $CL_{tot}/F$, $V_{dss}^u/F$, and log$(D)$. When the drugs undergoing extra-hepatic metabolism were excluded, as lipophilicity increased, $CL_{nonren}$ and $CL_{nonren}^u$ increased, which in turn, lead to increase in $ER_{hep}$, indicating
that increase in log (D)$_{7,4}$ favors partitioning into the liver. This was consistent with the results obtained for a set of 12 β-blockers in human wherein it was found that there was a significant increase in CL$_{nonren}$ with increase in lipophilicity.\textsuperscript{19} In-addition, CL$_{tot}$ is the combination of CL$_{ren}$ and CL$_{nonren}$. There were two opposing effects; CL$_{ren}$ decreasing with log (D)$_{7,4}$ and CL$_{nonren}$ increasing with log (D)$_{7,4}$, which offset each other. CL$_{nonren}$ is governed by f$_u$ and/or CL$_{int}$. CL$_{int}$ increased significantly with log (D)$_{7,4}$, and f$_u$ decreased with log (D)$_{7,4}$; however, there was a significant effect of log (D)$_{7,4}$ on CL$_{nonren}$ and CL$_{nonren}^u$ indicating dominance of CL$_{int}$ over CL$_{nonren}$ for β-ARLs. Van de Waterbeemd\textsuperscript{20} showed that there was a strong positive correlation between distribution coefficient of ten β-blockers and their unbound hepatic intrinsic clearance.

Irrespective of the dataset, the slopes remained similar indicating that the effect of log (D)$_{7,4}$ on the PK parameters was similar; however, exclusion of drugs undergoing extra-hepatic metabolism lead to improvement in $r^2$, $q^2$ and decrease in p-value indicating robustness of the analysis towards exclusion of outliers (Table 5.10). None of the molecular descriptors showed any significant relation with log (K$_i$) at β$_1$, β$_2$ and β$_3$-receptor, the most plausible reason being that affinity at the β-receptor depends on how the drug orients itself in the space at the receptor rather than its physicochemical properties.

Overall, for this study, log (D)$_{7,4}$ was found to be the most important descriptor in the prediction of systemic PK variables of β-ARLs, reflecting its role in the transfer across biological membranes during distribution and elimination. In the past, there have been in-vitro diffusion studies with six β-blockers which indicated that human skin permeation could be explained by parabolic relation to the partition coefficients\textsuperscript{83}. It was also shown by
Kawazu et al\textsuperscript{84} that there was a sigmoidal relation between permeability coefficient and lipophilicity for eight \-blockers across rabbit corneal epithelial cells.

Overall, in this research, as indicated by the $q^2$ and \% MPE and \% RMSE values, the QSPKR models developed provide useful predictions of relevant systemic PK properties of \-ARLs in humans.

5.2.4. Comparison of QSPKR Study of Opioids and \-ARLs

Both opioids and \-ARLs are basic drugs, targeting GPCR. Both datasets showed a wide range of physicochemical as well as PK properties: The opioid dataset was more biased towards more lipophilic compounds, and most of them were cleared by nonrenal elimination, \textit{i.e.}, hepatic and extrahepatic clearance. Out of 38 opioids, only two opioids, M3G and M6G, showed $f_e > 50\%$, while all others were mainly non-renally cleared ($f_e < 50\%$); 14 opioids showed $\text{CL}_{\text{tot}}$ or $\text{CL}_{\text{nonren}}^{\text{blood}}$ values exceeding LBF or even cardiac output, indicating extrahepatic/nonrenal clearance, \textit{e.g.}, ester hydrolysis in blood and other body tissues, while some had high $F_{\text{oral}}$ values although they had high apparent $E_{\text{R}_{\text{hep}}}$, indicating that they undergo extrahepatic clearance as well. Most of the opioids (except M3G and M6G) were intermediate-to- high $E_{\text{R}_{\text{hep}}}$ drugs. Glucuronidation and phase I metabolism were the main metabolic pathways. Amongst them, UGT2B7 and CYP2D6, CYP3A, CYP2C9, CY2C19 play the major role in opioid metabolism. In addition, membrane transporters like P-gp are known to determine the transport of some opioids like morphine, alfentanil, fentanyl, loperamide and sufentanil across membranes (GI, kidney, CNS, liver).\textsuperscript{85}

Compared to the opioids, the \-ARL dataset was a combination of more hydrophilic as well as lipophilic compounds: Out of 48 \-ARL, 14 compounds showed $f_e > 50\%$ while all
others were mainly metabolized (f_e < 50%), and seven compounds showed CL_tot or CL_{nonren}^{blood} value exceeding LBF or CO, indicating extrahepatic/nonrenal clearance. Thus, for most β-ARL, similar to opioids, CL_tot was primarily due to nonrenal elimination, i.e., hepatic and extrahepatic clearance. Glucuronidation and phase I metabolism (CYP2D6, CYP3A4) were the main metabolic pathways. Membrane transporters like P-gp, OCTs and MRP2 are known to be involved in the transport of some β-ARL. For both the datasets, PPB was highly variable, V_dss^u values indicated high tissue sequestration for most compounds; however, this was counteracted by high PPB, leading to lower V_dss values.

Table 5.11 shows a comparison of univariate effects of log (D)\_7.4 on the PK variables for opioids and β-ARLs: For both classes, PPB increased strongly with log (D)\_7.4, as did V_dss^u, CL_{tot}^u, and CL_{nonren}^u. As net result, the observed/reported CL_{tot}, V_dss and CL_{nonren} were not affected by log (D)\_7.4. Secondary to f_u, CL_{ren} decreased as log (D)\_7.4 increased. β-ARLs had a widerange of log (D)\_7.4 values since β-ARL dataset had a combination of hydrophilic and lipophilic compounds as opposed to opioid dataset, which was biased towards relatively lipophilic compounds. As a result, the slopes obtained in the univariate log–linear regression between log (D)\_7.4 and PK variables of β-ARLs were steeper than those obtained for opioids. For opioids, the final QSPKR models developed provided acceptable predictions for f_u, V_dss^u, CL_{nonren}^u and CL_{ren}. For β-ARL, QSPKR models showed acceptable predictive performance for f_u, V_dss^u, CL_{nonren}^u and CL_{tot}^u. CL_{nonren}^u and CL_{tot}^u, for both classes, using the reduced dataset showed improved r^2 and q^2, indicating the importance of extrahepatic clearance on QSPKR predictions. The results obtained in this study were consistent with published studies, however, the dataset in the present study was much larger, included more recent
(mainly lipophilic) β-ARL, antagonists and agonists, and the QSPKR analysis studied the effect of various molecular descriptors other than log (D)7.4 more systematically.

Overall, for both pharmacological classes of drugs:

- Lipophilicity, log (D)7.4, was found to be the biologically plausible and, statistically, the most significant molecular property affecting the biologically relevant, systemic PK variables, \( f_u, V_{ss}^u, \text{CL}_{\text{nonren}}^u \).

- QSPKR models using log (D)7.4 showed good predictive performance (\( r^2 > 0.40 \)) during cross-validation for \( f_u, V_{ss}^u \) and \( \text{CL}_{\text{nonren}}^u \).

- Poor predictive ability (\( r^2 < 0.40 \)) was obtained for \( \text{CL}_{\text{tot}}^u \) for opioids indicating that lipophilicity, a bulk property, is only one of many properties influencing nonrenal drug elimination (primarily hepatic metabolism and possibly biliary excretion).

- Presence of extra-hepatic clearance (e.g., hydrolysis in blood/tissues) worsened the predictive ability of log (D)7.4 on \( \text{CL}_{\text{nonren}}^u \) and \( \text{CL}_{\text{tot}}^u \), but not \( f_u \), as expected. This is consistent with the idea that extrahepatic clearance (e.g., ester hydrolysis) does not depend on log (D)7.4.

- For opioids, MV and log (D)7.4 combined showed a significant effect on \( f_u \). Secondary to \( f_u \), \( \text{CL}_{\text{ren}} \) decreased with MV and log (D)7.4. In addition, H-bonding (HBD and HBA) and PSA showed a significant effect on \( \text{CL}_{\text{nonren}}, V_{ss}^u, \text{CL}_{\text{nonren}}^u \) \( (r^2=0.30-0.70, n=18-28) \), however, the regression was leveraged by the extreme values for M3G and M6G and hence, these results were extremely sensitive to the inclusion of M3G and M6G.
• For the both the classes, none of the molecular descriptors had any effect on the affinity at the receptors.

Table 5.11. Univariate effects of log ($\text{D}_{\text{rel}}$): Opioids vs. $\beta$-ARLs

<table>
<thead>
<tr>
<th>PK variable</th>
<th>Dataset</th>
<th>n</th>
<th>Slope</th>
<th>$r^2$</th>
<th>$q^2$</th>
<th>n</th>
<th>Slope</th>
<th>$r^2$</th>
<th>$q^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_u$</td>
<td>Complete</td>
<td>29</td>
<td>-0.13</td>
<td>0.42</td>
<td>0.27</td>
<td>34</td>
<td>-0.23</td>
<td>0.63</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>20</td>
<td>-0.13</td>
<td>0.49</td>
<td>0.29</td>
<td>30</td>
<td>-0.22</td>
<td>0.64</td>
<td>0.60</td>
</tr>
<tr>
<td>log(Vd_{ss})</td>
<td>Complete</td>
<td>28</td>
<td>0.30</td>
<td>0.49</td>
<td>0.47</td>
<td>34</td>
<td>0.45</td>
<td>0.75</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>19</td>
<td>0.30</td>
<td>0.51</td>
<td>0.47</td>
<td>30</td>
<td>0.45</td>
<td>0.77</td>
<td>0.89</td>
</tr>
<tr>
<td>log (Cl_{tot})</td>
<td>Complete</td>
<td>29</td>
<td>0.21</td>
<td>0.31</td>
<td>0.37</td>
<td>34</td>
<td>0.41</td>
<td>0.54</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>20</td>
<td>0.20</td>
<td>0.35</td>
<td>0.39</td>
<td>30</td>
<td>0.42</td>
<td>0.66</td>
<td>0.61</td>
</tr>
<tr>
<td>log(Cl_{nonren})</td>
<td>Complete</td>
<td>18</td>
<td>0.34</td>
<td>0.73</td>
<td>0.66</td>
<td>29</td>
<td>0.51</td>
<td>0.43</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>10</td>
<td>0.34</td>
<td>0.88</td>
<td>0.75</td>
<td>26</td>
<td>0.52</td>
<td>0.51</td>
<td>0.43</td>
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</tbody>
</table>
CHAPTER 6. QSPKR OF β-LAs

6. β-lactam antibiotics

6.1. Background

β-lactam antibiotics (β-LAs), unlike opioids and β-ARLs, are acidic molecules, more polar in nature and are primarily eliminated by renal excretion in humans and is a widely used family of therapeutic agents. β-LAs are suggested to be not only filtered but also actively secreted by the proximal tubules.88. β-LAs are structural analogs and thus, it was thought that QSPKR study may provide insight in understanding the relation between structural properties and disposition of β-LAs. Depending on the structure/mechanism of action, the dataset was classified into cephalosporins (1st generation, 2nd generation, 3rd generation, 4th generation and 5th generation), carbapenems, beta lactamase inhibitors and penicillins, where compounds within each class are more closely related structural analogs. β-LA structures evolved over time of half a century in the quest of achieving better broad spectrum antibacterial activity, improved acid stability, improved β-lactamase resistance or specificity. Unlike opioids and β-ARLs, most of the β-LAs act by inhibiting the crosslinking step in the cell wall formation by bacteria. Below is a brief account on the structure-activity relationship (SAR) of β-LAs from early penicillins to broader spectrum penicillins to cephalosporins to β-lactamase inhibitors.89
Figure 6.1. Common Structural Backbone and Important Functional Groups of β-LA

Acid sensitivity of penicillins is due to:

- Bicyclic system adds ring strain which is relieved by acid catalysed reaction.
- Highly reactive lactam ring carbonyl group.
- Acyl side chain can cause opening up of lactam ring.

**Acid resistant penicillins**: Addition of electron withdrawing group (ewg) on side chain draws electrons away from carbonyl grp and reduces its tendency to act as a nucleophile. (eg. ampicillin, amoxicillin)
Figure 6.2. Example of a Penicillin, Ampicillin ('ewg' denotes the electron withdrawing group)

Figure 6.3. Example of a Penicillin, Amoxicillin
Figure 6.4. Common Structural Backbone of Cephalosporin

* Marked positions can be modified

Figure 6.5. Common Structural Backbone of First-Generation Cephalosporin

Figure 6.6. Example of First-Generation Cephalosporin, Cephalothin
Second generation cephalosporins

Introduction of methyl group at position 7 e.g. Cefoxitin (Figure 6.7) or introduction of iminomethoxy group at the alpha position of the acyl side chain e.g. Cefuroxime (Figure 6.8), gives rise to less susceptible to beta lactamases

![Figure 6.7 Common Structural Backbone of Second-Generation Cephalosporins](image)

![Figure 6.8. Example of Second-Generation Cephalosporin, Cefuroxime](image)

Third generation cephalosporins

Replacing the furan ring with aminothiazole ring lead to increases penetration through outer membrane of gram negative bacteria and also increases affinity to transpeptidase enzyme (Figure 6.9)
Fourth generation cephalosporins

Some are zwitterionic, positively charged substituent at the 3-position and a negatively charged group at the 4-position leads to increased penetration in the outer membrane of gram negative bacteria and good affinity to transpeptidase enzyme, e.g cefpirome (Figure 6.10)
Carbapenems

Inhibits transpeptidases produced by gram negative bacteria, e.g. aztreonam

Monobactams

Opposite stereochemistry to penicillins – lactamase resistant

Side chain – plays role in beta lactamase resistance

Double bond leading to high ring strain and increase in lactam reactivity

Figure 6.11. Common Structural Backbone of Carbapenems

Figure 6.12. Common Structural Backbone of a Monobactam, Aztreonam
**Beta lactamase inhibitors –suicide inhibitors**

Mechanism based inhibitors – fit in active site of beta lactamase and binds irreversibly. It has a strained beta lactam ring, enol ether, the double bond has Z configuration, no side chain and R-stereochemistry at 2 and 5 position, e.g. clavulanic acid (Figure 6.13) and sulbactam (Figure 6.14)

![Figure 6.13. Structure of Beta Lactamase Inhibitor, Clavulanic acid](image1)

![Figure 6.14. Structure of Sulbactam](image2)

Turner et al 73 predicted PK properties for 20 cephalosporins using ANN model and found molar volume and energy the major determinants of renal clearance and PPB, respectively. Karalis et al 90 developed multiple linear and nonlinear models using molecular descriptors to predict PK properties for 23 cephalosporins and found that non-linear models were superior to linear models. Thus, in literature, so far, QSPKR models have been developed only for cephalosporins. This research carried out a more comprehensive study using all the available β-
lactam antibiotics including β-lactamase inhibitors and secondary analyses even reviewed sub-categories of β-LAs.
6.2. Results

6.2.1. Comparison of molecular descriptors and PK of \( \beta \)-lactam antibiotic (\( \beta \)-LAs) in humans

The Table 6.1 and 6.2 show a dataset of 60 \( \beta \)-LAs with considerable diverse physicochemical and two dimensional molecular properties (1-12 fold range). \( \beta \)-LA are molecules, having a wide range of molecular weight from 199-672. Depending on the structure and mechanism of actions, the dataset can be classified into cephalosporins (1\textsuperscript{st} generation, 2\textsuperscript{nd} generation, 3\textsuperscript{rd} generation, 4\textsuperscript{th} generation and 5\textsuperscript{th} generation), carbapenems, beta lactamase inhibitors and penicillins. Most of the \( \beta \)-LAs are negatively charged while some act as zwitterions in physiological range of pH. Most of \( \beta \)-LAs are polar and show a relatively small range (-0.2 to -7.3) of log (D)\textsubscript{7.4} (except temocillin with log (D)\textsubscript{7.4} of 2.47). The majority of the \( \beta \)-LAs are completely ionized at plasma pH 7.4 and urinary pH 6.3. \( \beta \)-LAs which are zwitterions at pH 7.4 and 6.3 are neutral/partly neutral and hence show higher percentage of non-ionized form. \( \beta \)-LAs show higher number of nRot (mean = 6.9) and HBAs (mean = 10.6). Descriptive statistics (Table 6.3) show that some molecular descriptors like MW, PSA and energy have mean values greater than the median and the distribution is skewed towards the right. High standard deviations indicate diversity in molecular descriptors across the \( \beta \)-LAs, however, the diversity is less than opioids and \( \beta \)-ARLs. HBA, nRot, molar volume are highly correlated with MW (r \geq 0.80). PSA and HBA were also found to be collinear (r \geq 0.80).

The final mean PK variables obtained from different studies are shown in Table 6.4 and the biologically relevant PK parameters are shown in Table 6.5. Descriptive statistics (Table
6.6) showed that for most PK variables (except $f_u$), the mean value is greater than the median value. Though the variation in PK variables across the β-LAs was less than opioids and β-ARLs, for most of the variables, distribution were found to be skewed. Thus, for subsequent analyses, the PK variables (except $f_u$) were log transformed. Some of the PK variables such as $\text{CL}_{\text{nonren}}$, $\text{CL}_{\text{ren}}$ were strongly correlated with $\text{CL}_{\text{tot}}$ (Table 6.7). Most of the β-LAs are mainly excreted by kidneys ($f_e > 50\%$). Cefpiramide showed $f_e$ value of 20%, indicating that it is highly metabolized and/biliary excreted. PPB varies from 4 % to 97 %. Imipenem shows the highest $f_u$ (96 %), while cefpiramide shows the lowest $f_u$ (3 %). There is diversity in the PK properties amongst the β-LAs. The $V_{d_{ss}}$ varies (30- fold) across the β-LAs. $V_{d_{ss}}$ values for majority of β-LAs is less than BW, indicating that they are not widely distributed into body tissues. $\text{CL}_{\text{tot}}$ varies across the β-LAs (more than 66-fold). High PPB lowers $\text{CL}_{\text{tot}}$ values. For the majority of β-LAs, clearance is due to renal excretion. All the β-LAs are low hepatic clearance drugs ($\text{CL}_{\text{nonren}}$ ranging from 0.1- 4.8 ml/min/kg, less than 30% of the LBF). The $\text{CL}_{\text{tot}}$ and $V_{d_{ss}}$ values varied more than the total PK parameters, but not as much as for opioids and β-ARLs. All β-LAs show $\text{CL}_{\text{ren}}$ exceeding GFR, indicating net tubular secretion (except ertapenem and ceftriaxone, which show $\text{CL}_{\text{ren}} < \text{GFR}$, indicating that they undergo net tubular reabsorption).
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N: 60  Mean: 447  Minimum: 199  Maximum: 672  Fold-range: 3.4

A – Anion, Z – Zwitterion
Table 6.2. Molecular Properties of β-LAs (Ordered by Sub-class)

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| Mean            | 6.9  | 10.6| 3.6 | 258.6                  | 36.1                   | 67.6               | 277.8  |
| Maximum         | 12   | 17  | 6   | 364                    | 106                    | 154                | 447    |
| Minimum         | 1    | 6   | 1   | 120                    | 10                     | 36                 | 118    |
| fold-range      | 12   | 3   | 6   | 3                      | 11                     | 4                  | 4      |
Table 6.3. Molecular Descriptor Distributions and Correlations for β-LAs (Ordered by Sub-class)

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Correlation matrix

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Table 6.4. *In-vitro* and *In-vivo* PK Variables of β-LAs (Ordered by Sub-class)

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<th>Drug</th>
<th>$f_a$ (%)</th>
<th>$V_d_{ss}$ (l/kg)</th>
<th>$CL_{tot}$ (ml/min/kg)</th>
<th>$f_e$ (%)</th>
<th>$CL_{ren}$ (ml/min/kg)</th>
<th>$CL_{nonren}$ (ml/min/kg)</th>
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<td>( f_e ) (%)</td>
<td>( \text{CL}_{\text{ren}} ) (ml/min/kg)</td>
<td>( \text{CL}_{\text{nonren}} ) (ml/min/kg)</td>
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*In-vitro* PK variable

*In-vivo* PK variable
Table 6.5. Biologically Relevant *In-vivo* PK variables of β-LAs (Ordered by Sub-class)

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<th>$V_{dss}$&lt;sub&gt;u&lt;/sub&gt; (l/kg)</th>
<th>$CL_{tot}$&lt;sub&gt;u&lt;/sub&gt; (ml/min/kg)</th>
<th>$CL_{ren}$&lt;sub&gt;u&lt;/sub&gt; (ml/min/kg)</th>
<th>$CL_{nonren}$&lt;sub&gt;u&lt;/sub&gt; (ml/min/kg)</th>
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<td>$\text{CL}_{\text{nonren}}$ (ml/min/kg)</td>
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Table 6.6. Descriptive Statistics for PK variables and Correlations of β-LAs

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Correlation matrix

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6.2.2. QSPKR Analysis, Model Building and Evaluation for β-LAs

The results of univariate regression between PK variables and molecular descriptors are shown in Table 6.7. None of the relationships showed $r^2 \geq 0.30$ and $p < 0.05$, and none of the relationships met the criteria of $r^2 \geq 0.30$ to build final log-linear/multiple log-linear model. Nevertheless, in-vitro PK variable like $f_u$ and in-vivo variables like $\text{CL}_{\text{ren}}$, $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}^{\text{u}}$ were found to have a significant relationship with MW, with MW accounting for 26%, 23% and 19% variability, respectively. $\text{CL}_{\text{ren}}$ and $\text{CL}_{\text{nonren}}$ significantly decreased with MW while $\text{Vd}_{\text{ss}}^{\text{u}}$ increased with MW. There was no significant relationship between any of the PK variables and $\log(D)_{7.4}$. Molecular descriptors like nRot, HBA, MV and PSA showed significant relationship with $\text{CL}_{\text{ren}}$ and $f_u$, though they accounted for only 10-20% variability on an average.

Depending on the structure/mechanism of action, the dataset was classified into cephalosporins (1st generation, 2nd generation, 3rd generation, 4th generation and 5th generation), carbapenems, beta lactamase inhibitors and penicillins; compounds within each class are structural analogs. Hence, the effect of molecular descriptors on PK variables was studied by class (Table 6.8-6.13). Univariate analysis showed that molecular descriptors like MW, nRot, molar volume, HBA, HBD and PSA accounted for a higher variability ($r^2 = 30-90\%$, $p < 0.05$) in the PK variables when the entire β-LA dataset was analyzed by class (Table 6.8-6.13).
Effect of molecular descriptors on PK parameters by class:

Overall, as the MW increased, \( f_u \) decreased (Table 6.8). The relationship between \( f_u \) and MW for carbapenems and penicillins was not significant; however, the slopes were negative and smaller in magnitude than for cephalosporins. As the MW increased, \( V_{dss}^u \) increased for cephalosporins, however, for carbapenems, as MW increased, \( V_{dss}^u \) decreased. For penicillins, the relation between MW and \( V_{dss}^u \) showed a positive trend as cephalosporins, however, it was not significant. As nRot increased, \( f_u \) decreased for cephalosporins and penicillins, however, carbapenems showed a positive relationship between nRot and \( f_u \) (Table 6.9). As nRot increased, \( V_{dss}^u \) increased, except for carbapenems, which showed a negative slope. For \( V_{dss}^u \) and HBA, there was a positive trend observed for the cephalosporins and a negative trend for penicillins, beta lactamase inhibitors and carbapenems (Table 6.10). For \( V_{dss}^u \) and PSA, there was a positive trend observed for the cephalosporins and a negative trend for penicillins, beta lactamase inhibitors and carbapenems (Table 6.11). Overall, since the number of cephalosporins was more than all the other classes put together, the relationships for the complete dataset were dominated by cephalosporins (Table 6.7).

The effect of molecular descriptors on PK parameters was also studied by charge at pH 7.4 and pH 6.3, however, no specific trend was observed.
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<th>log (CL$_{ren,u}$) (ml/min/kg)</th>
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**Table 6.8. Log-linear Regression Between MW and PK Variables by Class of β-LAs**
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Table 6.9. Log-linear Regression Between nRot and PK Variables by Class of β-LAs

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Table 6.10. Log-linear Regression Between MV and PK Variables by Class of β-LAs

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Table 6.11. Log-linear Regression Between HBA and PK Variables by Class of β-LAs

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$n = 14$, $r^2 = 0.0008$, $r^2 = 0.03$, $r^2 = 0.01$, $r^2 = 0.04$, $r^2 = 0.0007$, $r^2 = 0.002$, $r^2 = 0.0003$, $r^2 = 0.01$, $r^2 = 0.005$, $r^2 = -0.01$.
Table 6.12. Log-linear Regression Between HBD and PK Variables by Class of β-LAs

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<th>log (Clren) (ml/min/kg)</th>
<th>log (Clnonren) (ml/min/kg)</th>
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Table 6.13. Log-linear Regression Between PSA and PK Variables by Class of β-LAs

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<td>r(^2) = 0.28</td>
<td>r(^2) = 0.02</td>
<td>r(^2) = 0.000006</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Range</td>
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</tr>
<tr>
<td></td>
<td>Median</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Beta lactamase</td>
<td>Inhibitors</td>
<td>n = 3</td>
<td>r(^2) = 0.99</td>
<td>r(^2) = 0.12</td>
<td>r(^2) = 0.31</td>
<td>r(^2) = 0.67</td>
<td>r(^2) = 0.99</td>
<td>r(^2) = 0.99</td>
<td>r(^2) = 0.38</td>
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<tr>
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<td></td>
<td>Range</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td>n = 5</td>
<td>r(^2) = 0.09</td>
<td>r(^2) = 0.07</td>
<td>r(^2) = 0.04</td>
<td>r(^2) = 0.21</td>
<td>r(^2) = 0.15</td>
<td>r(^2) = 0.09</td>
<td>r(^2) = 0.07</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Range</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>168.6</td>
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<td></td>
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</tr>
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<td></td>
<td>233.7</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>167.4-289.3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( r^2 \) indicates the coefficient of determination, \( f_u \) is the fraction of variance explained by the regression, and \( \log (\text{parameter}) \) refers to the logarithm of the parameter. Values in parentheses indicate statistical significance levels: (N.S.) for non-significant, (p < 0.05) for significant at the 0.05 level, and (p < 0.01) for significant at the 0.01 level.
<table>
<thead>
<tr>
<th>Median</th>
<th>256.3</th>
<th>(N.S.)</th>
<th>(N.S.)</th>
<th>(N.S.)</th>
<th>(N.S.)</th>
<th>(N.S.)</th>
<th>(N.S.)</th>
<th>(N.S.)</th>
<th>(N.S.)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>n = 14</td>
<td>n = 14</td>
<td>n = 14</td>
<td>n = 13</td>
<td>n = 13</td>
<td>n = 13</td>
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<td>n = 13</td>
</tr>
<tr>
<td>r² = 0.03</td>
<td>r² = 0.08</td>
<td>r² = 0.03</td>
<td>r² = 0.06</td>
<td>r² = 0.04</td>
<td>r² = 0.004</td>
<td>r² = 0.05</td>
<td>r² = 0.05</td>
<td>r² = 0.04</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>212.6</td>
<td>Slope =</td>
<td>-0.0005</td>
<td>Slope =</td>
<td>Slope =</td>
<td>Slope =</td>
<td>Slope =</td>
<td>Slope =</td>
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</tr>
<tr>
<td>117.6-279</td>
<td>-0.002</td>
<td>-0.001</td>
<td>-0.002</td>
<td>-0.001</td>
<td>-0.0003</td>
<td>-0.001</td>
<td>-0.0008</td>
<td>-0.002</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>209.7</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
<td>(N.S.)</td>
</tr>
</tbody>
</table>
6.3. Discussion

β-LAs are structurally similar, hydrophilic molecules with molecular weights ranging from 300-600 Dalton (except clavulanic acid, which, has a molecular weight of 199). All the β-LAs are low clearance drugs with PPB ranging from 4% to 97%. Overall, there was an upward trend between MW and PPB. Similar results were obtained from an analysis of 2939 diverse molecules with *in-vitro* PPB data in GSK database; as MW increased, PPB increased.  

Most of the β-LAs show $V_{dss}^u$ values less than 1.0 L/kg, indicating that they little tissue distribution. It was seen that as MW increased, $V_{dss}^u$ increased. This was consistent with the results obtained for rat PK data on a large dataset of compounds in the GSK database where in distribution increased with increase in MW. Literature studies which showed that clogP generally lead to an increase in $V_{dss}$ for acids and neutrals, however, the effect was not seen for acids and zwitterions. There was a positive relation obtained between $V_{dss}^u$ and MV which was consistent with the results obtained for a set of 20 cephalosporins. Majority of the β-LAs are completely ionized at plasma pH 7.4 and urinary pH 6.3. They also show higher number of nRot (mean = 6.9), HBAs (mean = 10.6) and higher PSA. For the majority of β-LAs, clearance is due to renal excretion, with $f_e > 50\%$ for most of the β-LAs. This observation is consistent with the results obtained for a dataset of 391 compounds, which showed that higher renal clearances were associated with a high PSA, high nRot and high hydrogen bond count.

All the β-LAs have $CL_{ren}^u$ greater than GFR indicating net tubular secretion (except ertapenem and ceftriaxone, which show $CL_{ren}^u < GFR$, indicating that they might undergo net
reabsorption). Literature studies show that cephalosporins and penicillins show net secretion, and it is has been reported that some cephalosporins interact with hOAT1, hOAT2 and hOAT3. Jariyawat et al showed inhibition of p-aminohippurate transport via rat-OAT1 by penicillins and cephalosporins. It is generally seen that hydrophobicity and acidity are associated with OAT interaction, however, often it is found that high affinity substrates are hydrophilic and high hydrogen bonding ability adds to the stability of the substrate – transporter complex. Varma et al showed that hydrophilic and ionized compounds with hydrogen bonding capacity are secreted because of their ability to interact with renal transporters in the proximal tubule and inability to undergo reabsorption. β-LAs are hydrophilic compounds with a core β-lactam ring and anionic group which can interact with the renal OATs and hence get secreted.

Univariate analysis showed that molecular descriptors like MW, nRot, MV, HBA, HBD and PSA accounted for a higher variability (r^2 = 30-90%, p < 0.05) in the PK parameters when the entire β-LA dataset was analyzed by class (cephalosporins, carbapenems, beta lactamase inhibitors and penicillins), the most plausible reason being that within each class, the drugs are structural analogs and hence, relations with higher r^2 values were obtained. Carbapenems were the outliers, which always showed an opposite trend to cephalosporins, however, this cannot be mechanistically explained. None of the relationships showed r^2 ≥ 0.30 and p < 0.05 and the relationships did not meet the criteria of r^2 ≥ 0.30 to build final log linear/multiple log linear model. The effect of molecular descriptors on Vdss and f_u was physiologically interpretable. However, in general, PK parameters were more difficult to predict as compared to the PK of the opioids and β-ARLs, most probably due to
involvement of specific renal transporters, whose contribution cannot be accounted for by bulk physicochemical properties.
CHAPTER 7. INTERSPECIES SCALING

7. Part II: Interspecies PK Scaling

7.1. Specific Aims

- Review the literature to collect pertinent, valid systemic PK properties of opioids, β-ARLs and β-LAs in different species and estimate relevant PK variables.
- Compare PK properties of all the three classes across species and assess for differences across species.
- Evaluate if interspecies differences can be explained by different allometric methods.
- Evaluate different prediction methods to predict human PK properties from animal PK.

7.2. Methods

7.2.1. Data collection – Animal PK studies

A comprehensive primary literature review was carried out. For the purposes of this study, data were collected without restrictions on gender or strain of dogs or rats. Data were only selected from those studies where the compounds were administered by the IV route to healthy individuals. Many articles studied hepatic or renal dysfunction population and in such cases, data from control population
were used. Other sources of IV PK data were absolute oral bioavailability studies. PK variables like CL$_{\text{tot}}$, Vd$_{\text{ss}}$, f$_{u}$ were derived from plasma exposure across all species, while variables like f$_{c}$ and CL$_{\text{ren}}$ were obtained from urinary excretion studies, if available. Of all the PK variables reported in the studies, the way of reporting varied the most for the volume of distribution. Most of the studies reported the terminal phase volume of distribution (Vd$_{\beta}$), central compartment volume of distribution (Vd$_{cc}$) or steady state volume (Vd$_{\text{ss}}$). The papers which reported Vd$_{\text{ss}}$ were selected. In some studies, micro-rate constants from compartmental analysis were reported but Vd$_{\text{ss}}$ was not calculated. In such cases, the reported Vd$_{cc}$ and micro-constants (k$_{12}$, k$_{21}$) were used to calculate Vd$_{\text{ss}}$ using the following equation:

\[
Vd_{\text{ss}} = Vd_{cc}\left(1 + \frac{k_{12}}{k_{21}}\right)
\]

This equation assumed two compartment model and k$_{12}$ is the rate of distribution from compartment 1 to compartment 2 and k$_{21}$ is the rate of redistribution from compartment 2 to compartment 1.

In some cases, where macro-rate constants (\(\alpha, \beta\)) and intercepts A and B from the biexponential equation describing the plasma concentration (Cp)-time (t) profile (Cpt = Ae$^{-\alpha t}$ + Be$^{-\beta t}$), the following equation was used:

\[
Vd_{\text{ss}} = \frac{\text{Dose} \left(\frac{A}{\alpha^2} + \frac{B}{\beta^2}\right)}{\left(\frac{A}{\alpha} + \frac{B}{\beta}\right)}
\]

In a few studies, PK parameters were not calculated, but concentration-time profiles were reported. In such cases, the plots were digitally read, and Vd$_{\text{ss}}$ and CL$_{\text{tot}}$ was calculated using non-compartmental analysis.$^{33}$
If the studies did not report BW corrected PK parameters, then the parameters were corrected for BW using the mean BW of the animals used in the study. In case, the BW was not mentioned, the following BWs were used by default (Table 7.1):

<table>
<thead>
<tr>
<th>Species</th>
<th>Body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>0.25</td>
</tr>
<tr>
<td>Dog</td>
<td>10</td>
</tr>
<tr>
<td>Human</td>
<td>70</td>
</tr>
</tbody>
</table>

The *in-vitro* PK variable $f_u$ was obtained from *in-vitro* PPB studies after careful scrutiny of the method and appropriate concentration range.

Estimation of *in-vivo* PK variables:

Variables such as $V_{dss}^u$, $CL_{tot}^u$, $CL_{ren}$, $CL_{ren}^u$ were estimated using the following formulae:

\[
V_{dss}^u = \frac{V_{dss}}{f_u}
\]

\[
CL_{tot}^u = \frac{CL_{tot}}{f_u}
\]

\[
CL_{ren} = CL_{tot} * f_c
\]

\[
CL_{ren}^u = \frac{CL_{ren}}{f_u}
\]

Some studies used compartmental analysis, whereas others used non-compartmental analysis and the amount of detail describing the conduct of the study varied across the studies. Thus, critical evaluation of study design, dosing regimen, sampling schedule, assay procedures and PK analysis methods was done before including the information with the analysis.
All relevant studies are compiled in Addendum II (A-C). The studies which were ultimately included in the analysis marked in the addendum. Using these methods, a total of 22 opioids, 24 β-ARLs and 27 β-LAs were used. Depending on the amount of information available in the literature, number of compounds used in each method varied.

7.2.2. Descriptive PK across species

Interspecies comparison: For the compounds in all the three datasets, preliminary in-vivo PK variables like CL_{tot}, V_d, CL_{ren}, f_u, dose, AUC, in-vitro variable, i.e., f_u and their respective unbound variables (CL_{tot}^u, V_d^u, CL_{ren}^u) for each compound were compared across different animal species. For each PK variable, the fold range across the species was calculated to assess variation across species. Simple linear regression was done between f_u (human)-f_u (rat) and f_u (human)-f_u (dog); goodness of fit assessed as r^2.

Since most of the opioids and β-ARLs are hepatically cleared, they were classified qualitatively as low clearance, intermediate clearance and high clearance in human, rats and dog. For each species, reported CL_{tot} values were compared to liver blood flow (LBF) in that particular species (Table 7.2). The following criteria were used:

\[
\frac{CL_{tot}}{LBF} < 30\% 
\]

- low hepatic clearance

\[
30\% < \frac{CL_{tot}}{LBF} > 70\% 
\]

- intermediate hepatic clearance

\[
\frac{CL_{tot}}{LBF} > 70\% 
\]

- high hepatic clearance
7.2.3. **Simple Allometry**

It is the study of body size and its physiological consequences. It is developed based on the relationship between organ size, perfusions and body weight, which can be explained by the equation: \( Y = aW^b \),

where \( Y \) is the parameter of interest (e.g. PK parameter like \( \text{CL}_{\text{tot}} \), \( \text{Vd}_{\text{ss}} \), etc.) and \( a \) and \( b \) are the intercept coefficient and exponent of the allometric equation, respectively. It is known that physiological parameters like LBF, kidney blood flow and GFR scale well with body weight (Figure 7.1-7.3).

Simple allometry was used for all available species and only three species (rat and dog), both including human. The following equation was used:\(^3\), \(^7\):

\[
\log \text{(PK variable)} = b \log \text{(BW)} + \log \text{(a)}
\]

Where BW is the body weight (kg), \( a \) and \( b \) represent the intercept and allometric exponent. Goodness of fit was assessed using coefficient of determination (\( r^2 \)). The exponents obtained were compared to scaling factors 0.75 and 1.0 for \( \text{CL}_{\text{tot}} \) and \( \text{Vd}_{\text{ss}} \), respectively.

Allometric plots are compiled in Appendix III (a-c).

### Table 7.2. LBF in different species

<table>
<thead>
<tr>
<th>Species</th>
<th>BW (kg)</th>
<th>Liver blood flow (ml/min)</th>
<th>Liver blood flow (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse (0.02 kg)</td>
<td></td>
<td>1.8</td>
<td>90</td>
</tr>
<tr>
<td>Rat (0.25 kg)</td>
<td></td>
<td>13.8</td>
<td>50</td>
</tr>
<tr>
<td>Rabbit (2.5 kg)</td>
<td></td>
<td>177</td>
<td>71</td>
</tr>
<tr>
<td>Rhesus monkey (5 kg)</td>
<td></td>
<td>218</td>
<td>44</td>
</tr>
<tr>
<td>Dog (10 kg)</td>
<td></td>
<td>309</td>
<td>30</td>
</tr>
<tr>
<td>Sheep (50 kg)</td>
<td></td>
<td>1033</td>
<td>21</td>
</tr>
<tr>
<td>Human (70 kg)</td>
<td></td>
<td>1450</td>
<td>21</td>
</tr>
</tbody>
</table>
Figure 7.1 Interspecies scaling of LBF

Figure 7.2 Interspecies scaling of kidney blood flow
7.3. Prediction Methods

7.3.1. One-species BW Scaling

Using PK data from one animal, the following equations were used to predict human PK:

\[ CL_{tot}^{human} = CL_{tot}^{animal} \times \frac{BW^{human}}{BW^{animal}} \]
\[ Vd_{ss}^{human} = Vd_{ss}^{animal} \times \frac{BW^{human}}{BW^{animal}} \]

\[ CL_{tot}^{u, human} = CL_{tot}^{u, animal} \times \frac{BW^{human}}{BW^{animal}} \]
\[ Vd_{ss}^{u, human} = Vd_{ss}^{u, animal} \times \frac{BW^{human}}{BW^{animal}} \]

7.3.2. Two-species BW Scaling

The two-species approach was used to predict human CL\(_{tot}\), Vd\(_{ss}\), CL\(_{tot}^{u}\), Vd\(_{ss}^{u}\) using PK from two common animal species by AS. Log-log regression was carried out using two species (rat and dog) to estimate the allometric parameters a and b, and the following equation was used to predict human PK variables;
\[ \log (\text{CL}_{\text{tot}} \text{ or } V_{\text{dss}}) = b \log (\text{BW}) + \log (a) \]

7.3.3. **LBF method for opioids and \(\beta\)-adrenergic receptor ligands**

Scaling of \(\text{CL}_{\text{tot}}\) and \(\text{CL}_{\text{tot}}^u\) from each available species to humans was conducted using \(\text{CL}_{\text{tot}}\) values as a percentage of LBF. Assuming that clearance is primarily by hepatic route and that B:P is constant across the species, the human clearance was predicted using the following equation: \(^{13}\)

\[
\text{CL}_{\text{tot}}^{\text{human}} = \frac{\text{CL}_{\text{tot}}^{\text{animal}}}{\text{BW}^{\text{animal}}} \times \left( \frac{\text{LBF}^{\text{human}}}{\text{LBF}^{\text{animal}}} \right)
\]

Scaling of \(\text{CL}_{\text{nonren}}\) and \(\text{CL}_{\text{nonren}}^u\) from each available species to humans was conducted using this method for \(\beta\)-ARLs.

7.3.4. **GFR ratio method for \(\beta\)-lactam antibiotics and \(\beta\)-adrenergic receptor ligands**

The GFR values vary considerably among species from 1.7 ml/min/kg in humans to 10 ml/min/kg in mice. The species differences are mainly attributed to their relative number of glomeruli (or nephrons) per kg body weight. The mouse has the largest relative number of nephrons and the largest GFR. It is believed that GFR reflects the renal function, thus \(\text{CL}_{\text{ren}}\) in humans can be predicted by using the ratio of GFR in animals (rats or dogs) to that in humans.

Scaling of \(\text{CL}_{\text{ren}}\) and \(\text{CL}_{\text{ren}}^u\) from each available species to humans was performed using \(\text{CL}_{\text{ren}}\) values as a percentage of GFR. Assuming that clearance is primarily by renal route, human clearance was predicted using the following equation: \(^{4}\)
The predictive ability of the various allometric methods was assessed using % MPE for bias and % RMSE for imprecision. The following equations were be used:

\[
\text{%MPE} = \sum \left( \frac{(\text{predicted} - \text{observed})}{\text{observed}} \times 100 \right) \\
\text{%RMSE} = \sqrt{\sum \left[ \left( \frac{\text{predicted} - \text{observed}}{\text{observed}} \times 100 \right)^2 \right]}
\]

For visual inspection, log (predicted PK variable) was plotted against log(observed PK variable). Goodness of fit was assessed using \( r^2 \) value. Residual plots were used to evaluate if the residuals are homoscedastic. In addition, predictive performance was assessed using the number of compounds whose human predicted values were within the pre-selected error ranges of 0.5-2.0-fold of the actual human observed values.
CHAPTER 8. INTERSPECIES SCALING OF OPIOIDS

8. Opioids

8.1. Results

8.1.1. Comparative pharmacokinetics of opioids across different species

There were large differences in reported, BW-corrected, CL$_{tot}$ and Vd$_{ss}$ values across species (range: 1 to 40-fold, 1 to 100-fold, respectively) for opioids (Table 8.1). Only unbound drug can diffuse through biological membranes and this may affect the distribution of drugs in the body. Opioids are weak bases and they not only bind to albumin but also to $\alpha_1$-acid glycoprotein. The albumin concentrations in rats and humans are similar\(^4,96\) while $\alpha_1$-acid glycoprotein concentration is higher in rats as compared to human (Table 8.2). Species differences in PPB of opioids were minor (Table 8.3). Figure 8.1 and 8.2 show a significant relationship between human $f_u$ – rat $f_u$ ($r^2 = 0.93$) and human $f_u$ – dog $f_u$ ($r^2 = 0.89$). Slopes just below 1.0 indicate slight overall under-prediction (Table 8.4). Small changes in $f_u$ for highly plasma protein bound drugs may cause large changes in concentrations. Thus, PPB was also compared between humans and rats for only highly plasma protein bound drugs ($f_u \leq 0.20$ in humans) and it was found that a significant relation existed between human $f_u$-rat $f_u$ ($r^2 = 0.56$). For dog, $f_u$ information was available for only three highly plasma protein bound drugs (fentanyl,
alfentanil and sufentanil), of which alfentanil showed differences in $f_u$ between dog and human. This finding was consistent even when human $f_u$ and rat $f_u$ are compared.

Table 8.5 shows hepatic clearance category for each drug in each species. Hepatic clearance in each species was compared with the LBF in that respective species. Morphine glucuronides were found to be low clearance in all the species. All opioids (except morphine glucuronides) were high clearance in rats and high or intermediate in dogs. Most of the opioids, except glucuronides, alfentanil and methadone, were found to be high clearance in human. Methadone, a low clearance drug in humans, was found to be high clearance in rat and dog. Alfentanil was found to be low clearance in human, high clearance in rat and intermediate clearance in dog. All the opioids, except morphine glucuronides, were found to be high clearance in rat. Hepatic categorization method assumes that $CL_{tot}$ represents $CL_{hepatic}$ and the contribution of $CL_{ren}$ is negligible. Although most of the opioids are high clearance drugs, there are some hydrophilic opioids like the morphine glucuronides, which show a significant renal contribution towards the $CL_{tot}$. In such cases, this assumption may have lead to misclassification.
Table 8.1. *In-vivo* and *In-vitro* PK Parameters of Opioids in Different Species

<table>
<thead>
<tr>
<th>Drug</th>
<th>Species</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>$CL_{tot}$ (ml/min)</th>
<th>$CL_{tot u}$ (ml/min)</th>
<th>$Vd_{ss}$ (L/kg)</th>
<th>$Vd_{ss u}$ (%)</th>
<th>$f_u$ (ml/min/kg)</th>
<th>$CL_{ren}$ (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Rats</td>
<td>0.3</td>
<td>0.0</td>
<td>29.5</td>
<td>8.1</td>
<td>4.9</td>
<td>1.4</td>
<td>0.9</td>
<td>34.4</td>
</tr>
<tr>
<td></td>
<td>Dogs</td>
<td>11.0</td>
<td>0.2</td>
<td>41.1</td>
<td>452.1</td>
<td>4.0</td>
<td>44.1</td>
<td>0.9</td>
<td>46.7</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>67.0</td>
<td>0.1</td>
<td>33.6</td>
<td>2251.2</td>
<td>2.1</td>
<td>142.0</td>
<td>0.7</td>
<td>48.0</td>
</tr>
<tr>
<td></td>
<td>Cat</td>
<td>3.7</td>
<td>0.2</td>
<td>24.1</td>
<td>88.0</td>
<td>2.6</td>
<td>9.5</td>
<td>0.9</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td>Sheep</td>
<td>48.0</td>
<td>0.2</td>
<td>32.9</td>
<td>1579.2</td>
<td>0.8</td>
<td>38.9</td>
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</tr>
<tr>
<td></td>
<td>Llamas</td>
<td>144.0</td>
<td>0.2</td>
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<td>21505.0</td>
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<td>158.4</td>
<td></td>
<td></td>
</tr>
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### Table 8.3. PPB of Opioids across Species

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### Table 8.4. Regression Parameters for Human and Animal PPB Relationship

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<td>10</td>
<td>0.92</td>
<td>(± 0.08)</td>
<td>0.89</td>
</tr>
<tr>
<td>Dog f_u</td>
<td></td>
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161
Figure 8.1. Human $f_u$ vs. Rat $f_u$

Figure 8.2. Human $f_u$ vs. Dog $f_u$
<table>
<thead>
<tr>
<th>Drug</th>
<th>CL\textsubscript{tot} (ml/min/kg)</th>
<th>Category</th>
<th>CL\textsubscript{tot} (ml/min/kg)</th>
<th>Category</th>
<th>CL\textsubscript{tot} (ml/min/kg)</th>
<th>Category</th>
</tr>
</thead>
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<tr>
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<td>3.37</td>
<td>Low</td>
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<td>Low</td>
<td>1.8</td>
<td>Low</td>
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<td></td>
<td>21.4</td>
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<td>Morphine</td>
<td>29.5</td>
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<td>1.8</td>
<td>Low</td>
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<tr>
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<td>10.9</td>
<td>Intermediate</td>
<td></td>
<td></td>
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<tr>
<td>Codeine</td>
<td>103.3</td>
<td>High</td>
<td>10.8</td>
<td>Intermediate</td>
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<td></td>
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<td>Tramadol</td>
<td>62.5</td>
<td>High</td>
<td>54.6</td>
<td>High</td>
<td>7.4</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>129.0</td>
<td>High</td>
<td>46.0</td>
<td>High</td>
<td>21.6</td>
<td>High</td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
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<td>214.5</td>
<td>High</td>
<td>198.5</td>
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<td>Remifentanil</td>
<td>390.0</td>
<td>High</td>
<td>47.9</td>
<td>High</td>
<td>50.6</td>
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<td>Butorphanol</td>
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<td>25.1</td>
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<td>4.0</td>
<td>High</td>
<td>19.4</td>
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<td>Alfentanil</td>
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<td>18.7</td>
<td>Intermediate</td>
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<td>Fentanyl</td>
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<td>High</td>
<td>47.9</td>
<td>High</td>
<td>13.9</td>
<td>Intermediate</td>
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<td>Sufentanil</td>
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<td>12.7</td>
<td>Intermediate</td>
<td>18.8</td>
<td>High</td>
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<td>Buprenorphine</td>
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<td>Intermediate</td>
<td>29.6</td>
<td>High</td>
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<td>Dezocine</td>
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<td>65.8</td>
<td>High</td>
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<td>Intermediate</td>
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<td>Dextropropoxyphene</td>
<td>61.4</td>
<td>High</td>
<td>19.9</td>
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<td>16.0</td>
<td>High</td>
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<td>Nalmefene</td>
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<td>16.0</td>
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<tr>
<td>Naloxone</td>
<td>103.0</td>
<td>High</td>
<td>28.4</td>
<td>High</td>
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</table>
8.1.2. Simple Allometry

For a set of 18 opioids, simple allometry was conducted using all available species and using only three species, both including human. Table 8.6 shows the allometric coefficients for $\text{CL}_{\text{tot}}$ and $V_{\text{dss}}$ for 18 opioids. Allometric plots are shown in the Appendix III (a). The exponents obtained were compared with a scaling factor 0.75 for $\text{CL}_{\text{tot}}$ and 1.0 for $V_{\text{dss}}$. Figure 8.3-8.4 shows interspecies scaling plots for a prototypical opioid like morphine. For $\text{CL}_{\text{tot}}$, allometric coefficients for meperidine and remifentanil were found to be very low for $n = 3$ as well as for $n = \text{all available animals}$ (Figure 8.5 and 8.6). Hence, they were excluded from allometric scaling. Butorphanol was suspected to undergo extra-hepatic metabolism and was excluded as well. Methadone showed a very low allometric coefficient with no obvious explanation.

For $V_{\text{dss}}$, allometric coefficients for morphine glucuronides were found to be low ($< 0.8$). For some opioids like alfentanil, low allometric coefficients were obtained for $V_{\text{dss}}$. However, when $V_{\text{dss}}$ was corrected for PPB, the allometric coefficient increased. For opioids like fentanyl, morphine and butorphanol, allometric coefficient increased above 1.0 when $V_{\text{dss}}$ was corrected for PPB.

For the remaining opioids, $\text{CL}_{\text{tot}}$ (mean slope: 0.79, 0.47-1.31) and $V_{\text{dss}}$ (mean slope: 0.90, 0.64-1.14) scaled well with BW, regardless of the number of species. For some opioids, like alfentanil and fentanyl, $f_u$ correction improved allometric scaling and both these drugs are highly plasma protein bound.
<table>
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<tr>
<th>Drug</th>
<th>(ml/min)</th>
<th>n</th>
<th>r²</th>
<th>Slope ± SE (L)</th>
<th>n</th>
<th>r²</th>
<th>Slope ± SE</th>
</tr>
</thead>
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<tr>
<td>Morphine-3-glucuronide</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9970</td>
<td>0.69 ± 0.04</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>0.9259</td>
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<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.9986</td>
<td>0.70 ± 0.02</td>
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<td>4</td>
<td>0.9592</td>
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<td>Morphine-6-glucuronide</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9893</td>
<td>0.73 ± 0.07</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>3</td>
<td>0.9964</td>
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<td>Morphine</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9977</td>
<td>1.03 ± 0.05</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>3</td>
<td>0.9800</td>
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<tr>
<td></td>
<td></td>
<td>8</td>
<td>0.8977</td>
<td>0.99 ± 0.14</td>
<td></td>
<td>7</td>
<td>0.9305</td>
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<tr>
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<td>CL&lt;sub&gt;tot&lt;sup&gt;u&lt;/sup&gt;&lt;/sub&gt;</td>
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<td>0.9997</td>
<td>1.06 ± 0.02</td>
<td>Vd&lt;sub&gt;ss&lt;sup&gt;u&lt;/sup&gt;&lt;/sub&gt;</td>
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<td>0.9879</td>
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<tr>
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<td></td>
<td>7</td>
<td>0.9531</td>
<td>0.91 ± 0.09</td>
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<td>6</td>
<td>0.9612</td>
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<td>Remifentanil</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9432</td>
<td>0.60 ± 0.15</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>4</td>
<td>0.9443</td>
<td>0.61 ± 0.11</td>
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<td>4</td>
<td>0.9426</td>
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<td>Alfentanil</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.8991</td>
<td>0.57 ± 0.19</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>CL&lt;sub&gt;tot&lt;sup&gt;u&lt;/sup&gt;&lt;/sub&gt;</td>
<td>3</td>
<td>0.9996</td>
<td>0.67 ± 0.01</td>
<td>Vd&lt;sub&gt;ss&lt;sup&gt;u&lt;/sup&gt;&lt;/sub&gt;</td>
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<td>0.68 ± 0.07</td>
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<td>0.9565</td>
<td>0.84 ± 0.18</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>3</td>
<td>0.9785</td>
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<tr>
<td></td>
<td></td>
<td>7</td>
<td>0.7761</td>
<td>0.69 ± 0.17</td>
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<td>7</td>
<td>0.9138</td>
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<td>0.9796</td>
<td>1.92 ± 0.28</td>
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<td>3</td>
<td>0.9982</td>
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<td>Hydromorphone</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
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<td>1.01 ± 0.04</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>3</td>
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<td>Meperidine</td>
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<td>0.47 ± 0.23</td>
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<td></td>
<td></td>
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<td>Tramadol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.8879</td>
<td>0.67 ± 0.24</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>0.72 ± 0.01</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>0.69 ± 0.03</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>3</td>
<td>0.9987</td>
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<td>Butorphanol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
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<td>0.99 ± 0.47</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>6</td>
<td>0.8383</td>
<td>0.83 ± 0.18</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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</tr>
<tr>
<td>Buprenorphine</td>
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<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>0.8861</td>
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<td>Pentazocine</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
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<td>0.69 ± 0.40</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>0.84 ± 0.17</td>
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<td>0.8085</td>
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<tr>
<td>Dezocine</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9712</td>
<td>0.71 ± 0.12</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>0.9950</td>
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<td>0.82 ± 0.20</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
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<td>3</td>
<td>0.9817</td>
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</table>

Note: For CL<sub>tot</sub> and CL<sub>tot<sup>u</sup></sub>, 0.6 > allometric exponents > 1.2 are highlighted
For Vd<sub>ss</sub> and Vd<sub>ss<sup>u</sup></sub>, 0.8 > allometric exponents > 1.2 are highlighted
Figure 8.3. Interspecies Allometric Scaling of $\text{CL}_{\text{tot}}$ for Morphine

Figure 8.4. Interspecies Allometric Scaling of $V_{dss}$ for Morphine
Figure 8.5. Interspecies Allometric Scaling of CL_{tot} for Remifentanil

Figure 8.6. Interspecies Allometric Scaling of CL_{tot} for Meperidine
8.1.3. Prediction of PK of opioids

8.1.3.1. One-species BW Scaling

8.1.3.1.1. One-species BW Scaling from rat PK

Table 8.7 shows the observed human PK parameters and predicted human PK parameters from rat PK. Table 8.8-8.9 and Figure 8.7-8.10 show that $\text{CL}_{\text{tot}}$ and $\text{CL}_{\text{tot}}^u$ were predicted more accurately and precisely when drugs undergoing extra-hepatic metabolism were excluded as indicated by their %MPE and %RMSE. In contrast, $\text{Vd}_{\text{ss}}$ and $\text{Vd}_{\text{ss}}^u$ are predicted more accurately and precisely when drugs undergoing extra-hepatic metabolism were not excluded, indicating that extra-hepatic metabolism does not affect distribution and the higher accuracy and precision is obtained due to higher number of drugs. PPB correction for both, $\text{Vd}_{\text{ss}}$ and $\text{CL}_{\text{tot}}$, increased $r^2$ value indicating improvement in the goodness of fit. $\text{CL}_{\text{tot}}^u$ and $\text{Vd}_{\text{ss}}^u$ were predicted accurately and precisely as compared to the $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$ (Table 8.8 and 8.9). In terms of no. of compounds in the 0.5-2 fold error range, only 1 out 15 opioids (7%) showed predicted $\text{CL}_{\text{tot}}$ in 0.5-2 fold error range, while 2 out of 11 opioids (18%) showed predicted $\text{CL}_{\text{tot}}^u$ in 0.5-2 fold error range. Out of 14, 7 opioids (50%) showed predicted $\text{Vd}_{\text{ss}}$ in 0.5-2 fold error range. Out of 10, 5 opioids (50%) showed $\text{Vd}_{\text{ss}}^u$ in 0.5-2 fold error range. Overall, there was over-prediction of total as well as unbound $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$. $f_u$-correction brought more number of compounds in the 0.5-2 fold error range.
Table 8.7. One species scaling from rat PK

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<th></th>
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<td>162</td>
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<td>32</td>
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<td>Oxycodone</td>
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<td>1316</td>
<td>314</td>
<td>5712</td>
<td>196</td>
<td>649%</td>
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<td>859</td>
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<td>933</td>
<td>190</td>
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<td>635%</td>
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<td>Remifentanil</td>
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<td>565%</td>
<td>7%</td>
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<td>Nalbuphine</td>
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<td>447</td>
<td>469%</td>
<td>63%</td>
<td>6%</td>
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<td>183</td>
<td>414</td>
<td>1831</td>
<td>4136</td>
<td>4368</td>
<td>25694</td>
<td>2286%</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>1377</td>
<td>100</td>
<td>3532</td>
<td>257</td>
<td>4977</td>
<td>987</td>
<td>261%</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>183</td>
<td>13</td>
<td>2286</td>
<td>163</td>
<td>2590</td>
<td>53</td>
<td>1316%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>973</td>
<td>159</td>
<td>6081</td>
<td>993</td>
<td>2940</td>
<td>204</td>
<td>202%</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>900</td>
<td>124</td>
<td>12859</td>
<td>1767</td>
<td>5390</td>
<td>387</td>
<td>499%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1272</td>
<td>190</td>
<td>31804</td>
<td>4740</td>
<td>3150</td>
<td>586</td>
<td>148%</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>959</td>
<td>895</td>
<td>3998</td>
<td>3728</td>
<td>4298</td>
<td>732</td>
<td>348%</td>
</tr>
<tr>
<td>Naloxone</td>
<td>1812</td>
<td>153</td>
<td>3355</td>
<td>284</td>
<td>7210</td>
<td>462</td>
<td>298%</td>
</tr>
</tbody>
</table>

% Prediction error:
- CL$_{tot}$ [ml/min]
- $V_d$$_\alpha$ [L]
- CL$_{tot}$ [ml/min]
- $V_d$$_\alpha$ [L]
Table 8.8. One Species Method using Rat PK (complete dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>18</td>
<td>692 (±178%)</td>
<td>1009</td>
<td>4.20 (± 1.25)</td>
<td>0.41</td>
<td>1/18 (6 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;</td>
<td>17</td>
<td>166 (±57%)</td>
<td>281</td>
<td>0.55 (± 0.28)</td>
<td>0.21</td>
<td>8/17 (47 %)</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>535 (±154 %)</td>
<td>676</td>
<td>1.59 (± 0.61)</td>
<td>0.40</td>
<td>2/12 (17 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>106 (±32 %)</td>
<td>176</td>
<td>1.86 (± 0.21)</td>
<td>0.89</td>
<td>6/11 (55 %)</td>
</tr>
</tbody>
</table>

Table 8.9. One Species Method using Rat PK (excluding Remifentanil, heroin, meperidine and butorphanol)

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>15</td>
<td>591 (±146%)</td>
<td>803</td>
<td>1.49 (± 0.93)</td>
<td>0.17</td>
<td>1/15 (7 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;</td>
<td>14</td>
<td>198(± 176%)</td>
<td>206</td>
<td>0.62 (± 0.32)</td>
<td>0.23</td>
<td>7/14 (50 %)</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>464 (±140 %)</td>
<td>584</td>
<td>1.66 (± 0.62)</td>
<td>0.44</td>
<td>2/11 (18 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10</td>
<td>117 (± 37 %)</td>
<td>185</td>
<td>1.88 (± 0.19)</td>
<td>0.92</td>
<td>5/10 (50 %)</td>
</tr>
</tbody>
</table>
Figure 8.7. Predicted Human $\text{CL}_{\text{tot}}$ from Rat PK vs. Observed Human $\text{CL}_{\text{tot}}$

Figure 8.8. Predicted Human $\text{Vd}_{\text{ss}}$ from Dog PK vs. Observed Human $\text{Vd}_{\text{ss}}$
Figure 8.9. Predicted Human $CL_{tot}^{u}$ from Rat PK vs. Observed Human $CL_{tot}^{u}$

Figure 8.10. Predicted Human $Vd_{ss}^{u}$ from DogPK vs. Observed Human $Vd_{ss}^{u}$
8.1.3.1.2. One-species BW Scaling from dog PK

Table 8.10 shows the observed human PK parameters and predicted human PK parameters from dog PK. Table 8.12-8.13 and Figure 8.11-8.14 show that $\text{CL}_{\text{tot}}^\text{u}$ was predicted more accurately and precisely than $\text{CL}_{\text{tot}}$ as indicated by $\%\text{MPE}$ and $\%\text{RMSE}$. For both $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$, PPB correction with exclusion of drugs undergoing extrahepatic metabolism resulted in more number of compounds in the acceptable 0.5-2.0 fold error range.

In terms of no. of compounds in the 0.5-2 fold error range, only 4 out 14 opioids (29 %) showed predicted $\text{CL}_{\text{tot}}$ in 0.5-2 fold error range, while 6 out of 7 opioids (86 %) showed predicted $\text{CL}_{\text{tot}}^\text{u}$ in 0.5-2 fold error range. Out of 12, 6 opioids (50 %) showed predicted $\text{Vd}_{\text{ss}}$ in 0.5-2 fold error range. Out of 7, 5 opioids (71 %) showed $\text{Vd}_{\text{ss}}^\text{u}$ in 0.5-2 fold error range. Overall, there was an over-prediction and it was more pronounced when $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$ were not corrected for PPB.
Table 8.10. One Species Scaling using Dog PK

| Drug      | Observed | | | | Predicted | | | | | % Prediction error |
|-----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|           | Human CL\textsubscript{tot} [ml/min] | Human V\textsubscript{dss} [L] | Human CL\textsubscript{tot} [ml/min] | Human V\textsubscript{dss} [L] | Human CL\textsubscript{tot u} [ml/min] | Human V\textsubscript{dss u} [L] | Human CL\textsubscript{tot} [ml/min] | Human V\textsubscript{dss} [L] | Human CL\textsubscript{tot u} [ml/min] | Human V\textsubscript{dss u} [L] |                |
|           | Human CL\textsubscript{tot} [ml/min] | Human V\textsubscript{dss} [L] | Human CL\textsubscript{tot} [ml/min] | Human V\textsubscript{dss} [L] | Human CL\textsubscript{tot u} [ml/min] | Human V\textsubscript{dss u} [L] | Human CL\textsubscript{tot} [ml/min] | Human V\textsubscript{dss} [L] | Human CL\textsubscript{tot u} [ml/min] | Human V\textsubscript{dss u} [L] |                |
|           | [ml/min] | [L] | [ml/min] | [L] | [ml/min] | [L] | [ml/min] | [L] | [ml/min] | [L] |                |
| M3G       | 162      | 20   | 190      | 24   | 236      | 15   | 241      | 15   | 46%       | -24%     | 26%       | -34%     |
| M6G       | 134      | 9    | 150      | 10   | 2877     | 281  | 3269     | 319  | 28%       | 98%      | 2%        | 57%      |
| Morphine  | 2251     | 142  | 3216     | 203  | 3824     | 211  | 543%     | -11% | 10%       | 876%     | 28%       | 1038%    |
| Tramadol  | 595      | 237  | 744      | 296  | 15015    | 683  | 25025    | 1138 | -18%      | 4%       | 103%      |
| Heroin    | 13697    | 70   | 19567    | 100  | 3353     | 25.2 | -4%      | 98%  | 2%        | 57%      | 26%       | -34%     |
| Remifentanil | 4104   | 24   |          |      | 3220     | 103% |
| Nalbuphine| 1588     | 274  |          |      | 103%     |
| Butorphanol| 2186     | 630  |          |      | 9651     | 1931 | 207%     |
| Meperidine| 594      | 343  | 2199     | 1272 | 2978.5   | 134.4| 402%     | -61% |
| Methadone | 183      | 414  | 1831     | 4136 | 1757     | 242  | 860%     | -41% |
| Pentazocine| 1377     | 100  | 3532     | 257  | 282      | 39   | -80%     | -61% |
| Alfentanil| 183      | 13   | 2286     | 163  | 1309     | 42   | 616%     | 222% |
| Fentanyl  | 973      | 159  | 6081     | 993  | 3353     | 282  | 245%     | 78%  |
| Sufentanil| 900      | 24   | 12859    | 1767 | 282      | 39   | 245%     | 78%  |
| Buprenorphine| 1272   | 90    | 31804    | 4740 | 1176     | 35   | 11%      | 11%  |
| Dezocine  | 2704     | 530  |          |      | 4606     | 588  | 348%     | -18% |
| Dextropropoxyphene| 959   | 895  | 3998     | 3728 | 4298     | 33062| 5632     | 348% |
| Naltrexone| 3500     | 185  | 4375     | 231  | 6913     | 722  | 98%      | 291% |
| Nalmefene | 1248     | 640  |          |      | 4690     | 276% |
| Naloxone  | 1812     | 153  | 3355     | 284  | 4862     | 6946 | 168%     | 170% |

174
### Table 8.12. One Species Method using Dog PK (Complete Dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach</td>
<td>( CL_{\text{tot}} )</td>
<td>17</td>
<td>218 (+ 63 %)</td>
<td>334</td>
<td>0.96 (± 0.16)</td>
<td>0.69</td>
<td>6/17 (35 %)</td>
</tr>
<tr>
<td></td>
<td>( V_{d_{\text{ss}}} )</td>
<td>16</td>
<td>104 (+ 59 %)</td>
<td>251</td>
<td>1.17 (± 0.42)</td>
<td>0.36</td>
<td>7/16 (44 %)</td>
</tr>
<tr>
<td></td>
<td>( CL_{\text{tot}}^u )</td>
<td>8</td>
<td>158 (+ 83 %)</td>
<td>271</td>
<td>1.09 (± 0.64)</td>
<td>0.32</td>
<td>3/8 (38 %)</td>
</tr>
<tr>
<td></td>
<td>( V_{d_{\text{ss}}}^u )</td>
<td>8</td>
<td>196 (+ 126 %)</td>
<td>388</td>
<td>1.42 (± 0.13)</td>
<td>0.95</td>
<td>5/8 (63 %)</td>
</tr>
</tbody>
</table>

### Table 8.13. One Species Method using Dog PK (Excluding Remifentanil, Heroin, Meperidine and Butorphanol)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach</td>
<td>( CL_{\text{tot}} )</td>
<td>14</td>
<td>237 (+ 72 %)</td>
<td>352</td>
<td>1.33 (± 0.42)</td>
<td>0.45</td>
<td>4/14 (29 %)</td>
</tr>
<tr>
<td></td>
<td>( V_{d_{\text{ss}}} )</td>
<td>12</td>
<td>52 (+ 35 %)</td>
<td>126</td>
<td>0.72 (± 0.24)</td>
<td>0.47</td>
<td>6/12 (50 %)</td>
</tr>
<tr>
<td></td>
<td>( CL_{\text{tot}}^u )</td>
<td>7</td>
<td>177 (+ 94 %)</td>
<td>290</td>
<td>3.28 (± 2.28)</td>
<td>0.29</td>
<td>6/7 (86 %)</td>
</tr>
<tr>
<td></td>
<td>( V_{d_{\text{ss}}}^u )</td>
<td>7</td>
<td>76 (+ 45 %)</td>
<td>133</td>
<td>1.47 (± 0.09)</td>
<td>0.98</td>
<td>5/7 (71 %)</td>
</tr>
</tbody>
</table>
Figure 8.11. Predicted Human CL$_{tot}$ from Rat PK vs. Observed Human CL$_{tot}$

Figure 8.12. Predicted Human Vd$_{ss}$ from Dog PK vs. Observed Human Vd$_{ss}$
Predicted human CL\textsubscript{tot} \((u)\) from dog (ml/min)

Figure 8.13 Predicted Human CL\textsubscript{tot} \((u)\) from Rat PK vs. Observed Human CL\textsubscript{tot} \((u)\)

Predicted human Vd\textsubscript{ss} \((u)\) from dog (L)

Figure 8.14. Predicted Human Vd\textsubscript{ss} \((u)\) from Dog PK vs. Observed Human Vd\textsubscript{ss} \((u)\)

- Line of identity
- Line with slope = 0.5
- Line with slope = 2.0
8.1.3.2. Two-species BW Scaling

Table 8.13 and 8.14 shows the observed human PK parameters and predicted human PK parameters from two species, rat and dog, for $CL_{tot}$ and $V_{dss}$. Table 8.15-8.16 and Figure 8.15-8.16 show that $CL_{tot}$ and $V_{dss}$ were predicted more accurately and precisely when drugs undergoing extra-hepatic metabolism were excluded as indicated by their %MPE and %RMSE.

In terms of no. of compounds in the 0.5-2 fold error range, only 5 out 11 opioids (45%) showed predicted $CL_{tot}$ in 0.5-2 fold error range, while 1 out of 9 opioids (11 %) showed predicted $V_{dss}$ in 0.5-2 fold error range. PPB for opioids was found to be fairly constant across opioids with exception of alfentanil (Table 8.3). PPB correction for $CL_{tot}$ and $V_{dss}$ resulted in very high % prediction errors (Table 8.17). Rat and dog $CL_{tot}^u$ and $V_{dss}^u$ differed to a great extent with rat showing lower $CL_{tot}^u$ and $V_{dss}^u$. Highly species dependent tissue binding and extra-hepatic metabolism in tissues may have lead to over-prediction of $V_{dss}^u$ and $CL_{tot}^u$, respectively.
### Table 8.14. Prediction of CL<sub>tot</sub>

<table>
<thead>
<tr>
<th>Drug</th>
<th>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;rat&lt;/sup&gt; (ml/min)</th>
<th>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;dog&lt;/sup&gt; (ml/min)</th>
<th>Intercept</th>
<th>Slope</th>
<th>Predicted CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;human&lt;/sup&gt; (ml/min)</th>
<th>Observed CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;human&lt;/sup&gt; (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>8.1</td>
<td>452.1</td>
<td>1.5</td>
<td>1.08</td>
<td>3398</td>
<td>2251</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>126.8</td>
<td>622.7</td>
<td>2.3</td>
<td>0.43</td>
<td>1288</td>
<td>4104</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>10.2</td>
<td>159.9</td>
<td>1.4</td>
<td>0.81</td>
<td>870</td>
<td>183</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>11.5</td>
<td>426.3</td>
<td>1.6</td>
<td>1.04</td>
<td>3625</td>
<td>973</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>22.8</td>
<td>3171.7</td>
<td>2.1</td>
<td>1.41</td>
<td>46554</td>
<td>2186</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50.6</td>
<td>448.1</td>
<td>2.1</td>
<td>0.55</td>
<td>1273</td>
<td>594</td>
</tr>
<tr>
<td>Methadone</td>
<td>17.2</td>
<td>255.2</td>
<td>1.6</td>
<td>0.75</td>
<td>1081</td>
<td>183</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>13.5</td>
<td>52.8</td>
<td>1.4</td>
<td>0.32</td>
<td>91</td>
<td>1377</td>
</tr>
<tr>
<td>Tramadol</td>
<td>15.7</td>
<td>518.9</td>
<td>1.8</td>
<td>0.96</td>
<td>3551</td>
<td>595</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>18.7</td>
<td>407.9</td>
<td>1.6</td>
<td>0.73</td>
<td>999</td>
<td>959</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>35.5</td>
<td>483</td>
<td>1.9</td>
<td>0.72</td>
<td>1882</td>
<td>1588</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>8.6</td>
<td>371.3</td>
<td>1.5</td>
<td>0.83</td>
<td>1145</td>
<td>1272</td>
</tr>
<tr>
<td>Naloxone</td>
<td>28.3</td>
<td>694.6</td>
<td>1.9</td>
<td>0.89</td>
<td>3928</td>
<td>1812</td>
</tr>
<tr>
<td>M3G</td>
<td>3.7</td>
<td>37.1</td>
<td>0.9</td>
<td>0.64</td>
<td>122</td>
<td>162</td>
</tr>
</tbody>
</table>

### Figure 8.15. Predicted Human CL<sub>tot</sub> from Rat and Dog PK vs. Observed Human CL<sub>tot</sub>

![Graph showing predicted vs. observed CL<sub>tot</sub> for various drugs.](image)

- **Line of identity**
- **Line with slope = 0.5**
- **Line with slope = 2.0**
Table 8.15. Prediction of Vdss

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vdss&lt;sub&gt;rat&lt;/sub&gt; (l)</th>
<th>Vdss&lt;sub&gt;dog&lt;/sub&gt; (l)</th>
<th>Intercept</th>
<th>Slope</th>
<th>Predicted Vdss&lt;sub&gt;human&lt;/sub&gt; (l)</th>
<th>Observed Vdss&lt;sub&gt;human&lt;/sub&gt; (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.4</td>
<td>44.1</td>
<td>0.3</td>
<td>1.29</td>
<td>485.5</td>
<td>142.0</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.2</td>
<td>5.1</td>
<td>-0.2</td>
<td>0.93</td>
<td>36.3</td>
<td>13.0</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.8</td>
<td>35.9</td>
<td>0.5</td>
<td>1.09</td>
<td>342.8</td>
<td>158.9</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>0.1</td>
<td>4.7</td>
<td>-0.4</td>
<td>0.99</td>
<td>24.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Meperidine</td>
<td>2.0</td>
<td>20.2</td>
<td>0.7</td>
<td>0.58</td>
<td>60.9</td>
<td>343.3</td>
</tr>
<tr>
<td>Tramadol</td>
<td>1.0</td>
<td>28.6</td>
<td>0.6</td>
<td>0.91</td>
<td>175.5</td>
<td>237.0</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.6</td>
<td>11.1</td>
<td>0.5</td>
<td>0.41</td>
<td>17.8</td>
<td>189.6</td>
</tr>
<tr>
<td>Naloxone</td>
<td>1.8</td>
<td>59.1</td>
<td>0.8</td>
<td>0.97</td>
<td>389.7</td>
<td>153.1</td>
</tr>
<tr>
<td>M3G</td>
<td>0.5</td>
<td>2.4</td>
<td>-0.07</td>
<td>0.43</td>
<td>5.2</td>
<td>20.0</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>1.2</td>
<td>634.8</td>
<td>0.9</td>
<td>1.72</td>
<td>13119.4</td>
<td>630.0</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>2.7</td>
<td>7.2</td>
<td>0.6</td>
<td>0.23</td>
<td>10.6</td>
<td>100.3</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>3.1</td>
<td>96.4</td>
<td>0.9</td>
<td>0.81</td>
<td>259.5</td>
<td>895.0</td>
</tr>
</tbody>
</table>

Figure 8.16. Predicted Human Vdss from Rat and Dog PK vs. Observed Human Vdss
Table 8.16. Two Species Method using Rat and Dog PK (Complete dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two species approach</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>14</td>
<td>270 (± 145)</td>
<td>590</td>
<td>2.90 (± 3.13)</td>
<td>0.07</td>
<td>5/14 (36 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;d&lt;/sub&gt;ss</td>
<td>12</td>
<td>187 (±167)</td>
<td>584</td>
<td>6.55 (± 3.92)</td>
<td>0.22</td>
<td>2/12 (17 %)</td>
</tr>
</tbody>
</table>

Table 8.17. Two Species Method using Rat and Dog PK (Excluding Remifentanil, Heroin, Meperidine and Butorphanol)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two species approach</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>11</td>
<td>154 (± 65)</td>
<td>257</td>
<td>0.99 (± 61)</td>
<td>0.23</td>
<td>5/11 (45 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;d&lt;/sub&gt;ss</td>
<td>9</td>
<td>38 (± 44)</td>
<td>131</td>
<td>0.17 (± 0.26)</td>
<td>0.06</td>
<td>1/9 (11 %)</td>
</tr>
</tbody>
</table>
Table 8.18. Prediction of $\text{CL}_{\text{tot}}^u$ and $\text{Vdss}^u$ using Two-species Method

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\text{CL}_{\text{tot}}^u$ [ml/min]</th>
<th>$\text{Vdss}^u$ [L]</th>
<th>$\text{CL}_{\text{tot}}^u$ [ml/min]</th>
<th>$\text{Vdss}^u$ [L]</th>
<th>$\text{CL}_{\text{tot}}^u$ [ml/min]</th>
<th>$\text{Vdss}^u$ [L]</th>
<th>Predicted Human $\text{CL}_{\text{tot}}^u$ (ml/min)</th>
<th>Prediction error %</th>
<th>Predicted human $\text{Vdss}^u$ (ml/min)</th>
<th>Prediction error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>M3G</td>
<td>190</td>
<td>24</td>
<td>4.0</td>
<td>0.6</td>
<td>37.8</td>
<td>2.4</td>
<td>61737</td>
<td>32342%</td>
<td>39</td>
<td>65%</td>
</tr>
<tr>
<td>Morphine</td>
<td>3216</td>
<td>203</td>
<td>9.5</td>
<td>0.4</td>
<td>513.8</td>
<td>50.1</td>
<td>3809</td>
<td>18%</td>
<td>546</td>
<td>169%</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>2286</td>
<td>163</td>
<td>62.0</td>
<td>1.3</td>
<td>590.0</td>
<td>18.8</td>
<td>2358</td>
<td>3%</td>
<td>97</td>
<td>-40%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>6081</td>
<td>993</td>
<td>69.6</td>
<td>4.8</td>
<td>1727.8</td>
<td>297.2</td>
<td>2290174038</td>
<td>37659494%</td>
<td>137869065</td>
<td>13882248%</td>
</tr>
<tr>
<td>Naloxone</td>
<td>3355</td>
<td>284</td>
<td>45.7</td>
<td>2.9</td>
<td>992.3</td>
<td>84.4</td>
<td>368736841</td>
<td>10989231%</td>
<td>158991942</td>
<td>56070726%</td>
</tr>
</tbody>
</table>
8.1.3.3. **LBF method**

Table 8.18 and 8.19 show the observed human PK parameters and predicted human PK parameters from rat and dog PK, respectively. Table 8.20-8.21 and Figure 8.17 and 8.18 shows that LBF method using dog PK data predicted CL\(_{tot}\) accurately and precisely. When the drugs undergoing extra-hepatic metabolism were excluded, prediction errors decreased for predictions using rat PK. In terms of no. of compounds predicted in the 0.5-2 fold error range, from rat PK, only 5 out 15 opioids (33%) showed predicted CL\(_{tot}\) in 0.5-2 fold error range, while from dog PK, 7 out of 14 opioids (50%) showed predicted CL\(_{tot}\) in 0.5-2 fold error range.

Table 8.22-8.24 and Figure 8.19-8.20 indicate that when CL\(_{tot}\) was corrected for PPB, lower %MPE and %RMSE were obtained for predictions from both rat and dog PK. PPB correction for CL\(_{tot}\) increased \(r^2\) value indicating improvement in the goodness of fit. In terms of no. of compounds predicted in the 0.5-2 fold error range, from rat PK, only 3 out of 11 opioids (27%) showed predicted CL\(_{tot}\)\(^u\) in 0.5-2 fold error range, while from dog PK, 7 out of 8 opioids (88%) showed predicted CL\(_{tot}\)\(^u\) in 0.5-2 fold error range.
Table 8.19. LBF Method using Rat PK

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human $\text{CL}_{\text{tot}}$ [ml/min/kg]</th>
<th>Observed Rat $\text{CL}_{\text{tot}}$ [ml/min/kg]</th>
<th>Predicted Human $\text{CL}_{\text{tot}}$ [ml/min/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF (ml/min/kg)</td>
<td>21</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>M3G</td>
<td>2.3</td>
<td>12.1</td>
<td>5.1</td>
</tr>
<tr>
<td>M6G</td>
<td>1.8</td>
<td>13.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Morphine</td>
<td>33.6</td>
<td>29.5</td>
<td>12.4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10.9</td>
<td>81.6</td>
<td>34.3</td>
</tr>
<tr>
<td>Codeine</td>
<td>10.8</td>
<td>103.3</td>
<td>43.4</td>
</tr>
<tr>
<td>Tramadol</td>
<td>7.4</td>
<td>62.5</td>
<td>26.3</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>21.6</td>
<td>129.0</td>
<td>54.2</td>
</tr>
<tr>
<td>Remifentanil</td>
<td><strong>50.6</strong></td>
<td><strong>390.0</strong></td>
<td><strong>163.8</strong></td>
</tr>
<tr>
<td>Meperidine</td>
<td>11.5</td>
<td>253.0</td>
<td>106.3</td>
</tr>
<tr>
<td>Butorphanol</td>
<td><strong>28.7</strong></td>
<td><strong>76.0</strong></td>
<td><strong>31.9</strong></td>
</tr>
<tr>
<td>Methadone</td>
<td>2.7</td>
<td>62.4</td>
<td>26.2</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>19.4</td>
<td>71.1</td>
<td>29.9</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>3.1</td>
<td>37.0</td>
<td>15.5</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>13.9</td>
<td>42.0</td>
<td>17.6</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>12.7</td>
<td>77.0</td>
<td>32.3</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>18.8</td>
<td>45.0</td>
<td>18.9</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>13.4</td>
<td>61.4</td>
<td>25.8</td>
</tr>
<tr>
<td>Naloxone</td>
<td>28.4</td>
<td>103.0</td>
<td>43.3</td>
</tr>
</tbody>
</table>

Figure 8.17. Predicted vs. Observed-LBF for $\text{CL}_{\text{tot}}$ (from Rat PK)

![Graph showing predicted vs. observed CLtot (from Rat PK)](image-url)

Line of identity    
Line with slope = 0.5    
Line with slope = 2.0
Table 8.20. LBF Method using Dog PK

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human $\text{CL}_{\text{tot}}$ [ml/min/kg]</th>
<th>Observed Dog $\text{CL}_{\text{tot}}$ [ml/min/kg]</th>
<th>Predicted Human $\text{CL}_{\text{tot}}$ [ml/min/kg]</th>
<th>Prediction error</th>
<th>Prediction error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF (ml/min/kg)</td>
<td>21</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M3G</td>
<td>2.3</td>
<td>3.37</td>
<td>2.4</td>
<td>0.04</td>
<td>1.9%</td>
</tr>
<tr>
<td>Morphine</td>
<td>33.6</td>
<td>41.1</td>
<td>28.8</td>
<td>-4.83</td>
<td>-14.4%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>7.4</td>
<td>54.6</td>
<td>38.2</td>
<td>30.85</td>
<td>417.5%</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>21.6</td>
<td>46.0</td>
<td>32.2</td>
<td>10.60</td>
<td>49.1%</td>
</tr>
<tr>
<td>Heroin</td>
<td>198.5</td>
<td>214.5</td>
<td>150.2</td>
<td>-48.35</td>
<td>-24.4%</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>50.6</td>
<td>47.9</td>
<td>33.5</td>
<td>-17.07</td>
<td>-33.7%</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>28.7</td>
<td>137.9</td>
<td>96.5</td>
<td>67.81</td>
<td>236.3%</td>
</tr>
<tr>
<td>Meperidine</td>
<td>11.5</td>
<td>42.6</td>
<td>29.8</td>
<td>18.32</td>
<td>159.7%</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.7</td>
<td>25.1</td>
<td>17.6</td>
<td>14.87</td>
<td>550.7%</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>19.4</td>
<td>4.0</td>
<td>2.8</td>
<td>-16.58</td>
<td>-85.5%</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>3.1</td>
<td>18.7</td>
<td>13.1</td>
<td>9.99</td>
<td>322.3%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>13.9</td>
<td>47.9</td>
<td>33.5</td>
<td>19.63</td>
<td>141.2%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>18.8</td>
<td>16.8</td>
<td>11.8</td>
<td>-7.04</td>
<td>-37.4%</td>
</tr>
<tr>
<td>Dezocine</td>
<td>29.6</td>
<td>65.8</td>
<td>46.1</td>
<td>16.46</td>
<td>55.6%</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>13.4</td>
<td>19.9</td>
<td>13.9</td>
<td>0.53</td>
<td>4.0%</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>25.0</td>
<td>98.8</td>
<td>69.1</td>
<td>44.13</td>
<td>176.5%</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>16.0</td>
<td>67.0</td>
<td>46.9</td>
<td>30.90</td>
<td>193.1%</td>
</tr>
<tr>
<td>Naloxone</td>
<td>28.4</td>
<td>69.5</td>
<td>48.6</td>
<td>20.22</td>
<td>71.2%</td>
</tr>
</tbody>
</table>

![Figure 8.18. Predicted vs. Observed-LBF for $\text{CL}_{\text{tot}}$ (from Dog PK) with lines](image)

Line with slope = 0.5  
Line of identity  
Line with slope = 2.0
Table 8.21. LBF Method using Rat and Dog PK (Complete dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>CLₜ₀t</td>
<td>18</td>
<td>217 (± 61)</td>
<td>332</td>
<td>1.85 (± 0.59)</td>
<td>0.37</td>
<td>6/18 (33 %)</td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>CLₜ₀t</td>
<td>18</td>
<td>114 (± 41)</td>
<td>203</td>
<td>0.67 (± 0.12)</td>
<td>0.66</td>
<td>9/18 (50 %)</td>
</tr>
</tbody>
</table>

Table 8.22. LBF Method using Rat and Dog PK (Excluding Remifentanil, Heroin, Meperidine and Butorphanol)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>CLₜ₀t</td>
<td>15</td>
<td>190 (± 58)</td>
<td>288</td>
<td>0.54 (± 0.38)</td>
<td>0.14</td>
<td>5/15 (33 %)</td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>CLₜ₀t</td>
<td>14</td>
<td>122 (± 50)</td>
<td>217</td>
<td>0.99 (± 0.47)</td>
<td>0.28</td>
<td>7/14 (50 %)</td>
</tr>
</tbody>
</table>
Table 8.23. LBF Method using Rat PK for CL\textsubscript{tot}^u

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL\textsubscript{tot}^u [ml/min/kg]</th>
<th>Observed Rat CL\textsubscript{tot}^u [ml/min/kg]</th>
<th>Predicted Human CL\textsubscript{tot}^u from rat [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF (ml/min/kg)</td>
<td>21  50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M3G</td>
<td>2.7  13.2</td>
<td>5.5</td>
<td>102.9%</td>
<td></td>
</tr>
<tr>
<td>M6G</td>
<td>2.0  15.6</td>
<td>6.6</td>
<td>224.9%</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>48.0 34.3</td>
<td>14.4</td>
<td>-70.0%</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>18.8 109.8</td>
<td>46.1</td>
<td>145.4%</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>11.7 139.0</td>
<td>58.4</td>
<td>397.4%</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>27.0 367.1</td>
<td>154.2</td>
<td>471.0%</td>
<td></td>
</tr>
<tr>
<td>Alfentanil</td>
<td>38.8 231.3</td>
<td>97.1</td>
<td>150.6%</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>86.9 247.1</td>
<td>103.8</td>
<td>19.4%</td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>180.9 1115.9</td>
<td>468.7</td>
<td>159.2%</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>470.0 642.9</td>
<td>270.0</td>
<td>-42.6%</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>52.6 166.1</td>
<td>69.8</td>
<td>32.7%</td>
<td></td>
</tr>
</tbody>
</table>

Figure 8.19. Predicted vs. Observed-LBF for CL\textsubscript{tot}^u (from Rat PK)

- Line with slope = 0.5
- Line of identity
- Line with slope = 2.0

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Table 8.24. LBF Method using Dog PK for $\text{CL}_{\text{tot}}^u$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human $\text{CL}_{\text{tot}}^u$ [ml/min/kg]</th>
<th>Observed Dog $\text{CL}_{\text{tot}}^u$ [ml/min/kg]</th>
<th>Predicted Human $\text{CL}_{\text{tot}}^u$ from dog [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF (ml/min/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M3G</td>
<td>2.7</td>
<td>3.4</td>
<td>2.4</td>
<td>-11.6%</td>
</tr>
<tr>
<td>Morphine</td>
<td>48.0</td>
<td>46.7</td>
<td>32.7</td>
<td>-31.9%</td>
</tr>
<tr>
<td><strong>Heroin</strong></td>
<td><strong>283.6</strong></td>
<td><strong>357.5</strong></td>
<td><strong>250.3</strong></td>
<td><strong>1.4%</strong></td>
</tr>
<tr>
<td>Alfentanil</td>
<td>38.8</td>
<td>69.3</td>
<td>48.5</td>
<td>25.1%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>86.9</td>
<td>217.7</td>
<td>152.4</td>
<td>75.4%</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>55.8</td>
<td>153.1</td>
<td>107.2</td>
<td>91.9%</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>31.3</td>
<td>133.4</td>
<td>93.4</td>
<td>198.9%</td>
</tr>
<tr>
<td>Naloxone</td>
<td>52.6</td>
<td>99.2</td>
<td>69.5</td>
<td>32.1%</td>
</tr>
</tbody>
</table>

Figure 8.20. Predicted vs. Observed-LBF for $\text{CL}_{\text{tot}}^u$ (from Dog PK)
Table 8.25. LBF Method using Rat and Dog PK for $CL_{tot}^a$

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter $CL_{tot}^a$</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (± SE)</th>
<th>$r^2$</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>11</td>
<td>145 (± 51)</td>
<td>217</td>
<td>0.66 (± 0.26)</td>
<td>0.42</td>
<td>3/11 (27 %)</td>
<td></td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>8</td>
<td>28 (± 16)</td>
<td>50</td>
<td>0.81 (± 0.15)</td>
<td>0.82</td>
<td>7/8 (88 %)</td>
<td></td>
</tr>
<tr>
<td>Excluding heroin</td>
<td>7</td>
<td>34 (± 17)</td>
<td>54</td>
<td>1.62 (± 0.49)</td>
<td>0.69</td>
<td>6/7 (86 %)</td>
<td></td>
</tr>
</tbody>
</table>
Table 8.26. Summary Table for Prediction of \( CL_{\text{tot}} \) and \( CL_{\text{tot}}^u \) (Excluding Remifentanil, Heroin, Meperidine and Butorphanol)

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
<th>Prediction errors</th>
<th>Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parameter</td>
<td>Bias</td>
</tr>
<tr>
<td>One species approach (from rat data)</td>
<td>1/15 (7 %)</td>
<td>CL\textsubscript{tot}</td>
<td>15</td>
</tr>
<tr>
<td>One species approach (from dog data)</td>
<td>4/14 (28 %)</td>
<td>CL\textsubscript{tot}</td>
<td>14</td>
</tr>
<tr>
<td>Two species approach</td>
<td>5/11 (46 %)</td>
<td>CL\textsubscript{tot}</td>
<td>11</td>
</tr>
<tr>
<td>LBF method (from rat data)</td>
<td>5/15 (33 %)</td>
<td>CL\textsubscript{tot}</td>
<td>15</td>
</tr>
<tr>
<td>LBF method (from dog data)</td>
<td>7/14 (50 %)</td>
<td>CL\textsubscript{tot}</td>
<td>14</td>
</tr>
<tr>
<td>One species approach (from rat) Unbound values</td>
<td>2/11 (18 %)</td>
<td>CL\textsubscript{tot}^u</td>
<td>11</td>
</tr>
<tr>
<td>One species approach (from dog) Unbound values</td>
<td>6/7 (86 %)</td>
<td>CL\textsubscript{tot}^u</td>
<td>7</td>
</tr>
<tr>
<td>LBF method using unbound values (from rat data)</td>
<td>3/11 (27 %)</td>
<td>CL\textsubscript{tot}^u</td>
<td>11</td>
</tr>
<tr>
<td>LBF method using unbound values (from dog data)</td>
<td>6/7 (86 %)</td>
<td>CL\textsubscript{tot}^u</td>
<td>7</td>
</tr>
<tr>
<td>Method</td>
<td>No. of compounds</td>
<td>Parameter</td>
<td>Prediction errors</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------</td>
<td>-----------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td>In the 0.5-2 fold error range</td>
<td></td>
<td>Bias</td>
</tr>
<tr>
<td>One species approach (from rat data)</td>
<td>7/14 (50%)</td>
<td>Vdss</td>
<td>14</td>
</tr>
<tr>
<td>One species approach (from dog data)</td>
<td>6/12 (50%)</td>
<td>Vdss</td>
<td>12</td>
</tr>
<tr>
<td>Two species approach</td>
<td>1/9 (11%)</td>
<td>Vdss</td>
<td>9</td>
</tr>
<tr>
<td>One species approach (from rat) Unbound values</td>
<td>5/10 (50 %)</td>
<td>Vdss u</td>
<td>10</td>
</tr>
<tr>
<td>One species approach (from dog) Unbound values</td>
<td>5/7 (71 %)</td>
<td>Vdss u</td>
<td>7</td>
</tr>
</tbody>
</table>
8.1.4. Discussion

There were large differences in reported, BW-corrected, $CL_{tot}$ and $V_{dss}$ values across species (range: 1 to 40-fold, 1 to 100-fold, respectively) for opioids. A significant relationship between human $f_u$ - rat $f_u$ ($r^2 = 0.93$) and human $f_u$ - dog $f_u$ ($r^2 = 0.89$) was found. Sawada et al.\textsuperscript{99} compared PPB for nine weakly acidic and six weakly basic drugs and a significant relation was obtained between $f_u$ - human and $f_u$ - rat ($n = 14$, Slope = 1.17, $r^2 = 0.92$). Sawada et al.\textsuperscript{100} reported plasma protein binding values for 10 basic drugs in different species and found that the interspecies differences in distribution maybe attributed to the differences in $f_u$. Hepatic clearance categorization of opioids showed that there were interspecies differences in metabolism of opioids. All the opioids were high clearance in rats, while some were intermediate and high in humans and dogs. Bjorkman et al.\textsuperscript{101} compared $CL_{tot}$ with hepatic blood flow for fentanyl and alfentanil and it was found that fentanyl was a high extraction ratio drug in all species except human while alfentanil was high extraction ratio in rats while it was medium-to-low extraction in larger animals and human. Most of the opioids are metabolized by CYP450 (mainly CYP3A and CYP2C isoforms) and UGTs. Some opioids like remifentanil, heroin and meperidine are esters and are known/suspected to undergo extra-hepatic metabolism by nonspecific esterases in blood and tissues. De Wazier et al.\textsuperscript{97} found that hepatic enzyme levels of CYP1A, CYP2C and CYP3A in rats were approximately 28, 638 and 165 pmol/gm microsomal protein while Guengerich et al.\textsuperscript{98} reported corresponding values for humans as 37, 55, 87 pmol/gm of microsomal protein (Table 8.2). Similarly, Clarke et al.\textsuperscript{102} found that there were interspecies differences in UGT activities in rat and humans. Soars et al.\textsuperscript{103} looked at \textit{in-vitro} glucuronidation of a range of
structurally diverse chemicals in hepatic and renal microsomes from human and dogs and found that glucuronidation was several fold more rapid in dog liver microsomes than human liver microsomes. In-addition, they found regioselective differences in morphine glucuronidation. Quon et al\textsuperscript{104} found that blood esmolol esterase activity is higher in rats and dogs as compared to humans. Sawada et al\textsuperscript{99} compared unbound intrinsic clearance in rat and human for nine weakly acidic and six weakly acidic drugs and found that these drugs are metabolized ten times more rapidly in rat than in human. Overall, in addition to species differences in amino acid sequences and substrate specificity, different enzyme activities may result in differences in clearance category.

Remifentanil and meperidine are esters and are known/suspected to undergo extra-hepatic metabolism. For CL\textsubscript{tot}, their allometric coefficients were found to be very low for n =3 as well as for n = all available animals. Butorphanol was suspected to undergo extra-hepatic metabolism and is excluded as well. Hence, these drugs were excluded from AS. It was found in a study carried out on 36 marketed oral drugs that for drugs like nitrendipine (metabolized extrahepatically by esterases) and granisetron (metabolized extrahepatically by CYP1A1), predicted clearance from hepatic metabolism unestimated the total clearance.\textsuperscript{30} Thus, this shows the importance of a priori knowledge of metabolic routes. Bjorkman et al\textsuperscript{101} used body weight, brain weight and MLP method to predict CL\textsubscript{tot} and CL\textsubscript{tot} \textsuperscript{u} and body weight to scale Vd\textsubscript{ss} and Vd\textsubscript{ss} \textsuperscript{u} in humans for five anaesthetic drugs: fentanyl, alfentanil, methohexitone, thiopentone and ketamine. Scaling to body weight gave an allometric exponent of 0.89 (r\textsuperscript{2} = 0.982) and 0.76 (r\textsuperscript{2} = 0.971) for fentanyl and alfentanil, respectively. Prediction of CL\textsubscript{tot} \textsuperscript{u} was not accurate by any of the methods used. Predictions of Vd\textsubscript{ss} of alfentanil by AS was successful (within ± 30 % of the true value), however, Vd\textsubscript{ss} \textsuperscript{u} invariably failed to give
accurate predictions in humans. Sawada et al\textsuperscript{100} found a significant correlation between human and animal Vd\textsubscript{ss} (r = 0.748, p < 0.001) and the relation improved when human and animal V\textsubscript{f}/f\textsubscript{u} were compared (r = 0.944, p < 0.001) for ten weak basic drugs indicating that there is little difference in the tissue distribution of these drugs. Sawada et al\textsuperscript{99} studied nine weakly acidic and six weakly basic drugs across different species and found that interspecies differences in metabolic clearance and Vd\textsubscript{ss} maybe attributed to differences in f\textsubscript{u}. In the present research on opioids, in general, Vd\textsubscript{ss} was scaled well with body weight, however, there were some exceptions like morphine glucuronides, for which, allometric coefficients were found to be low. This maybe because morphine glucuronides are polar in nature and this limits their distribution. For the remaining opioids, CL\textsubscript{tot} (mean slope: 0.79, 0.47-1.31) and Vd\textsubscript{ss} (mean slope: 0.90, 0.64-1.14) scaled well with body weight, regardless of the number of species. For some opioids, f\textsubscript{u} correction improved AS.

Table 8.25 and 8.26 shows the summary for the prediction of PK variables. Table 8.27 gives the best prediction methods for total and unbound PK parameters. For CL\textsubscript{tot} prediction, LBF method from dog was found to be the best method. This finding was consistent with prediction of human PK for 103-compound dataset of structurally diverse compounds; it was found that allometric scaling approaches using two species were less successful at predicting CL\textsubscript{tot} than LBF method in an individual species.\textsuperscript{13} In the past, scaling from monkey LBF method was proven to the accurate methodology when 124 compound dataset of structurally diverse compounds was studied.\textsuperscript{45} In general, f\textsubscript{u} correction for CL\textsubscript{tot} and Vd\textsubscript{ss} increased r\textsuperscript{2} value indicating improvement in the goodness of fit, resulted in more accurate and precise predictions as indicated by lower %MPE and % RMSE and resulted in more number of compounds in the 0.5-2.0 fold error range. Feng et al\textsuperscript{55} predicted human systemic CL\textsubscript{tot} using
unbound concentrations for eight Parke Davis compounds and 26 literature drugs. These all
drugs were small molecules eliminated hepatically, renally and with mixed functions. It was
found that in general, human CL\textsubscript{tot}\textsuperscript{u} was predicted more accurately with the average fold error
reduced from 2.8 to 2.2. For drugs with significant variation in PPB across species, the fold
error decreased from 3.3-15.8 to 0.99-2.0, and overestimation only occurred for drugs which
were mainly eliminated by metabolism. All the methods used for the prediction of opioids in
this research showed an overall overprediction as indicated by the positive % MPEs. A
qualitative analysis of 102 compounds (57 metabolized by liver - 29 low clearance, 17
intermediate clearance, 11 high clearance and 33 excreted by kidneys and 11 eliminated by
renal as well as by metabolism) by Tang et al\textsuperscript{52} revealed the application of two potential
rules for predicting the occurrence of large vertical allometry/overprediction in prediction of
systemic CL\textsubscript{tot}, ratio of unbound fraction of drug in plasma (f\textsubscript{u}) between rats and humans
greater than 5; and clogP greater than 2. It was concluded that metabolic elimination could
also serve as an additional indicator for expecting large vertical allometry. With the
exception of f\textsubscript{u} ratio criteria, opioids followed these rules; since most of them were
eliminated by liver and showed clogP more than 2.0.

In terms of number of compounds predicted in 0.5-2.0 fold error range, LBF method
using dog data was the best prediction method for CL\textsubscript{tot} and CL\textsubscript{tot}\textsuperscript{u}. For V\textsubscript{dss}, one species-rat
and one species-dog, both, predicted 50% compounds fall in 0.5-2.0 fold error range. For
V\textsubscript{dss}\textsuperscript{u}, one-species-dog predicted 71% compounds predicted in 0.5-2.0 fold error range.
Overall, the rat, dog, rat-dog methods provided reasonable predictions. Thus, use of three or
more species may not be necessary. Similar conclusion was made by by Tang et al\textsuperscript{5} when
one- or two- species based methods were used to predict human CL\textsubscript{tot} from rat, dog and
monkey in a 26-Wyeth compound test dataset using a 102-compound training dataset. The authors compared their newly deviced data driven one – and two- species approach for prediction $\text{CL}_{\text{tot}}$ with LBF method and allometrically based rule of exponents (ROE). It was found that the rat, dog, monkey, rat-dog, and rat-monkey methods provided improved predictions relative to the ROE for 17 of 26, 14 of 21, 5 of 9, 14 of 21 and 7 of 9 compounds, respectively. Hosea et al$^{56}$ conducted a retrospective analysis using 50 proprietary compounds for which oral single dose human PK data was available. It was found that use of single species lead to more accurate predictions than using multiple species and use of unbound concentrations resulted in accurate predictions. Feng et al$^{55}$ carried out a direct $\text{CL}_{\text{tot}}^u$ correlation between single animal species and human for 37 diverse set of compounds and found a good correlation between human-monkey ($n = 16, r^2 = 0.93$) and human-rat ($n = 37, r^2 = 0.89$), with monkey and rat predicting 75 % and 63 % compounds in 0.5-2 fold error range, respectively. Data were found to be more scattered for dog and rabbit data. Based on this, they suggested that rat and monkey should be considered first for preclinical studies while dog should be the third species of selection. In contrast to this finding, Tang et al$^{36}$ used Monte Carlo simulations for different combinations of species to select the “best” or optimal combination of species and found that the predicted values were heavily dependent on certain species like dog, whereas, parameter values from rat made no contribution to the predicted human values, as long as the rat was not the smallest species used.

In this research, for most of the opioids, only rat and dog PK data was available. Overall, dog was found to be the species giving best prediction of clearance as well as volume of distribution. Acceptable predictions were obtained after interspecies scaling using single-species methods; however, overall, there was a positive bias. This suggests non-rodent
species in preclinical PK may be useful and for most opioids, body size accounts for most of
the observed variability in systemic PK

<table>
<thead>
<tr>
<th>PK variable</th>
<th>Method</th>
<th>n</th>
<th>%MPE</th>
<th>%RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{dss}$</td>
<td>Dog-BW</td>
<td>12</td>
<td>52</td>
<td>126</td>
</tr>
<tr>
<td>$V_{dss}^a$</td>
<td>Dog-BW</td>
<td>7</td>
<td>76</td>
<td>133</td>
</tr>
<tr>
<td>$CL_{tot}$</td>
<td>Dog-LBF</td>
<td>14</td>
<td>122</td>
<td>217</td>
</tr>
<tr>
<td>$CL_{tot}^a$</td>
<td>Dog-LBF</td>
<td>7</td>
<td>34</td>
<td>54</td>
</tr>
</tbody>
</table>
CHAPTER 9. INTERSPECIES SCALING OF β-ARLS

9. β-adrenergic receptor ligands (β-ARL)

9.1. Results

9.1.1. Comparative pharmacokinetics of β-adrenergic receptor ligands across different species

There were large differences in reported, BW-corrected, CL<sub>tot</sub> and V<sub>dss</sub> values across species (range: 6 to 80-fold, 3 to 50-fold, respectively) (Table 9.1). A significant relationship between human f<sub>u</sub> – rat f<sub>u</sub> (n = 10, r<sup>2</sup> = 0.74) and human f<sub>u</sub> – dog f<sub>u</sub> (n = 4, r<sup>2</sup> = 0.97) was found (Figure 9.1-9.2 and Table 9.2-9.3). Amongst all the β-ARL, propranolol and oxprenolol showed major species differences in the f<sub>u</sub>.

Table 9.4 shows hepatic clearance categorization for each drug in each species. Xamoterol, sotalol, atenolol and bisoprolol were found to be low clearance in dog and human. All the β-ARLs (except timolol and landiolol) were found to be high clearance in rats and this finding was similar to our finding for interspecies scaling of opioids. In this method, CL<sub>tot</sub> is compared to the liver blood flow in each species. Many of the β-ARLs are high clearance drugs, however, some hydrophilic β-ARL like xamoterol, sotalol are mainly excreted by kidneys. This method assumes that CL<sub>tot</sub> represents CL<sub>hepatic</sub> and the contribution of CL<sub>ren</sub> is negligible. This assumption might lead to some misclassification of the hydrophilic β-ARL.
Table 9.1. *In-vivo* and *in-vitro* PK parameters of β-ARLs in Different Species

<table>
<thead>
<tr>
<th>Drug</th>
<th>Species</th>
<th>BW</th>
<th>Dose</th>
<th>CL$_{\text{tot}}$</th>
<th>CL$_{\text{tot}}$</th>
<th>Vd$_{\text{ss}}$</th>
<th>Vd$_{\text{ss}}$</th>
<th>f$_u$</th>
<th>CL$_{\text{tot}}^u$</th>
<th>Vd$_{\text{ss}}^u$</th>
<th>f$_e$</th>
<th>CL$_{\text{ren}}$</th>
<th>CL$_{\text{ren}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(kg)</td>
<td>(mg/kg)</td>
<td>(ml/min/kg)</td>
<td>(ml/min)</td>
<td>(L/kg)</td>
<td>(L)</td>
<td>(%)</td>
<td>(ml/min/kg)</td>
<td>(L/kg)</td>
<td>(%)</td>
<td>(ml/min/kg)</td>
<td>(ml/min)</td>
</tr>
<tr>
<td>Xamoterol</td>
<td>Dog</td>
<td>14.9</td>
<td>1</td>
<td>4.5</td>
<td>66.9</td>
<td>3.2</td>
<td>46.9</td>
<td>97%</td>
<td>3.1</td>
<td>0.66</td>
<td>61.6%</td>
<td>1.8</td>
<td>138.0</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>75</td>
<td>0.19</td>
<td>3.0</td>
<td>224.3</td>
<td>0.6</td>
<td>48.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>Rat</td>
<td>0.275</td>
<td>0.2</td>
<td>6.5</td>
<td>1.8</td>
<td>2.2</td>
<td>0.6</td>
<td>40%</td>
<td>22.9</td>
<td>4.22</td>
<td>26.4%</td>
<td>2.5</td>
<td>132.8</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>54</td>
<td>0.067</td>
<td>9.2</td>
<td>497.9</td>
<td>1.7</td>
<td>91.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carteolol</td>
<td>Rat</td>
<td>0.275</td>
<td>30</td>
<td>16.0</td>
<td>4.4</td>
<td>4.8</td>
<td>1.3</td>
<td>97%</td>
<td>16.6</td>
<td>4.97</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>62</td>
<td>0.21</td>
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<td>628.1</td>
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<td>5.85</td>
<td>65.0%</td>
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<td>Propranolol</td>
<td>Rat</td>
<td>0.47</td>
<td>1</td>
<td>54.0</td>
<td>25.2</td>
<td>2.7</td>
<td>1.3</td>
<td>11%</td>
<td>490.9</td>
<td>24.9</td>
<td>0.92%</td>
<td>0.01</td>
<td>0.005</td>
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<td>Dog</td>
<td>10</td>
<td>0.6</td>
<td>50.3</td>
<td>503.0</td>
<td>6.6</td>
<td>65.7</td>
<td>15%</td>
<td>330.9</td>
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<tr>
<td></td>
<td>Horse</td>
<td>533</td>
<td>0.2</td>
<td>22.9</td>
<td>12179.1</td>
<td>3.0</td>
<td>1625.1</td>
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<tr>
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<td>Human</td>
<td>66.5</td>
<td>0.15</td>
<td>13.6</td>
<td>904.4</td>
<td>2.9</td>
<td>194.2</td>
<td>8%</td>
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<tr>
<td>Minimum</td>
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<td>13.60</td>
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<td>1.28</td>
<td>0.8%</td>
<td>181.33</td>
<td>0.04</td>
<td>0.02%</td>
<td>0.01</td>
<td>0.0</td>
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<td>Maximum</td>
<td></td>
<td>533</td>
<td>1.00</td>
<td>86</td>
<td>12179</td>
<td>8.7</td>
<td>1625</td>
<td>36.0%</td>
<td>491</td>
<td>43</td>
<td>4.8%</td>
<td>2.4</td>
<td>24</td>
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<tr>
<td>Mean</td>
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<td>0.59</td>
<td>45</td>
<td>2791</td>
<td>4.8</td>
<td>384</td>
<td>14.1%</td>
<td>310</td>
<td>23</td>
<td>1.7%</td>
<td>0.8</td>
<td>9</td>
</tr>
<tr>
<td>SD</td>
<td></td>
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<td>0.41</td>
<td>28</td>
<td>5258</td>
<td>2.7</td>
<td>698</td>
<td></td>
<td>135</td>
<td>18</td>
<td>0.03%</td>
<td>1.4</td>
<td>13</td>
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<td>6</td>
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<td>1270</td>
<td></td>
<td>45</td>
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<td>984</td>
<td>259</td>
<td>241</td>
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<tr>
<td>COV</td>
<td></td>
<td>188</td>
<td>70</td>
<td>63</td>
<td>188</td>
<td>56</td>
<td>182</td>
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<td>44</td>
<td>77</td>
<td>155</td>
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<td>144</td>
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<tr>
<td>Sotalol</td>
<td>Rat</td>
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<td>5</td>
<td>22.5</td>
<td>8.0</td>
<td>2.5</td>
<td>0.9</td>
<td>95.0%</td>
<td>23.6</td>
<td>2.7</td>
<td>74.6%</td>
<td>16.7</td>
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<td>11.8</td>
<td>3</td>
<td>4.5</td>
<td>53.6</td>
<td>1.6</td>
<td>18.5</td>
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### Data Table

**Drug Species BW Dose CL<sub>tot</sub> CL<sub>tot</sub> Vd<sub>ss</sub> Vd<sub>ss</sub> f<sub>a</sub> CL<sub>tot</sub> Vd<sub>ss</sub> f<sub>a</sub> CL<sub>ren</sub> CL<sub>ren</sub>**

**Cat 2.9 2 4.3 12.5 1.1 3.1**

**Rabbit 1.9 2.5 7.7 14.6 3.4 6.5**

**Human 74.1 0.70**

**Metoprolol**

**Rat 0.27 5 73.4 19.8 2.1 0.6**

**Dog 12 0.4 35.8 429.8 4.7 56.8**

**Cat 3.25 2.6 108.3 351.8 8.3 27.0**

**Rabbit 2.75 3.2 62.0 170.5 2.8 7.6**

**Human 74 0.27 10.8 799.9 3.2 236.8**

**Amosulalol**

**Mice 0.02 10 178.3 3.6 19.8 0.4**

**Rat 0.205 1 56.7 11.6 10.7 2.2**

**Dog 12 1 33.3 399.6 5.5 66.0**

**Monkey 4.65 1 10.0 46.5 1.2 5.6**

**Human 62.1 0.16 2.2 134.8 0.4 24.8**

**Minimum**

**0.5 0.7 2.4 12.5 1.1 3.1**

**74.1 12.9 33.4 178.6 3.4 77.8**

**19.0 4.0 10.4 57.8 1.9 22.0**

**31.4 5.0 13.0 71.2 1.1 32.2**

**147 18 14 14 3 58**

**165 125 125 123 56 147**

**Fold range**

**COV**

**Minimum**

**0.27 0.27 10.81 19.82 2.13 0.58**

**74 5 108.3 799.9 8.3 236.8**

**18.5 2.3 58.1 354.4 4.2 65.8**

**31.4 2.0 37.1 295.8 2.5 98.1**

**274 19 10 40 4 412**

**170 87 64 83 58 149**

**Fold range**

**COV**

**Minimum**

**0.02 0.16 2.17 3.57 0.40 0.40**

**62.1 10 178.33 399.6 19.79 66**

**15.8 2.6 56.1 119.2 7.5 19.8**

**26.3 4.1 71.6 165.1 8.0 27.6**

**3105 63 82 112 49 167**

**Human 167 157 128 139 106 139**

**Fold range**

**COV**

**Minimum**

**0.27 0.27 10.81 19.82 2.13 0.58**

**74 5 108.3 799.9 8.3 236.8**

**18.5 2.3 58.1 354.4 4.2 65.8**

**31.4 2.0 37.1 295.8 2.5 98.1**

**274 19 10 40 4 412**

**170 87 64 83 58 149**

**Fold range**

**COV**

**Minimum**

**0.02 0.16 2.17 3.57 0.40 0.40**

**62.1 10 178.33 399.6 19.79 66**

**15.8 2.6 56.1 119.2 7.5 19.8**

**26.3 4.1 71.6 165.1 8.0 27.6**

**3105 63 82 112 49 167**

**Human 167 157 128 139 106 139**

**Fold range**

**COV**
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203
Table 9.2. Plasma protein binding of β-ARLs across species

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Table 9.3. Regression Parameters for Human and Animal PPB Relationship

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Figure 9.1. Human $f_u$ vs. Rat $f_u$

Figure 9.2. Human $f_u$ vs. Dog $f_u$
Table 9.4. Hepatic clearance categorization of β-ARLs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human</th>
<th>Rat</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$CL_{tot}$ (ml/min/kg)</td>
<td>Category</td>
<td>$CL_{tot}$ (ml/min/kg)</td>
</tr>
<tr>
<td>Xamoterol</td>
<td>3.0</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>9.2</td>
<td>Intermediate</td>
<td>6.5</td>
</tr>
<tr>
<td>Carteolol</td>
<td>10.1</td>
<td>Intermediate</td>
<td>16.0</td>
</tr>
<tr>
<td>Propranolol</td>
<td>13.6</td>
<td>Intermediate</td>
<td>54.0</td>
</tr>
<tr>
<td>Sotalol</td>
<td>2.2</td>
<td>Low</td>
<td>22.5</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2.4</td>
<td>Low</td>
<td>33.4</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>10.8</td>
<td>Intermediate</td>
<td>73.4</td>
</tr>
<tr>
<td>Amsulalol</td>
<td>2.2</td>
<td>Low</td>
<td>56.7</td>
</tr>
<tr>
<td>Nafetolol</td>
<td>19.6</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>6.8</td>
<td>Intermediate</td>
<td>60.2</td>
</tr>
<tr>
<td>Pafenolol</td>
<td>4.3</td>
<td>Low</td>
<td>42</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>3.7</td>
<td>Low</td>
<td>50.7</td>
</tr>
<tr>
<td>Pindolol</td>
<td>7.4</td>
<td>Intermediate</td>
<td>48.5</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>4.6</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>7.6</td>
<td>Intermediate</td>
<td>114.8</td>
</tr>
<tr>
<td>Landiolol</td>
<td>37.3</td>
<td>High</td>
<td>9.3</td>
</tr>
<tr>
<td>Epanolol</td>
<td>26.8</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>5.9</td>
<td>Low</td>
<td>280</td>
</tr>
<tr>
<td>Esmolol</td>
<td>285</td>
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</tr>
<tr>
<td>Betaxolol</td>
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<td>Low</td>
<td>205</td>
</tr>
<tr>
<td>Albuterol</td>
<td>7.8</td>
<td>Intermediate</td>
<td>39.2</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>37.9</td>
<td>High</td>
<td>53.8</td>
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</tbody>
</table>
9.1.2. Simple Allometry

For a set of 10 β-ARLs, simple allometry was conducted using all available species and using only three species (rat, dog), both including human. Allometric plots are shown in the Appendix III (b). Table 9.5 shows the allometric coefficients for $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$ for β-ARLs. The exponents obtained were compared with a scaling factor 0.75 for $\text{CL}_{\text{tot}}$ and 1.0 for $\text{Vd}_{\text{ss}}$. Figure 9.2-9.3 shows interspecies scaling plots for a prototypical β-ARL like propranolol. Sotalol and atenolol showed their allometric coefficients to be very low for $n = 3$ as well as for $n = \text{all available animals}$ for $\text{CL}_{\text{tot}}$. Amosulalol, bisoprolol, carvedilol and betaxolol show a very low allometric coefficient ($< 0.60$). Out of these β-ARLs showing allometric coefficients $< 0.60$ for $\text{CL}_{\text{tot}}$, $\text{CL}_{\text{ren}}$ information across species was available on only sotalol, atenolol and amosulalol, hence, for these drugs, allometric scaling was carried out for $\text{CL}_{\text{ren}}$ too. Table 9.6 shows that low allometric coefficients were obtained even for $\text{CL}_{\text{ren}}$ for sotalol, atenolol and amosulalol.

For $\text{Vd}_{\text{ss}}$, allometric coefficients for amosulalol, carvediolol and betaxolol were found to be low. For the remaining β-ARL, $\text{CL}_{\text{tot}}$ (mean slope: 0.62, 0.46-1.31) and $\text{Vd}_{\text{ss}}$ (mean slope: 0.89, 0.50-1.11) scaled well with body weight, regardless of the number of species.
Table 9.5. Allometric PK scaling of β-ARLs

<table>
<thead>
<tr>
<th>Drug</th>
<th>(ml/min)</th>
<th>n</th>
<th>r²</th>
<th>Slope ± SE</th>
<th>(L)</th>
<th>n</th>
<th>r²</th>
<th>Slope ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9455</td>
<td>0.75 ± 0.18</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3</td>
<td>0.9673</td>
<td>1.04 ± 0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>0.9473</td>
<td>0.80 ± 0.11</td>
<td></td>
<td>5</td>
<td>0.9608</td>
<td>0.95 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9960</td>
<td>0.81 ± 0.05</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9967</td>
<td>1.10 ± 0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.9850</td>
<td>0.82 ± 0.07</td>
<td></td>
<td>4</td>
<td>0.9922</td>
<td>1.11 ± 0.07</td>
</tr>
<tr>
<td>Sotalol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9997</td>
<td>0.55 ± 0.01</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3</td>
<td>0.9999</td>
<td>0.86 ± 0.003</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
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<td>0.9995</td>
<td>0.55 ± 0.01</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
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<td>0.9999</td>
<td>0.85 ± 0.0002</td>
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<tr>
<td>Atenolol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
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<td>0.46 ± 0.06</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3</td>
<td>0.9999</td>
<td>0.82 ± 0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>0.8284</td>
<td>0.54 ± 0.14</td>
<td></td>
<td>5</td>
<td>0.9431</td>
<td>0.80 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9701</td>
<td>0.50 ± 0.09</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
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<td>0.9448</td>
<td>0.77 ± 0.19</td>
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<td>Metoprolol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9728</td>
<td>0.68 ± 0.11</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
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<td>0.9915</td>
<td>1.09 ± 0.10</td>
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<td></td>
<td>5</td>
<td>0.8702</td>
<td>0.65 ± 0.14</td>
<td></td>
<td>5</td>
<td>0.9509</td>
<td>1.07 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9206</td>
<td>0.64 ± 0.19</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9934</td>
<td>1.07 ± 0.09</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.6927</td>
<td>0.51 ± 0.34</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3</td>
<td>0.7119</td>
<td>0.50 ± 0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>0.8411</td>
<td>0.53 ± 0.13</td>
<td></td>
<td>5</td>
<td>0.8428</td>
<td>0.57 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9911</td>
<td>0.53 ± 0.05</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9999</td>
<td>1.02 ± 0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.9896</td>
<td>0.53 ± 0.04</td>
<td></td>
<td>4</td>
<td>0.9975</td>
<td>1.02 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9963</td>
<td>0.56 ± 0.03</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9999</td>
<td>1.06 ± 0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.9952</td>
<td>0.56 ± 0.03</td>
<td></td>
<td>4</td>
<td>0.9973</td>
<td>1.06 ± 0.04</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9869</td>
<td>0.54 ± 0.06</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3</td>
<td>0.9948</td>
<td>0.76 ± 0.05</td>
</tr>
<tr>
<td>Landiolol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9634</td>
<td>1.30 ± 0.25</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3</td>
<td>0.9869</td>
<td>0.84 ± 0.09</td>
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<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9546</td>
<td>1.31 ± 0.28</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9760</td>
<td>0.87 ± 0.14</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9760</td>
<td>0.29 ± 0.05</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
<td>3</td>
<td>0.9892</td>
<td>0.76 ± 0.08</td>
</tr>
<tr>
<td>Albuterol</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>3</td>
<td>0.9983</td>
<td>0.74 ± 0.03</td>
<td>Vd&lt;sub&gt;α&lt;/sub&gt;</td>
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<td>0.9871</td>
<td>1.06 ± 0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.9176</td>
<td>0.69 ± 0.15</td>
<td></td>
<td>4</td>
<td>0.9630</td>
<td>1.03 ± 0.14</td>
</tr>
</tbody>
</table>

Note: For CL<sub>tot</sub> and CL<sub>tot</sub><sup>u</sup> 0.6 > allometric exponents > 1.2 are highlighted
For Vd<sub>α</sub> and Vd<sub>α</sub><sup>u</sup>, 0.8 > allometric exponents > 1.2 are highlighted

Table 9.6. Allometric PK scaling for sotalol, atenolol and amosulalol

<table>
<thead>
<tr>
<th>Drug</th>
<th>(ml/min)</th>
<th>n</th>
<th>r²</th>
<th>Slope ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt;</td>
<td>3</td>
<td>0.9968</td>
<td>0.57 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>0.9973</td>
<td>0.56 ± 0.03</td>
</tr>
<tr>
<td>Atenolol</td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt;</td>
<td>3</td>
<td>0.9859</td>
<td>0.52 ± 0.06</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt;</td>
<td>3</td>
<td>0.8986</td>
<td>0.59 ± 0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.9203</td>
<td>0.58 ± 0.09</td>
</tr>
</tbody>
</table>
Figure 9.3. Interspecies Allometric Scaling of $\text{CL}_{\text{tot}}$ for Propranolol

$y = 63.592x^{0.801}$
$R^2 = 0.9475$

Figure 9.4. Interspecies Allometric Scaling of $V_{dss}$ for Propranolol

$y = 4.8146x^{0.9536}$
$R^2 = 0.9606$
9.1.3. Prediction of PK of β-ARs

9.1.3.1. One-species BW Scaling

9.1.3.1.1. One-species BW Scaling from rat PK

Table 9.7 shows the observed human PK parameters and predicted human PK parameters from rat PK. Table 9.8-9.9 and Figure 9.5-9.8 show that large overprediction from rat PK and even exclusion of drugs undergoing extra-hepatic metabolism, does not decrease %MPE for CL$_{tot}$, Vd$_{ss}$ and Vd$_{ss}^u$. PPB correction for Vd$_{ss}$ increased r$^2$ value indicating improvement in the goodness of fit and brought more number of compounds in the 0.5-2.0 fold error range, from 41% to 50%.
Table 9.7. One species scaling using rat PK for β-ARLs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human Observed CL$_{tot}$ [ml/min]</th>
<th>Human Observed Vd$_{ss}$ [l]</th>
<th>Human Predicted CL$_{tot}$ [ml/min]</th>
<th>Human Predicted Vd$_{ss}$ [l]</th>
<th>Human Predicted CL$_{tot}^u$ [ml/min]</th>
<th>Human Predicted Vd$_{ss}^u$ [l]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CL$_{tot}$</td>
</tr>
<tr>
<td>Timolol</td>
<td>497.9</td>
<td>91.8</td>
<td>742.4</td>
<td>362.5</td>
<td>457.8</td>
<td>152.6</td>
<td>1160.6</td>
</tr>
<tr>
<td>Carteolol</td>
<td>628.1</td>
<td>306.7</td>
<td>12058.7</td>
<td>2589.3</td>
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<td>336</td>
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<td>194.2</td>
<td>151.6</td>
<td>84.9</td>
<td>3780</td>
<td>189</td>
<td>1657.9</td>
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<td>84.1</td>
<td>183.7</td>
<td>80.0</td>
<td>1575</td>
<td>175</td>
<td>2361.6</td>
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<td>178.6</td>
<td>77.8</td>
<td>871.4</td>
<td>258.0</td>
<td>2338</td>
<td>189</td>
<td>5609.2</td>
</tr>
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<td>5138</td>
<td>147</td>
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<td>749</td>
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<td>3834.2</td>
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<td>166.1</td>
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<td>3735.9</td>
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<td>317.5</td>
<td>72.0</td>
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<td>270.1</td>
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<td>560</td>
<td>4150.9</td>
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<td>Bisoprolol</td>
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<td>1128.5</td>
<td>318.9</td>
<td>3549</td>
<td>168</td>
<td>6429.9</td>
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<td>Pindolol</td>
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<td>136.5</td>
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<td></td>
<td>2912</td>
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<td>Carvedilol</td>
<td>532</td>
<td>152.6</td>
<td>2533.4</td>
<td>11.2</td>
<td>8036</td>
<td>578.2</td>
<td>676.0</td>
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<td>Landiolol</td>
<td><strong>2424.5</strong></td>
<td><strong>10.7</strong></td>
<td><strong>651</strong></td>
<td><strong>35</strong></td>
<td></td>
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<td>-1773.5</td>
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<td>Epanolol</td>
<td>2101.1</td>
<td>336.3</td>
<td>476.8</td>
<td>70.1</td>
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<td></td>
<td>47228.9</td>
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<td>Oxprenolol</td>
<td>381.4</td>
<td>56.1</td>
<td>32491.9</td>
<td>135.7</td>
<td>19600</td>
<td>938</td>
<td>1160.6</td>
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<tr>
<td>Betaxolol</td>
<td>254.6</td>
<td>398.7</td>
<td>742.4</td>
<td>362.5</td>
<td>14399</td>
<td>1449</td>
<td>14144.4</td>
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<tr>
<td>Drug</td>
<td>Observed</td>
<td>Predicted</td>
<td>% Prediction error</td>
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</tr>
<tr>
<td></td>
<td>Human $\text{CL}_{\text{tot}}$ [ml/min]</td>
<td>Human $\text{Vd}_{ss}$ [l]</td>
<td>Human $\text{CL}_{\text{tot}}$ $^u$ [ml/min]</td>
<td>Human $\text{Vd}_{ss}$ $^u$ [l]</td>
<td>Human $\text{CL}_{\text{tot}}$ $^u$ [ml/min]</td>
<td>Human $\text{Vd}_{ss}$ $^u$ [l]</td>
<td>$%$ Prediction error $\text{CL}_{\text{tot}}$ $^u$ [ml/min]</td>
</tr>
<tr>
<td>Albuterol</td>
<td>585</td>
<td>141.8</td>
<td>2744</td>
<td>70</td>
<td>2159</td>
<td>-71.8</td>
<td></td>
</tr>
<tr>
<td>Fenoterol</td>
<td>2122.4</td>
<td>40.9</td>
<td>3766</td>
<td>70</td>
<td>1643.6</td>
<td>29.1</td>
<td></td>
</tr>
</tbody>
</table>
Table 9.8. One Species Method using Rat PK (Complete Dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>17</td>
<td>1282 (± 311 %)</td>
<td>2065</td>
<td>-0.27 (± 0.29)</td>
<td>0.05</td>
<td>3/17 (18 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;</td>
<td>17</td>
<td>391 (± 185 %)</td>
<td>835</td>
<td>0.34 (± 0.27)</td>
<td>0.09</td>
<td>7/17 (41 %)</td>
</tr>
<tr>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>10</td>
<td></td>
<td>1482 (± 935 %)</td>
<td>3171</td>
<td>0.34 (± 0.36)</td>
<td>0.10</td>
<td>1/10 (10 %)</td>
</tr>
<tr>
<td>V&lt;sub&gt;dss&lt;/sub&gt; &lt;sup&gt;u&lt;/sup&gt;</td>
<td>10</td>
<td></td>
<td>380 (± 307 %)</td>
<td>997</td>
<td>0.49 (± 0.24)</td>
<td>0.34</td>
<td>5/10 (50 %)</td>
</tr>
</tbody>
</table>

Table 9.9. One Species Method using Rat PK (Reduced dataset excluding nafetolol, landiolol, esmolol and fenoterol)

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach</td>
<td>CL&lt;sup&gt;tot&lt;/sup&gt;</td>
<td>15</td>
<td>1452 (± 375 %)</td>
<td>2198</td>
<td>-0.007 (± 0.34)</td>
<td>0.00003</td>
<td>2/15 (13 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;</td>
<td>15</td>
<td>423 (± 208 %)</td>
<td>887</td>
<td>0.01 (± 0.32)</td>
<td>0.0001</td>
<td>4/15 (27 %)</td>
</tr>
<tr>
<td>CL&lt;sup&gt;tot&lt;/sup&gt; &lt;sup&gt;u&lt;/sup&gt;</td>
<td>9</td>
<td></td>
<td>1654 (± 1027 %)</td>
<td>3342</td>
<td>0.58 (± 0.30)</td>
<td>0.34</td>
<td>1/9 (11 %)</td>
</tr>
<tr>
<td>V&lt;sub&gt;dss&lt;/sub&gt; &lt;sup&gt;u&lt;/sup&gt;</td>
<td>9</td>
<td></td>
<td>397 (± 343 %)</td>
<td>1048</td>
<td>0.98 (± 0.10)</td>
<td>0.99</td>
<td>5/9 (55 %)</td>
</tr>
</tbody>
</table>
Figure 9.5. Predicted Human CL$_{tot}$ from Rat PK vs. Observed Human CL$_{tot}$

Figure 9.6. Predicted Human Vd$_{ss}$ from Rat PK vs. Observed Human Vd$_{ss}$

- Line of identity
- Line with slope = 0.5
- Line with slope = 2.0
Figure 9.7. Predicted Human CL_{tot} from Rat PK vs. Observed Human CL_{tot}.

Figure 9.8. Predicted Human Vd_{ss} from Rat PK vs. Observed Human Vd_{ss}.
9.1.3.1.2. One-species BW Scaling using dog PK

Table 9.10 shows the observed human PK parameters and predicted human PK parameters from dog PK. Table 9.11-9.12 and Figure 9.9-9.12 show that $\text{CL}_{\text{tot}}^u$ and $\text{Vd}_{\text{ss}}^u$ were predicted more accurately and precisely than $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$ as indicated by % MPE and % RMSE. PPB correction resulted in more number of compounds in the acceptable 0.5-2.0 fold error range. However, $f_u$ information was available on only for 5 $\beta$-ARLs.

In terms of no. of compounds in the 0.5-2 fold error range, only 6 out 16 $\beta$-ARLs (38 %) showed predicted $\text{CL}_{\text{tot}}$ in 0.5-2 fold error range, while 2 out of 5 $\beta$-ARLs (40 %) showed predicted $\text{CL}_{\text{tot}}^u$ in 0.5-2 fold error range. Out of 15, 10 $\beta$-ARLs (67 %) showed predicted $\text{Vd}_{\text{ss}}$ in 0.5-2 fold error range. Out of 4, 3 $\beta$-ARLs (75 %) showed $\text{Vd}_{\text{ss}}^u$ in 0.5-2 fold error range. Overall, there was an overprediction and it was more pronounced when $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$ were not corrected for PPB, however, % MPE and % RMSEs were lower than those obtained from rat PK predictions.
Table 9.10. One Species Method using Dog PK for β-ARLs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human Observed</th>
<th>Human Predicted</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xamoterol</td>
<td>224.3</td>
<td>48</td>
<td>314.3</td>
</tr>
<tr>
<td>Timolol</td>
<td>497.9</td>
<td>91.8</td>
<td>1235.5</td>
</tr>
<tr>
<td>Carteolol</td>
<td>628.1</td>
<td>306.7</td>
<td>742.4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>904.4</td>
<td>194.2</td>
<td>12058.7</td>
</tr>
<tr>
<td>Sotalol</td>
<td>150.1</td>
<td>84.1</td>
<td>151.6</td>
</tr>
<tr>
<td>Atenolol</td>
<td>178.6</td>
<td>77.8</td>
<td>183.7</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>799.9</td>
<td>236.8</td>
<td>871.4</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>134.8</td>
<td>24.8</td>
<td>2331</td>
</tr>
<tr>
<td>Nafetolol</td>
<td>1146.6</td>
<td>166.1</td>
<td>2128</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>259.7</td>
<td>190.4</td>
<td>368.4</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>314</td>
<td>530.6</td>
<td>3234</td>
</tr>
<tr>
<td>Landiolol</td>
<td>2424.5</td>
<td>10.7</td>
<td>2533.4</td>
</tr>
<tr>
<td>Epanolol</td>
<td>2101.1</td>
<td>336.3</td>
<td>5775</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>381.4</td>
<td>56.1</td>
<td>476.8</td>
</tr>
<tr>
<td>Esmolol</td>
<td>19950</td>
<td>83.3</td>
<td>32491.9</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>254.6</td>
<td>398.7</td>
<td>1400</td>
</tr>
<tr>
<td>Albuterol</td>
<td>585</td>
<td>141.8</td>
<td>882</td>
</tr>
<tr>
<td>Drug</td>
<td>Observed</td>
<td>Predicted</td>
<td>% Prediction error</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>-----------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>Human $\text{CL}_{\text{tot}}$ [ml/min]</td>
<td>Human $\text{Vd}_{\text{ss}}$ [l]</td>
<td>Human $\text{CL}_{\text{tot}}^u$ [ml/min]</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>2122.4</td>
<td>40.9</td>
<td>742</td>
</tr>
</tbody>
</table>
### Table 9.11. One Species Method using Dog PK (Complete Dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach (from dog PK)</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>16</td>
<td>263 (± 109 %)</td>
<td>499</td>
<td>0.54 (± 0.23)</td>
<td>0.29</td>
<td>6/16 (38 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;</td>
<td>15</td>
<td>-131 (± 99 %)</td>
<td>391</td>
<td>0.54 (± 0.18)</td>
<td>0.43</td>
<td>10/15 (67 %)</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>5</td>
<td>114 (± 57 %)</td>
<td>162</td>
<td>-0.49 (± 0.99)</td>
<td>0.08</td>
<td>2/5 (40 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>4</td>
<td>37 (± 56 %)</td>
<td>105</td>
<td>0.82 (± 0.10)</td>
<td>0.97</td>
<td>3/4 (75 %)</td>
</tr>
</tbody>
</table>

### Table 9.12. One Species Method using Dog PK (Reduced dataset excluding nafetolol, landiolol and esmolol)

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach (from dog data)</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>12</td>
<td>335 (± 140 %)</td>
<td>573</td>
<td>0.66 (± 0.19)</td>
<td>0.51</td>
<td>4/12 (33 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;</td>
<td>12</td>
<td>-175 (± 119 %)</td>
<td>435</td>
<td>0.01 (± 0.32)</td>
<td>0.0001</td>
<td>8/12 (67 %)</td>
</tr>
<tr>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>164 (± 37 %)</td>
<td>172</td>
<td>0.58 (± 0.30)</td>
<td>0.34</td>
<td>3/3 (100 %)</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;&lt;sup&gt;u&lt;/sup&gt;</td>
<td>3</td>
<td>-19.2 (± 8%)</td>
<td>22</td>
<td>0.98 (± 0.10)</td>
<td>0.99</td>
<td>3/3 (100 %)</td>
</tr>
</tbody>
</table>
Figure 9.9. Predicted Human CL_{tot} from Dog PK vs. Observed Human CL_{tot}

Figure 9.10. Predicted Human Vd_{ss} from Dog PK vs. Observed Human Vd_{ss}

Line of identity  Line with slope = 0.5  Line with slope = 2.0
Figure 9.11. Predicted Human CL\textsubscript{tot} \textsuperscript{u} from Dog PK vs. Observed Human CL\textsubscript{tot} \textsuperscript{u}

Figure 9.12. Predicted Human Vd\textsubscript{ss} \textsuperscript{u} from Dog PK vs. Observed Human Vd\textsubscript{ss} \textsuperscript{u}
9.1.3.2. Two-species BW Scaling

Table 9.13 and 9.14 shows the observed human PK parameters and predicted human PK parameters from two species, rat and dog, for CL$_{\text{tot}}$ and Vd$_{ss}$. Table 9.15-9.16 show that CL$_{\text{tot}}$ was predicted more accurately and precisely when drugs undergoing extra-hepatic metabolism were excluded as indicated by their % MPE and % RMSE. In terms of no. of compounds in the 0.5-2 fold error range, only 6 out 9 β-ARLs (67 %) showed predicted CL$_{\text{tot}}$ in 0.5-2 fold error range, while 6 out of 9 β-ARLs (67 %) showed predicted Vd$_{ss}$ in 0.5-2 fold error range. PPB was found to be fairly constant for β-ARLs across species with exception of propranolol and oxycodone (Table 9.3). PPB correction for CL$_{\text{tot}}$ and Vd$_{ss}$ resulted in very high % prediction errors (Table 9.17). Rat and dog CL$_{\text{tot}}^u$ and Vd$_{ss}^u$ differed to a great extent with rat showing lower CL$_{\text{tot}}^u$ and Vd$_{ss}^u$. Highly species dependent tissue binding and extra-hepatic metabolism in tissues may have lead to over-prediction of Vd$_{ss}^u$ and CL$_{\text{tot}}^u$, respectively.
### Table 9.13. Two Species Method using Rat and Dog PK for β-ARLs

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\text{CL}_{\text{tot}}^\text{rat}$ (ml/min)</th>
<th>$\text{CL}_{\text{tot}}^\text{dog}$ (ml/min)</th>
<th>Intercept</th>
<th>Slope</th>
<th>Predicted $\text{CL}_{\text{tot}}^\text{human}$ (ml/min)</th>
<th>Observed $\text{CL}_{\text{tot}}^\text{human}$ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>25.2</td>
<td>503.0</td>
<td>1.72</td>
<td>0.98</td>
<td>3379</td>
<td>904.4</td>
</tr>
<tr>
<td>Sotalol</td>
<td>8.0</td>
<td>53.6</td>
<td>1.14</td>
<td>0.54</td>
<td>141</td>
<td>150.1</td>
</tr>
<tr>
<td>Atenolol</td>
<td>16.8</td>
<td>66.3</td>
<td>1.35</td>
<td>0.39</td>
<td>121</td>
<td>178.6</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>19.8</td>
<td>429.8</td>
<td>1.76</td>
<td>0.81</td>
<td>1797</td>
<td>799.9</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>11.6</td>
<td>399.6</td>
<td>1.66</td>
<td>0.87</td>
<td>1853</td>
<td>134.8</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>12.7</td>
<td>72.8</td>
<td>1.39</td>
<td>0.47</td>
<td>178</td>
<td>259.7</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>26.4</td>
<td>262.7</td>
<td>1.81</td>
<td>0.61</td>
<td>859</td>
<td>532</td>
</tr>
<tr>
<td>Landiolol</td>
<td>2.3</td>
<td>825.0</td>
<td>1.32</td>
<td>1.59</td>
<td>18244</td>
<td>2424.5</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>51.3</td>
<td>180.0</td>
<td>1.92</td>
<td>0.35</td>
<td>369</td>
<td>254.6</td>
</tr>
<tr>
<td>Albuterol</td>
<td>7.84</td>
<td>308.7</td>
<td>1.43</td>
<td>0.77</td>
<td>689</td>
<td>585</td>
</tr>
</tbody>
</table>
Figure 9.13. Predicted Human $CL_{tot}$ from Rat and Dog PK vs. Observed Human $CL_{tot}$
Table 9.14. Two Species Method using Rat and Dog PK

<table>
<thead>
<tr>
<th>Drug</th>
<th>$V_{d_{ss}}^{\text{rat}}$ (l)</th>
<th>$V_{d_{ss}}^{\text{dog}}$ (l)</th>
<th>Intercept</th>
<th>Slope</th>
<th>$V_{d_{ss}}^{\text{human}}$ (l)</th>
<th>Predicted $V_{d_{ss}}^{\text{human}}$ (l)</th>
<th>Observed $V_{d_{ss}}^{\text{human}}$ (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>1.3</td>
<td>65.7</td>
<td>0.53</td>
<td>1.28</td>
<td>797.6</td>
<td>194.2</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>0.9</td>
<td>18.5</td>
<td>0.34</td>
<td>0.87</td>
<td>86.5</td>
<td>84.1</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>1.3</td>
<td>21.0</td>
<td>0.36</td>
<td>0.81</td>
<td>71.2</td>
<td>77.8</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>0.6</td>
<td>56.8</td>
<td>1.76</td>
<td>0.81</td>
<td>470.9</td>
<td>236.8</td>
<td></td>
</tr>
<tr>
<td>Amosulalol</td>
<td>2.2</td>
<td>66.0</td>
<td>0.92</td>
<td>0.84</td>
<td>288.2</td>
<td>24.8</td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>0.6</td>
<td>26.0</td>
<td>0.39</td>
<td>1.01</td>
<td>178.7</td>
<td>190.4</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>1.9</td>
<td>25.9</td>
<td>0.72</td>
<td>0.69</td>
<td>99.7</td>
<td>152.6</td>
<td></td>
</tr>
<tr>
<td>Landiolol</td>
<td>0.1</td>
<td>3.7</td>
<td>0.38</td>
<td>0.95</td>
<td>23.6</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>5.2</td>
<td>56.4</td>
<td>1.11</td>
<td>0.67</td>
<td>221.5</td>
<td>398.7</td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>0.19</td>
<td>20.3</td>
<td>0.03</td>
<td>0.96</td>
<td>55.7</td>
<td>141.8</td>
<td></td>
</tr>
</tbody>
</table>
Figure 9.14. Predicted Human Vdss from Rat and Dog PK vs. Observed Human Vdss
Table 9.15. Two Species Scaling using Rat and Dog PK (Complete Dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two species approach</td>
<td>CLₜot</td>
<td>10</td>
<td>238 (±133)</td>
<td>464</td>
<td>1.36</td>
<td>0.64</td>
<td>6/10 (60 %)</td>
</tr>
<tr>
<td></td>
<td>Vdₜot</td>
<td>10</td>
<td>144 (±108)</td>
<td>354</td>
<td>0.53</td>
<td>0.30</td>
<td>6/10 (60 %)</td>
</tr>
</tbody>
</table>

Table 9.16. Two Species Scaling using Rat and Dog PK (Reduced dataset excluding nafetolol, landiolol and esmolol)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two species approach</td>
<td>CLₜot</td>
<td>9</td>
<td>192 (±139)</td>
<td>438</td>
<td>1.05</td>
<td>0.39</td>
<td>6/9 (67 %)</td>
</tr>
<tr>
<td></td>
<td>Vdₜot</td>
<td>9</td>
<td>147 (±121)</td>
<td>372</td>
<td>0.24</td>
<td>0.04</td>
<td>6/9 (67 %)</td>
</tr>
</tbody>
</table>
Table 9.17. Two Species Method using Rat and Dog PK for CL\textsubscript{tot} and Vd\textsubscript{ss}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human CL\textsubscript{tot} [ml/min]</th>
<th>Human Vd\textsubscript{ss} [L]</th>
<th>Rat CL\textsubscript{tot} [ml/min]</th>
<th>Rat Vd\textsubscript{ss} [L]</th>
<th>Dog CL\textsubscript{tot} [ml/min]</th>
<th>Dog Vd\textsubscript{ss} [L]</th>
<th>Prediction of human CL\textsubscript{tot} [ml/min]</th>
<th>% Prediction error</th>
<th>Prediction of human Vd\textsubscript{ss} [L]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>12056</td>
<td>2.66</td>
<td>230.7</td>
<td>11.7</td>
<td>3309</td>
<td>432</td>
<td>18093.9</td>
<td>50.1%</td>
<td>4321.5</td>
<td>162363.9%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>152.9</td>
<td>83.4</td>
<td>8.50</td>
<td>0.97</td>
<td>54.28</td>
<td>18.88</td>
<td>139.9</td>
<td>-8.5%</td>
<td>85.6</td>
<td>2.6%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>371.0</td>
<td>190.4</td>
<td>14.83</td>
<td>0.70</td>
<td>104</td>
<td>37.4</td>
<td>283.5</td>
<td>-23.6%</td>
<td>287.1</td>
<td>50.8%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>2535</td>
<td>13</td>
<td>2.425</td>
<td>0.125</td>
<td>1006</td>
<td>5</td>
<td>24321.6</td>
<td>859.4%</td>
<td>33.5</td>
<td>157.8%</td>
</tr>
</tbody>
</table>

Table 9.18. Two Species Method using Rat and Dog PK for CL\textsubscript{tot} and Vd\textsubscript{ss}

| Prediction errors |
|-------------------|-----------------|----------------|-----------------|
| Method Parameter  | Bias            | Imprecision   |
|                  | n               | %MPE (±SE)    | %RMSE |
| Two species      | CL\textsubscript{tot} | 4             | 219 (± 2.1)    | 430   |
| approach         |                 |               |                 |       |
| Vd\textsubscript{ss} | 4               | 40644 (± 40573) | 81182 |
9.1.3.3.LBF method

9.1.3.3.1. LBF method using rat and dog PK for CL\textsubscript{tot} and CL\textsubscript{tot} \textsuperscript{u}

Table 9.19 and 9.20 show the observed human PK parameters and predicted human PK parameters from rat and dog PK, respectively. Table 9.21-9.22 and Figure 9.15 and 9.16 shows that LBF method using dog PK data predicted CL\textsubscript{tot} more accurately and precisely.

Table 9.25 and Figure 9.17-9.18 indicate that when CL\textsubscript{tot} was corrected for PPB, lower %MPE and %RMSE were obtained for predictions from both rat and dog PK. PPB correction for CL\textsubscript{tot} increased $r^2$ value indicating improvement in the goodness of fit. In terms of no. of compounds predicted in the 0.5- 2 fold error range, from rat PK, only 2 out of 10 $\beta$-ARLs (20 %) showed predicted CL\textsubscript{tot} \textsuperscript{u} in 0.5-2 fold error range, while from dog PK, 4 out of 4 $\beta$-ARLs (100 %) showed predicted CL\textsubscript{tot} \textsuperscript{u} in 0.5-2 fold error range.

When the drugs undergoing extra-hepatic metabolism were excluded, prediction errors did not decrease (Table 9.22 and Table 9.26).
Table 9.19. LBF Method using Rat PK for β-ARLs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human $CL_{tot}$ [ml/min/kg]</th>
<th>Observed Rat $CL_{tot}$ [ml/min/kg]</th>
<th>Predicted Human $CL_{tot}$ [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF (ml/min/kg)</td>
<td>21</td>
<td>50</td>
<td>2.6</td>
<td>-71.6%</td>
</tr>
<tr>
<td>Timolol</td>
<td>9.2</td>
<td>6.5</td>
<td>2.6</td>
<td>-71.6%</td>
</tr>
<tr>
<td>Carteolol</td>
<td>10.1</td>
<td>16.0</td>
<td>6.4</td>
<td>-36.8%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>13.6</td>
<td>54.0</td>
<td>21.6</td>
<td>58.8%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>2.2</td>
<td>22.5</td>
<td>9.0</td>
<td>309.1%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2.4</td>
<td>33.4</td>
<td>13.4</td>
<td>456.7%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>10.8</td>
<td>73.4</td>
<td>29.4</td>
<td>171.9%</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>2.2</td>
<td>56.7</td>
<td>22.7</td>
<td>930.9%</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>6.8</td>
<td>60.2</td>
<td>24.1</td>
<td>254.1%</td>
</tr>
<tr>
<td>Pafenolol</td>
<td>4.3</td>
<td>42</td>
<td>16.8</td>
<td>290.7%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>3.7</td>
<td>50.7</td>
<td>20.3</td>
<td>448.1%</td>
</tr>
<tr>
<td>Pindolol</td>
<td>7.4</td>
<td>48.5</td>
<td>19.4</td>
<td>162.2%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>7.6</td>
<td>114.8</td>
<td>45.9</td>
<td>504.2%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>37.3</td>
<td>9.3</td>
<td>3.7</td>
<td>-90.0%</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>5.9</td>
<td>280</td>
<td>112.0</td>
<td>1798.3%</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>3.8</td>
<td>205</td>
<td>82.0</td>
<td>2057.9%</td>
</tr>
<tr>
<td>Albuterol</td>
<td>7.8</td>
<td>39.2</td>
<td>15.7</td>
<td>101.0%</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>37.9</td>
<td>53.8</td>
<td>21.5</td>
<td>-43.2%</td>
</tr>
</tbody>
</table>

Figure 9.15. Predicted Human $CL_{tot}$ from Rat PK vs. Observed Human $CL_{tot}$

- **Line of identity**
- **Line with slope = 0.5**
- **Line with slope = 2.0**
Table 9.20. LBF Method using Dog PK for β-ARLs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL&lt;sub&gt;tot&lt;/sub&gt; [ml/min/kg]</th>
<th>Observed Dog CL&lt;sub&gt;tot&lt;/sub&gt; [ml/min/kg]</th>
<th>Predicted Human CL&lt;sub&gt;tot&lt;/sub&gt; [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF (ml/min/kg)</td>
<td>21</td>
<td>30</td>
<td>1.8</td>
<td>-39.9%</td>
</tr>
<tr>
<td>Xamoterol</td>
<td>3.0</td>
<td>4.49</td>
<td>1.8</td>
<td>-39.9%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>13.6</td>
<td>50.3</td>
<td>20.1</td>
<td>47.9%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>2.2</td>
<td>4.5</td>
<td>1.8</td>
<td>-18.2%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2.4</td>
<td>4.3</td>
<td>1.7</td>
<td>-28.3%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>10.8</td>
<td>35.8</td>
<td>14.3</td>
<td>32.6%</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>2.2</td>
<td>33.3</td>
<td>13.3</td>
<td>505.5%</td>
</tr>
<tr>
<td>Nafetolol</td>
<td>19.6</td>
<td>30.4</td>
<td>12.2</td>
<td>-38.0%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>3.7</td>
<td>7.0</td>
<td>2.8</td>
<td>-24.3%</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>4.6</td>
<td>46.2</td>
<td>18.5</td>
<td>301.7%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>7.6</td>
<td>26.3</td>
<td>10.5</td>
<td>38.4%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>37.3</td>
<td>82.5</td>
<td>33.0</td>
<td>-11.5%</td>
</tr>
<tr>
<td>Epanolol</td>
<td>26.8</td>
<td>2.0</td>
<td>0.8</td>
<td>-97.0%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>285</td>
<td>355</td>
<td>142.0</td>
<td>-50.2%</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>3.8</td>
<td>20</td>
<td>8.0</td>
<td>110.5%</td>
</tr>
<tr>
<td>Albuterol</td>
<td>7.8</td>
<td>12.6</td>
<td>5.0</td>
<td>-35.4%</td>
</tr>
</tbody>
</table>

Figure 9.16. Predicted Human CL<sub>tot</sub> from Dog PK vs. Observed Human CL<sub>tot</sub>
Table 9.21. LBF Method using Rat and Dog PK for β-ARLs (Complete Dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (± SE)</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>CLₜₜ</td>
<td>17</td>
<td>430 (± 151)</td>
<td>741</td>
<td>-0.29 (± 0.29)</td>
<td>0.06</td>
<td>8/17 (47 %)</td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>CLₜₜ</td>
<td>15</td>
<td>144 (± 68)</td>
<td>292</td>
<td>0.63 (± 0.22)</td>
<td>0.38</td>
<td>10/15 (67 %)</td>
</tr>
</tbody>
</table>

Table 9.22. LBF method using rat and dog PK (reduced dataset excluding nafetolol, epanolol, landiolol, esmolol and fenoterol)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (± SE)</th>
<th>r²</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>CLₜₜ</td>
<td>15</td>
<td>474 (± 167)</td>
<td>784</td>
<td>-0.12 (± 0.29)</td>
<td>0.006</td>
<td>5/15 (33 %)</td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>CLₜₜ</td>
<td>11</td>
<td>251 (± 91)</td>
<td>382</td>
<td>0.95 (± 0.39)</td>
<td>0.39</td>
<td>8/11 (73 %)</td>
</tr>
</tbody>
</table>
Table 9.23. LBF method using rat PK for CL$_{\text{tot}}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL$_{\text{tot}}$ (ml/min/kg)</th>
<th>Observed Rat CL$_{\text{tot}}$ (ml/min/kg)</th>
<th>Predicted Human CL$_{\text{tot}}$ from rat (ml/min/kg)</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF</td>
<td>21</td>
<td>50</td>
<td>6.64</td>
<td>-44.7%</td>
</tr>
<tr>
<td>Carteolol</td>
<td>12</td>
<td>16.6</td>
<td>6.64</td>
<td>-44.7%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>181.3</td>
<td>490.9</td>
<td>196.36</td>
<td>8.3%</td>
</tr>
<tr>
<td>Sotalol</td>
<td>2.2</td>
<td>23.6</td>
<td>9.44</td>
<td>329.1%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2.48</td>
<td>33.7</td>
<td>13.48</td>
<td>443.5%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>11.8</td>
<td>80.1</td>
<td>32.04</td>
<td>171.5%</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>9.2</td>
<td>66.3</td>
<td>26.52</td>
<td>188.3%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5.3</td>
<td>59.3</td>
<td>23.72</td>
<td>347.5%</td>
</tr>
<tr>
<td>Pindolol</td>
<td>17.4</td>
<td>91.9</td>
<td>36.76</td>
<td>111.3%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>39</td>
<td>9.7</td>
<td>3.88</td>
<td>-90.1%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>464.2</td>
<td>483</td>
<td>193.2</td>
<td>-58.4%</td>
</tr>
</tbody>
</table>

Figure 9.17. Predicted Human CL$_{\text{tot}}$ from Rat PK vs. Observed Human CL$_{\text{tot}}$
Table 9.24. LBF method using dog PK for CL\textsubscript{tot} \textsuperscript{u}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL\textsubscript{tot} \textsuperscript{u} [ml/min/kg]</th>
<th>Observed Dog CL\textsubscript{tot} \textsuperscript{u} [ml/min/kg]</th>
<th>Predicted Human CL\textsubscript{tot} \textsuperscript{u} from dog [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF (ml/min/kg)</td>
<td>21</td>
<td>30</td>
<td>260.6</td>
<td>43.7%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>181.3</td>
<td>390.9</td>
<td>43.7%</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>2.2</td>
<td>4.6</td>
<td>3.07</td>
<td>39.4%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5.3</td>
<td>10</td>
<td>6.7</td>
<td>25.8%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>39</td>
<td>100.6</td>
<td>67.1</td>
<td>72.0%</td>
</tr>
</tbody>
</table>

Figure 9.18. Predicted Human CL\textsubscript{tot} \textsuperscript{u} from Dog PK vs. Observed Human CL\textsubscript{tot} \textsuperscript{u}
### Table 9.25. LBF method using rat and dog PK for CL$_{tot}^u$ (Complete dataset)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r$^2$</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>CL$_{tot}^u$</td>
<td>10</td>
<td>141 (± 60)</td>
<td>228</td>
<td>0.63 (± 0.22)</td>
<td>0.38</td>
<td>2/10 (20 %)</td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>CL$_{tot}^u$</td>
<td>4</td>
<td>45.2 (± 9.7)</td>
<td>48.2</td>
<td>1.03 (± 0.04)</td>
<td>0.99</td>
<td>4/4 (100 %)</td>
</tr>
</tbody>
</table>

### Table 9.26. LBF method using rat and dog PK for CL$_{tot}^u$ (reduced dataset excluding nafetolol, epanolol, landiolol, esmolol and fenoterol)

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r$^2$</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>CL$_{tot}^u$</td>
<td>8</td>
<td>194 (± 60)</td>
<td>251</td>
<td>0.50 (± 0.19)</td>
<td>0.45</td>
<td>2/8 (25 %)</td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>CL$_{tot}^u$</td>
<td>3</td>
<td>36 (± 5)</td>
<td>37</td>
<td>1.03 (± 0.04)</td>
<td>0.99</td>
<td>3/3 (100 %)</td>
</tr>
</tbody>
</table>
9.1.3.3.2. LBF method using rat and dog PK for $CL_{nonren}$ and $CL_{nonren}^u$

Table 9.27 and 9.28 show the observed human PK parameters and predicted human PK parameters from rat and dog PK. Table 9.29-9.30 and Figure 9.19 and 9.20 shows that LBF method using dog PK data predicted $CL_{nonren}$ more accurately and precisely.

Table 9.29 indicate that when $CL_{tot}$ was corrected for PPB, lower % MPE and % RMSE were obtained for predictions from dog PK. PPB correction for $CL_{tot}$ increased $r^2$ value indicating improvement in the goodness of fit. None of the compounds were in 0.5-2.0 fold range for predictions using rat PK. From dog PK, only 3 out of 9 $\beta$-ARLs (33 %) showed predicted $CL_{nonren}$ in 0.5-2 fold error range while 2 out of 3 $\beta$-ARLs (67 %) showed predicted $CL_{nonren}^u$ in 0.5-2 fold error range.
Table 9.27. LBF method using rat PK for $\text{CL}_{\text{nonren}}$ and $\text{CL}_{\text{nonren}}^u$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human $\text{CL}_{\text{nonren}}$ [ml/min/kg]</th>
<th>Observed Human $\text{CL}_{\text{nonren}}^u$ [ml/min/kg]</th>
<th>Observed Rat $\text{CL}_{\text{nonren}}$ [ml/min/kg]</th>
<th>Observed Rat $\text{CL}_{\text{nonren}}^u$ [ml/min/kg]</th>
<th>Predicted Human $\text{CL}_{\text{nonren}}$ [ml/min/kg]</th>
<th>Predicted Human $\text{CL}_{\text{nonren}}^u$ [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>0.5</td>
<td>0.5</td>
<td>5.8</td>
<td>6.1</td>
<td>2.3</td>
<td>2.44</td>
<td>338%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.1</td>
<td>0.1</td>
<td>10</td>
<td>10.1</td>
<td>4.0</td>
<td>4.04</td>
<td>3900%</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>1.5</td>
<td>2.5</td>
<td>47</td>
<td>47</td>
<td>18.8</td>
<td>18.8</td>
<td>1153%</td>
</tr>
<tr>
<td>Acebutalol</td>
<td>4.0</td>
<td>5.4</td>
<td>45</td>
<td>49.6</td>
<td>18.0</td>
<td>19.82</td>
<td>350%</td>
</tr>
<tr>
<td>Acebutalol</td>
<td>4.0</td>
<td>5.4</td>
<td>45</td>
<td>49.6</td>
<td>18.0</td>
<td>19.82</td>
<td>350%</td>
</tr>
<tr>
<td>Pafenolol</td>
<td>1.9</td>
<td>2.0</td>
<td>35.5</td>
<td>41.5</td>
<td>14.2</td>
<td>16.61</td>
<td>914%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.4</td>
<td>2.0</td>
<td>35.5</td>
<td>41.5</td>
<td>14.2</td>
<td>16.61</td>
<td>914%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>34.4</td>
<td>35.9</td>
<td>7.38</td>
<td>7.7</td>
<td>3.0</td>
<td>3.07</td>
<td>-91%</td>
</tr>
</tbody>
</table>

Figure 9.19. Predicted Human $\text{CL}_{\text{nonren}}$ from Rat PK vs. Observed Human $\text{CL}_{\text{nonren}}$
Figure 9.20. Predicted Human CL_{nonren} u from Rat PK vs. Observed Human CL_{nonren} u
Table 9.28. LBF method using dog PK for CL\textsubscript{nonren} and CL\textsubscript{nonren} \textasciitilde

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL\textsubscript{nonren} [ml/min/kg]</th>
<th>Observed CL\textsubscript{nonren} \textasciitilde [ml/min/kg]</th>
<th>Observed Dog CL\textsubscript{nonren} [ml/min/kg]</th>
<th>Observed Dog CL\textsubscript{nonren} \textasciitilde [ml/min/kg]</th>
<th>Predicted Human CL\textsubscript{nonren} [ml/min/kg]</th>
<th>Predicted Human CL\textsubscript{nonren} \textasciitilde [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>0.5</td>
<td>0.5</td>
<td>0.29</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>-64%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.1</td>
<td>0.1</td>
<td>0.70</td>
<td>0.71</td>
<td>0.5</td>
<td>0.47</td>
<td>367% 358%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>9.2</td>
<td>10.0</td>
<td>33.8</td>
<td>22.5</td>
<td>19.2</td>
<td>19.3</td>
<td>145%</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>1.5</td>
<td></td>
<td>28.8</td>
<td></td>
<td>19.2</td>
<td></td>
<td>1180%</td>
</tr>
<tr>
<td>Nafetolol</td>
<td>16.9</td>
<td></td>
<td>28.9</td>
<td></td>
<td>19.3</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.4</td>
<td>2.0</td>
<td>4.8</td>
<td>6.9</td>
<td>3.2</td>
<td>3.2</td>
<td>129% 61%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>34.4</td>
<td>35.9</td>
<td>82.02</td>
<td>100.0</td>
<td>54.7</td>
<td>54.68</td>
<td>59% 52%</td>
</tr>
<tr>
<td>Epanolol</td>
<td>19.8</td>
<td></td>
<td>14.54</td>
<td></td>
<td>9.7</td>
<td></td>
<td>-51%</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>1.5</td>
<td>1.9</td>
<td>2.2</td>
<td></td>
<td>1.5</td>
<td></td>
<td>-2%</td>
</tr>
</tbody>
</table>

Figure 9.21. Predicted Human CL\textsubscript{nonren} from Dog PK vs. Observed Human CL\textsubscript{nonren}
Figure 9.22. Predicted Human CL\textsubscript{nonren} \textsuperscript{u} from Dog PK vs. Observed Human CL\textsubscript{nonren} \textsuperscript{u}

Table 9.29. LBF method using rat and dog PK for CL\textsubscript{nonren} and CL\textsubscript{nonren} \textsuperscript{u}

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope</th>
<th>r\textsuperscript{2}</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBF method (from rat PK)</td>
<td>CL\textsubscript{nonren}</td>
<td>9</td>
<td>987 (± 510 %)</td>
<td>1592</td>
<td>-0.20 (± 0.24)</td>
<td>0.12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CL\textsubscript{nonren} \textsuperscript{u}</td>
<td>5</td>
<td>1019 (± 714 %)</td>
<td>1755</td>
<td>-0.16 (± 0.30)</td>
<td>0.09</td>
<td>0</td>
</tr>
<tr>
<td>LBF method (from dog PK)</td>
<td>CL\textsubscript{nonren}</td>
<td>9</td>
<td>197 (± 130 %)</td>
<td>418</td>
<td>1.23 (± 0.30)</td>
<td>0.70</td>
<td>3/9 (33 %)</td>
</tr>
<tr>
<td></td>
<td>CL\textsubscript{nonren} \textsuperscript{u}</td>
<td>3</td>
<td>157 (± 101 %)</td>
<td>212</td>
<td>1.52 (± 0.004)</td>
<td>0.99</td>
<td>2/3 (67 %)</td>
</tr>
</tbody>
</table>
9.1.3.4. GFR ratio method

9.1.3.4.1. GFR ratio method using rat and dog PK data

Table 9.30 and 9.31 show the observed human PK parameters and predicted human PK parameters from rat and dog PK. Table 9.32 and Figure 9.23-9.26 shows that GFR ratio method using dog PK data predicted $\text{CL}_{\text{ren}}$ and $\text{CL}_{\text{ren}}^{u}$ more accurately and precise. There was an under-prediction when dog PK was used as indicated by the negative % MPE values while over-prediction when rat PK was used.

Table 9.32 indicate that when $\text{CL}_{\text{ren}}$ was corrected for PPB, lower % MPE and % RMSE were obtained for predictions from dog PK. PPB correction for $\text{CL}_{\text{tot}}$ increased $r^2$ value indicating improvement in the goodness of fit. From rat PK, only 1 out of 7 $\beta$-ARLs (14 %) showed predicted $\text{CL}_{\text{ren}}$ in 0.5-2 fold error range while 2 out of 5 $\beta$-ARLs (40 %) showed predicted $\text{CL}_{\text{ren}}^{u}$ in 0.5-2 fold error range. From dog PK, only 3 out of 9 $\beta$-ARLs (33 %) showed predicted $\text{CL}_{\text{ren}}$ in 0.5-2 fold error range while 1 out of 3 $\beta$-ARLs (33 %) showed predicted $\text{CL}_{\text{ren}}^{u}$ in 0.5-2 fold error range.
Table 9.30. GFR ratio method using rat PK for CL\textsubscript{ren} and CL\textsubscript{ren}^u

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL\textsubscript{ren} [ml/min/kg]</th>
<th>Observed Human CL\textsubscript{ren}^u [ml/min/kg]</th>
<th>Predicted Human CL\textsubscript{ren} [ml/min/kg]</th>
<th>Predicted Human CL\textsubscript{ren}^u [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>1.67</td>
<td>1.69</td>
<td>5.4</td>
<td>5.73</td>
<td>225.7% 239.5%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2.3</td>
<td>2.37</td>
<td>8.0</td>
<td>8.04</td>
<td>245.9% 239.6%</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>0.7</td>
<td>3.77</td>
<td>3.3</td>
<td>3.3</td>
<td>371.1%</td>
</tr>
<tr>
<td>Acebutalol</td>
<td>2.8</td>
<td>7.1</td>
<td>5.2</td>
<td>5.69</td>
<td>84.6% 51.0%</td>
</tr>
<tr>
<td>Pafenolol</td>
<td>2.4</td>
<td>0.7</td>
<td>7.1</td>
<td>0.7</td>
<td>197.5%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2.3</td>
<td>3.26</td>
<td>5.2</td>
<td>6.04</td>
<td>124.7% 85.3%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>2.93</td>
<td>3.06</td>
<td>0.7</td>
<td>0.70</td>
<td>-77.0% -77.2%</td>
</tr>
</tbody>
</table>

Figure 9.23. Predicted Human CL\textsubscript{ren} from Rat PK vs. Observed Human CL\textsubscript{ren}

- Line of identity
- Line with slope = 0.5
- Line with slope = 2.0
Figure 9.24. Predicted Human $\text{CL}_{\text{ren}}$ from Rat PK vs. Observed Human $\text{CL}_{\text{ren}}$

- **Line of identity**
- **Line with slope = 0.5**
- **Line with slope = 2.0**
Table 9.31. GFR ratio method using dog PK for $CL_{\text{ren}}$ and $CL_{\text{ren}}^u$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human $CL_{\text{ren}}$ [ml/min/kg]</th>
<th>Observed Human $CL_{\text{ren}}^u$ [ml/min/kg]</th>
<th>Predicted Human $CL_{\text{ren}}$ [ml/min/kg]</th>
<th>Predicted Human $CL_{\text{ren}}^u$ [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>1.67</td>
<td>1.69</td>
<td>1.2</td>
<td>1.2</td>
<td>-26.9%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>2.3</td>
<td>2.37</td>
<td>1.0</td>
<td></td>
<td>-54.6%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.6</td>
<td>1.74</td>
<td>0.6</td>
<td></td>
<td>-63.8%</td>
</tr>
<tr>
<td>Amosulalol</td>
<td>0.7</td>
<td></td>
<td>1.3</td>
<td></td>
<td>86.4%</td>
</tr>
<tr>
<td>Nafetolol</td>
<td>2.7</td>
<td></td>
<td>0.4</td>
<td></td>
<td>-83.9%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2.3</td>
<td>3.26</td>
<td>0.6</td>
<td>0.9</td>
<td>-72.3%</td>
</tr>
<tr>
<td>Landiolol</td>
<td>2.93</td>
<td>3.06</td>
<td>0.1</td>
<td>0.2</td>
<td>-95.2%</td>
</tr>
<tr>
<td>Epanolol</td>
<td>6.97</td>
<td></td>
<td>0.1</td>
<td></td>
<td>-98.1%</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>1.91</td>
<td>2.37</td>
<td>2.4</td>
<td></td>
<td>27.5%</td>
</tr>
</tbody>
</table>

Figure 9.25. Predicted Human $CL_{\text{ren}}$ from Dog PK vs. Observed Human $CL_{\text{ren}}$
Figure 9.26. Predicted Human $\text{CL}_{\text{ren}}^u$ from Dog PK vs. Observed Human $\text{CL}_{\text{ren}}^u$
Table 9.32. GFR ratio method using rat and dog PK for $\text{CL}_{\text{ren}}$ and $\text{CL}_{\text{ren}}^u$

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>$r^2$</th>
<th>No. of compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR ratio method (from rat PK)</td>
<td>$\text{CL}_{\text{ren}}$</td>
<td>7</td>
<td>168 (± 54%)</td>
<td>213</td>
<td>0.02 (± 1.42)</td>
<td>0.00002</td>
<td>1/7 (14 %)</td>
</tr>
<tr>
<td></td>
<td>$\text{CL}_{\text{ren}}^u$</td>
<td>5</td>
<td>108 (± 60%)</td>
<td>162</td>
<td>-0.81 (± 1.88)</td>
<td>0.06</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>GFR ratio method (from dog PK)</td>
<td>$\text{CL}_{\text{ren}}$</td>
<td>9</td>
<td>-42 (± 21%)</td>
<td>72</td>
<td>-0.22 (± 0.13)</td>
<td>0.29</td>
<td>3/9 (33 %)</td>
</tr>
<tr>
<td></td>
<td>$\text{CL}_{\text{ren}}^u$</td>
<td>3</td>
<td>-64 (± 20%)</td>
<td>70</td>
<td>-0.39 (± 0.46)</td>
<td>0.42</td>
<td>1/3 (33 %)</td>
</tr>
</tbody>
</table>
Table 9.33. Summary table for prediction of $\text{CL}_{\text{tot}}$, $\text{CL}_{\text{ren}}$ and $\text{CL}_{\text{nonren}}$ (excluding drugs undergoing extrahepatic metabolism)

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of compounds</th>
<th>Parameter</th>
<th>Prediction errors</th>
<th>Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In the 0.5-2 fold error range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parameter</td>
<td>n</td>
<td>%MPE</td>
</tr>
<tr>
<td>One species approach (from rat data)</td>
<td>2/15 (15%)</td>
<td>$\text{CL}_{\text{tot}}$</td>
<td>15</td>
<td>1452 (± 375 %)</td>
</tr>
<tr>
<td>One species approach (from dog data)</td>
<td>6/16 (38 %)</td>
<td>$\text{CL}_{\text{tot}}$</td>
<td>16</td>
<td>263 (± 109 %)</td>
</tr>
<tr>
<td>Two species approach</td>
<td>6/9 (67 %)</td>
<td>$\text{CL}_{\text{tot}}$</td>
<td>9</td>
<td>192 (± 139)</td>
</tr>
<tr>
<td>LBF method (from rat data)</td>
<td>5/15 (33 %)</td>
<td>$\text{CL}_{\text{tot}}$</td>
<td>15</td>
<td>474 (± 167)</td>
</tr>
<tr>
<td>LBF method (from dog data)</td>
<td>8/11 (73 %)</td>
<td>$\text{CL}_{\text{tot}}$</td>
<td>11</td>
<td>251 (± 91)</td>
</tr>
<tr>
<td>LBF method (from rat data)</td>
<td>0</td>
<td>$\text{CL}_{\text{nonren}}$</td>
<td>9</td>
<td>987 (± 510 %)</td>
</tr>
<tr>
<td>LBF method (from dog data)</td>
<td>3/9 (33 %)</td>
<td>$\text{CL}_{\text{nonren}}$</td>
<td>9</td>
<td>197 (± 130 %)</td>
</tr>
<tr>
<td>GFR ratio method (from rat data)</td>
<td>1/7 (14 %)</td>
<td>$\text{CL}_{\text{ren}}$</td>
<td>7</td>
<td>168 (± 54 %)</td>
</tr>
<tr>
<td>GFR ratio method (from dog data)</td>
<td>3/9 (33 %)</td>
<td>$\text{CL}_{\text{ren}}$</td>
<td>9</td>
<td>-42 (± 21%)</td>
</tr>
</tbody>
</table>
Table 9.34. Summary table for prediction of $CL_{\text{tot}}^u$, $CL_{\text{ren}}^u$ and $CL_{\text{nonren}}^u$ (excluding drugs undergoing extrahepatic metabolism).

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE</th>
<th>%RMSE</th>
<th>Slope</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach (from rat)</td>
<td>1/9 (11 %)</td>
<td>$CL_{\text{tot}}^u$</td>
<td>9</td>
<td>1654 (+1027 %)</td>
<td>3342</td>
<td>0.58 (+0.30)</td>
<td>0.34</td>
</tr>
<tr>
<td>One species approach (from dog)</td>
<td>3/3 (100 %)</td>
<td>$CL_{\text{tot}}^u$</td>
<td>3</td>
<td>164 (+37 %)</td>
<td>172</td>
<td>0.58 (+0.30)</td>
<td>0.34</td>
</tr>
<tr>
<td>LBF method (from rat)</td>
<td>2/8 (25 %)</td>
<td>$CL_{\text{tot}}^u$</td>
<td>8</td>
<td>194 (+60 %)</td>
<td>251</td>
<td>0.50 (+0.19)</td>
<td>0.45</td>
</tr>
<tr>
<td>LBF method (from dog)</td>
<td>3/3 (100 %)</td>
<td>$CL_{\text{nonren}}^u$</td>
<td>3</td>
<td>36 (+5)</td>
<td>37</td>
<td>1.03 (+0.004)</td>
<td>0.99</td>
</tr>
<tr>
<td>LBF method (from rat)</td>
<td>0</td>
<td>$CL_{\text{nonren}}^u$</td>
<td>5</td>
<td>1019 (+714 %)</td>
<td>1755</td>
<td>-0.16 (+0.30)</td>
<td>0.09</td>
</tr>
<tr>
<td>LBF method (from dog)</td>
<td>2/3 (67 %)</td>
<td>$CL_{\text{nonren}}^u$</td>
<td>3</td>
<td>157 (+101 %)</td>
<td>212</td>
<td>1.52 (+0.004)</td>
<td>0.99</td>
</tr>
<tr>
<td>GFR ratio method (from rat)</td>
<td>2/5 (40 %)</td>
<td>$CL_{\text{ren}}^u$</td>
<td>5</td>
<td>108 (+60 %)</td>
<td>162</td>
<td>-0.81 (+1.88)</td>
<td>0.06</td>
</tr>
<tr>
<td>GFR ratio method (from dog)</td>
<td>1/3 (33 %)</td>
<td>$CL_{\text{ren}}^u$</td>
<td>3</td>
<td>-64 (+20 %)</td>
<td>70</td>
<td>-0.39 (+0.46)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Table 9.35. Summary table for prediction of Vd<sub>ss</sub> and Vd<sub>ss,u</sub> (excluding drugs undergoing extrahepatic metabolism)

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE</th>
<th>%RMSE</th>
<th>Slope</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach (from rat data)</td>
<td>4/15 (27 %)</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>15</td>
<td>423 (± 208 %)</td>
<td>887</td>
<td>0.01 (± 0.32)</td>
<td>0.0001</td>
</tr>
<tr>
<td>One species approach (from dog data)</td>
<td>8/12 (67 %)</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>12</td>
<td>-175 (± 119 %)</td>
<td>435</td>
<td>0.01 (± 0.32)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Two species approach</td>
<td>6/9 (67 %)</td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt;</td>
<td>9</td>
<td>147 (±121)</td>
<td>372</td>
<td>0.24 (± 0.42)</td>
<td>0.04</td>
</tr>
<tr>
<td>One species approach (from rat) Unbound values</td>
<td>5/9 (55 %)</td>
<td>Vd&lt;sub&gt;ss,u&lt;/sub&gt;</td>
<td>9</td>
<td>397 (± 343 %)</td>
<td>1048</td>
<td>0.98 (± 0.10)</td>
<td>0.99</td>
</tr>
<tr>
<td>One species approach (from dog) Unbound values</td>
<td>3/3 (100 %)</td>
<td>Vd&lt;sub&gt;ss,u&lt;/sub&gt;</td>
<td>3</td>
<td>-19.2 (± 8%)</td>
<td>22</td>
<td>0.98 (± 0.10)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
9.1.4. Discussion

There were large differences in reported, BW-corrected, CL_{tot} and V_dss values across species (range: 6 to 80-fold, 3 to 50-fold, respectively) for β-ARLs. PPB was found to be similar across different species: only propranolol (human f_u = 0.08, rat f_u = 0.11) and oxprenolol (human f_u 0.80, rat f_u = 0.42) showed major species differences in the f_u. Based on the comparison of CL_{tot} to the LBF in each species, hepatic clearance categorization was done for each drug in each species. Hydrophilic β-ARLs xamoterol, sotalol, atenolol and bisoprolol were found to be low clearance in dog and human. All the β-ARLs (except timolol and landiolol) were found to be high clearance in rats. This showed that hepatic extraction ratios for β-ARL are species dependent and lower in man and big animals than in small animals. Smaller species deliver drugs more frequently and faster to the eliminating organs, eliminate the drugs, particularly those with high clearances, more rapidly. This finding was similar to the findings from the present research for the interspecies scaling of opioids and interspecies scaling of anesthetic drugs. Evans et al categorized a dataset of 21 compounds (MW > 300 g/mol or clog P > 3) into low clearance (< 30 % LBF), intermediate clearance (30 %-70 % LBF) and high clearance (> 70 % LBF). It was found that 40 % of these compounds, though high clearance in the rat, were not high clearance in humans. Most of the β-ARL are metabolized by CYP450 (mainly CYP2D6) and UGTs. Some β-ARLs like esmolol and landiolol are esters and are known/suspected to undergo extra-hepatic metabolism by nonspecific esterases in blood and tissues. Quon et al found that blood esmolol esterase activity is higher in rats and dogs as compared to humans. β-agonist like fenoterol shows CL_{tot} more than LBF in both, humans and rats, indicating that it might
undergo extra-hepatic metabolism. Fenoterol is an analog of catecholamines like epinephrine or norepinephrine and catecholamines are known to undergo metabolism by catechol O-methyl transferases (COMT), which is present in several tissues like brain, liver, kidneys and gastrointestinal tract. Human, hamster, guinea pig, dog, rat and monkey erythrocytes contain some COMT activity, which is higher in rats and quite low in humans. De Wazier et al found that hepatic enzyme levels of CYP1A, CYP2C and CYP3A in rats were approximately 28, 638 and 165 pmol/gm microsomal protein while Guengerich et al reported corresponding values for humans as 37, 55, 87 pmol/gm of microsomal protein (Table 8.2). Similarly, Clarke et al found that there were interspecies differences in UGT activities in rat and humans. Soars et al looked at in-vitro glucuronidation of a range of structurally diverse chemicals in hepatic and renal microsomes from human and dogs and found that glucuronidation was several fold more rapid in dog liver microsomes than human liver microsomes.

CL\textsubscript{tot} (mean slope: 0.62, 0.46-1.31) and V\textsubscript{dss} (mean slope: 0.89, 0.50-1.11) scaled well with BW, regardless of the number of species. Sotalol and atenolol showed their allometric coefficients to be very low (< 0.60) for n =3 as well as for n = all available animals for CL\textsubscript{tot}. Amosulalol, bisoprolol, carvedilol and betaxolol also showed a very low allometric coefficient (< 0.60). Out of these β-ARLs showing allometric exponents < 0.60 for CL\textsubscript{tot}, CL\textsubscript{ren} information across species was available on only sotalol, atenolol and amosulalol, hence, for these drugs, AS was carried out for CL\textsubscript{ren} too. When CL\textsubscript{ren} was scaled with body BW for sotalol, atenolol and amosulalol, low allometric exponents were obtained. Sotalol and atenolol, both, are hydrophilic drugs, show very high f\textsubscript{u} values (> 90 %) and f\textsubscript{c} values (> 60-90 %) across different species like rat, dog, rabbit and humans. CL\textsubscript{ren} for sotalol was
found to be higher than GFR in rat and dog, while equivalent to GFR in humans, indicating that it might undergo net tubular secretion in rat and dog while net filtration in humans. 

$CL_{\text{ren}}$ of atenolol was found to be more than GFR in rat and human, indicating net tubular secretion in both the species. Amosulalol showed $f_e < 20\%$ in mouse, rat, dog, monkey and humans while $f_e = 34\%$ in human. Due to lack of $f_{u}$ information for amosulalol in different species, mechanism at the kidneys cannot be known. Renal blood flow (RBF) and GFR (ml/min/kg) decrease as the animal size increases in an allometric manner. The exponent values were 0.84 for RBF and 0.78 for GFR $^4$ were steeper than the slopes obtained from allometric relationships for $CL_{\text{tot}}$ and $CL_{\text{ren}}$ for sotalol, atenolol, bisoprolol, carvedilol, amolsulalol and betaxolol. This may be due to the possible involvement of drug transporters in the disposition of $\beta$-blockers. Transporters like OCT and PGP are known to be involved in the elimination of $\beta$-blockers.$^{86,87}$ Mahmood et al$^{43}$ tried to predict $CL_{\text{tot}}, CL_{\text{ren}}$ and $V_{dss}$ in humans from animal data for ten drugs which were mainly renally secreted in humans. The exponents for simple allometry for $CL_{\text{tot}}$ ranged from 0.71-0.93, however, ofloxacin, a suspected OAT substrate, showed a low exponent of 0.583. Sawada et al$^{108}$ predicted the disposition of six $\beta$-lactam antibiotics using mouse, rat, rabbit, dog and human PK data. The log-log relationship between clearances ($CL_{\text{tot}}$ and $CL_{\text{ren}}$) and BW showed low slopes, 0.405-0.662 ($n = 5$, mean: 0.574) for $CL_{\text{tot}}$ and 0.429-0.713 ($n = 5$, mean: 0.628) for $CL_{\text{ren}}$. Literature studies show that $\beta$-lactam antibiotics like cephalosporins and penicillins show net secretion and it is has been reported that some cephalosporins interact with hOAT1, hOAT2 and hOAT3.$^{22,93,94}$ Jariyawat et al$^{88}$ showed inhibition of p-aminohippurate transport via rat-OAT1 by penicillins and cephalosporins. The relation between $V_{dss}$ and BW showed good correlation, but the allometric exponents for amosulalol, carvedilol and betaxolol were found
to be low (range: 0.50-0.77). Similar low slopes were obtained for morphine glucuronides during interspecies scaling of opioids. This might be due to the polar nature of compounds which limits their distribution. Mahmood et al\textsuperscript{43} tried to predict $V_{dss}$ in humans from animal data for ten drugs which were mainly renally secreted in humans and found a very good correlation between $V_{ss}$ and body weight and exponents were found be in the range 0.88-1.35.

Various prediction methods like one-species BW scaling, two-species (rat, dog) BW scaling, LBF method and GFR ratio methods were used to predict total and unbound CL\textsubscript{tot}, $CL_{ren}$, $CL_{nonren}$ and $V_{dss}$. Table 9.33-9.35 shows the summary for the prediction of PK variables. Table 9.36 gives the best prediction methods for total and unbound PK parameters. Overall, one-species-LBF methods provided acceptable predictions for $CL_{tot}$ and $CL_{tot}^u$ and one species – BW method for $V_{dss}$ and $V_{dss}^u$. Thus, the use of three or more species does not appear justified. This suggests a single, non-rat species in preclinical PK may be most informative. Similar conclusion was made by by Tang et al\textsuperscript{5} when one- or two- species based methods were used to predict human $CL_{tot}$ from rat, dog and monkey in a 26-Wyeth compound test dataset using a 102-compound training dataset. In a study on the prediction of human PK for 103-compound dataset of structurally diverse compounds; it was found that allometric scaling approaches using two species were less successful at predicting $CL_{tot}$ than LBF method in an individual species.\textsuperscript{13} Scaling from a nonrodent species like monkey showed that LBF method was the most accurate when 124 compound dataset of structurally diverse compounds was studied.\textsuperscript{45} Ward et al\textsuperscript{109} showed that single species like monkey gave accurate predictions for $V_{dss}$ as compared to predictions from two or three species for a 103 compound diverse dataset. Hosea et al\textsuperscript{56} conducted a retrospective analysis using 50
proprietary compounds for which oral single dose human PK data was available and concluded that the use of single species lead to more accurate predictions than using multiple species and use of unbound concentrations resulted in accurate predictions.

In the present research on β-ARLs, in general, the fu correction of CL\text{tot} and Vd\text{ss} increased the r² value indicating improvement in the goodness of fit; lowered %MPE and %RMSE, thus, improving predictability; and resulted in predictions within acceptable range for a larger number of compounds. A study on 36 marketed oral drugs showed that Vd\text{ss} estimated in rat and dog when corrected for PPB, predicted human Vd\text{ss} successfully with 73 % of the compounds within 2-fold error range. Sawada et al reported PPB values for 10 basic drugs in different species and found that the interspecies differences in distribution maybe attributed to the differences in fu. Feng et al predicted human systemic CL\text{tot} for eight Parke Davis compounds and 26 literature drugs and it was found that in general, human CL\text{tot} was predicted more accurately with reduction in the average fold error. CL\text{ren} and CL\text{ren} \text{u} were under-predicted, possibly due the associated interspecies differences in the metabolic pathways, renal and hepatobiliary drug transporters and partly due to lack of f\text{c} and f\text{u} data on all compounds across all the species. Similar findings are reported by Mahmood et al in a study which predicted CL\text{tot}, CL\text{ren} and CL\text{nonren} in humans from animal data for ten drugs which were mainly renally secreted in humans. McGinnity et al showed that GFR ratio method gave accurate predictions for compounds even when their CL\text{ren} > GFR.

For most β-ARLs, body size accounted for most of the observed variability (r² > 0.80) in systemic PK variables in the animal species studied. For β-ARLs, the dog was found to be the species giving the best prediction of CL\text{tot}, Vd\text{ss}, CL\text{ren}, CL\text{nonren}, CL\text{tot} \text{u}, Vd\text{ss} \text{u}, CL\text{ren} \text{u} and CL\text{nonren} \text{u}. Similar conclusions were obtained from the interspecies scaling study on opioids.
<table>
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<tr>
<th>PK variable</th>
<th>Method</th>
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<th>%RMSE</th>
<th>% compounds in acceptable range</th>
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<td>212</td>
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CHAPTER 10. INTERSPECIES SCALING OF β-LAs

10. β-lactam antibiotics

10.1. Results

10.1.1. Comparative pharmacokinetics of β-lactam antibiotics (β-LAs) across different species

Table 10.1 and 10.2 show the in-vivo, in-vitro, and estimated PK parameters for 27 β-LAs, respectively. There were large differences in reported, BW-corrected, CL_{tot} and V_{dss} values across species (range: 1 to 80-fold, 1 to 25-fold, respectively) for β-LAs. PPB was not similar across different species, with rat f_{u} accounting for only 60 % variability in human f_{u} (Table 10.3-10.4). Most of the β-LAs showed intermediate PPB (30-70 %) except cefazolin and showed f_{c} values > 50 % indicating that these drugs are mainly excreted by kidneys across different species. Human CL_{ren}^{u} values for most of the β-LAs in the dataset were higher than GFR indicating net tubular secretion in humans, however, the information on f_{u}, CL_{ren}, CL_{nonren} was available on very few β-LAs for rats and dogs, hence interspecies differences in excretion mechanism at the kidneys cannot be known.
Table 10.1. *In-vivo* PK parameters of β-LAs

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<th>Dose (mg/kg)</th>
<th>CI(_{\text{tot}}) (ml/min/kg)</th>
<th>CI(_{\text{tot}}) (ml/min)</th>
<th>Vd(_{\text{ss}}) (L/kg)</th>
<th>Vd(_{\text{ss}}) (L)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
<th>Fold range</th>
<th>COV</th>
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### Table 10.2. Estimated *in-vivo* PK parameters of β-LAs

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<td>f_e</td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt;</td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt;</td>
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<td>CL&lt;sub&gt;nonren&lt;/sub&gt;</td>
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<td>7.20</td>
<td>0.10</td>
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<tr>
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<td>Drug</td>
<td>Species</td>
<td>( f_u )</td>
<td>( \text{CL}_{\text{tot}} )</td>
<td>( \text{Vd}_{ss} )</td>
<td>( f_e )</td>
<td>( \text{CL}_{\text{ren}} )</td>
<td>( \text{CL}_{\text{ren}} )</td>
<td>( \text{CL}_{\text{ren}} )</td>
<td>( \text{CL}_{\text{nonren}} )</td>
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<tr>
<td></td>
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<td>(ml/min/kg)</td>
<td>(L/kg)</td>
<td>(%)</td>
<td>(ml/min/kg)</td>
<td>(ml/min)</td>
<td>(ml/min/kg)</td>
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<tr>
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<td>1.5</td>
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</tr>
<tr>
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<td>Rabbit</td>
<td>50.0%</td>
<td>0.2</td>
<td>0.7</td>
<td>0.2</td>
<td></td>
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<td></td>
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<td>76.1%</td>
<td>0.8</td>
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<td>Minimum</td>
<td>Dog</td>
<td>50.0%</td>
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<tr>
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<td>Rabbit</td>
<td>76.9%</td>
<td>5.0</td>
<td>60.2</td>
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<tr>
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<td>37.0</td>
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<td>2.6</td>
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<td>86</td>
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<td>Dog</td>
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<td>3.6</td>
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<tr>
<td></td>
<td>Human</td>
<td>48.5%</td>
<td>4.5</td>
<td>317.4</td>
<td>4.8</td>
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Table 10.3. Plasma protein binding across different species

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human $f_u$</th>
<th>Rat $f_u$</th>
<th>Dog $f_u$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mezlocillin</td>
<td>0.65</td>
<td>0.70</td>
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</tr>
<tr>
<td>Ticarcillin</td>
<td>0.34</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.70</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Ceftizoxime</td>
<td>0.69</td>
<td>0.68</td>
<td>0.83</td>
</tr>
<tr>
<td>Cefalexine</td>
<td>0.88</td>
<td>0.82</td>
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</tr>
<tr>
<td>Cefoxitin</td>
<td>0.48</td>
<td>0.66</td>
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</tr>
<tr>
<td>Cefazolin</td>
<td>0.10</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Cephradine</td>
<td>0.86</td>
<td>0.82</td>
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<tr>
<td>Cefalothin</td>
<td>0.29</td>
<td>0.51</td>
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<tr>
<td>Cefaloridine</td>
<td>0.63</td>
<td>0.46</td>
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Table 10.4. Regression Parameters for Human and Animal PPB Relationship

<table>
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<tr>
<th>Parameter</th>
<th>n</th>
<th>Slope</th>
<th>Confidence interval</th>
<th>$r^2$</th>
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<tbody>
<tr>
<td>Human $f_u$ vs. Rat $f_u$</td>
<td>10</td>
<td>1.02</td>
<td>(± 0.28)</td>
<td>0.62</td>
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</tbody>
</table>

Figure 10.1. Human $f_u$ vs. Rat $f_u$
10.1.2. Simple Allometry

For a set of 11 β-LAs, simple allometry was conducted using all available species and using only three species (rat, dog), both including human. Allometric plots are shown in the Appendix III (c). Table 10.5 shows the slopes for CL$_{\text{tot}}$ and Vd$_{\text{ss}}$ for β-LAs. The slopes obtained were compared with a scaling factor 0.75 for CL$_{\text{tot}}$ and 1.0 for Vd$_{\text{ss}}$. Figure 10.2-10.3 shows interspecies scaling plots for a prototypical β-LA like amoxicillin. Most of the β-LAs showed low slopes (< 0.70) for n = 3 as well as for n = all available animals for CL$_{\text{tot}}$. In general, a good correlation was obtained between the PK parameters like CL$_{\text{tot}}$ and Vd$_{\text{ss}}$ and body weight, except for few β-LAs moxalactam and ceftriaxone. PPB correction improved the good-of-fit, as indicated by the improvement in the $r^2$ value. CL$_{\text{ren}}$ information across species was available on only cefpiramide, and AS was carried out for CL$_{\text{ren}}$ for cefpiramide. Table 10.5 shows that low slopes were obtained even for CL$_{\text{ren}}$ for cefpiramide.

Overall for β-LAs, CL$_{\text{tot}}$ (mean slope: 0.65, 0.29-0.88) and Vd$_{\text{ss}}$ (mean slope: 0.95, 0.48-1.18) scaled well with BW, regardless of the number of species
Figure 10.2. Interspecies Allometric Scaling of $\text{CL}_{\text{tot}}$ for Amoxicillin

Amoxicillin

$$y = 13.608x^{0.6919}$$
$$R^2 = 0.9023$$

Figure 10.3. Interspecies Allometric Scaling of $V_{dss}$ for Amoxicillin

Amoxicillin

$$y = 0.5242x^{0.7723}$$
$$R^2 = 0.9828$$
Table 10.5. Allometric PK Scaling of β-LAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>(ml/min)</th>
<th>n</th>
<th>$r^2$</th>
<th>Slope ± SE</th>
<th>(L)</th>
<th>n</th>
<th>$r^2$</th>
<th>Slope ± SE</th>
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<td>Amoxicillin</td>
<td>$CL_{tot}$</td>
<td>4</td>
<td>0.9023</td>
<td>0.69 ± 0.16</td>
<td>$Vd_{ss}$</td>
<td>4</td>
<td>0.9828</td>
<td>0.77 ± 0.07</td>
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<td>Ticarcillin</td>
<td>$CL_{tot}$</td>
<td>3</td>
<td>0.9984</td>
<td>0.63 ± 0.02</td>
<td>$Vd_{ss}$</td>
<td>3</td>
<td>0.8835</td>
<td>0.96 ± 0.35</td>
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<tr>
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<td>$CL_{tot}^u$</td>
<td>3</td>
<td>0.9996</td>
<td>0.73 ± 0.01</td>
<td>$Vd_{ss}^u$</td>
<td>3</td>
<td>0.8837</td>
<td>1.06 ± 0.39</td>
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<tr>
<td>Cefepime</td>
<td>$CL_{tot}$</td>
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<td>0.9043</td>
<td>0.65 ± 0.15</td>
<td>$Vd_{ss}$</td>
<td>4</td>
<td>0.9793</td>
<td>0.90 ± 0.09</td>
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<tr>
<td>Moxalactam</td>
<td>$CL_{tot}$</td>
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<td>0.6369</td>
<td>0.66 ± 0.35</td>
<td>$Vd_{ss}$</td>
<td>4</td>
<td>0.9994</td>
<td>1.05 ± 0.02</td>
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<tr>
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<td>0.6676</td>
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<td>0.79 ± 0.27</td>
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<td>0.8128</td>
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<tr>
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<td>$Vd_{ss}$</td>
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<td>0.9988</td>
<td>0.84 ± 0.03</td>
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<td>5</td>
<td>0.9922</td>
<td>0.59 ± 0.03</td>
<td>$Vd_{ss}$</td>
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<td>0.9977</td>
<td>0.80 ± 0.02</td>
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<td>$CL_{tot}^u$</td>
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<td>0.9719</td>
<td>0.59 ± 0.10</td>
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<td>0.9999</td>
<td>1.02 ± 0.008</td>
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<td>0.9884</td>
<td>0.59 ± 0.05</td>
<td>$Vd_{ss}^u$</td>
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<td>0.9999</td>
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</tr>
<tr>
<td>Cefalexine</td>
<td>$CL_{tot}$</td>
<td>3</td>
<td>0.9514</td>
<td>0.81 ± 0.18</td>
<td>$Vd_{ss}$</td>
<td>3</td>
<td>0.9800</td>
<td>0.63 ± 0.09</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>$CL_{tot}$</td>
<td>4</td>
<td>0.063</td>
<td>0.29 ± 0.81</td>
<td>$Vd_{ss}$</td>
<td>4</td>
<td>0.5981</td>
<td>0.71 ± 0.41</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>$CL_{tot}$</td>
<td>4</td>
<td>0.9880</td>
<td>0.57 ± 0.04</td>
<td>$Vd_{ss}$</td>
<td>4</td>
<td>0.7685</td>
<td>0.48 ± 0.19</td>
</tr>
<tr>
<td>Cefpiramide</td>
<td>$CL_{tot}$</td>
<td>3</td>
<td>0.9029</td>
<td>0.61 ± 0.20</td>
<td>$Vd_{ss}$</td>
<td>3</td>
<td>0.9599</td>
<td>0.94 ± 0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>0.6887</td>
<td>0.51 ± 0.17</td>
<td>$Vd_{ss}$</td>
<td>6</td>
<td>0.9442</td>
<td>1.18 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>$CL_{ren}$</td>
<td>3</td>
<td>0.6082</td>
<td>0.54 ± 0.43</td>
<td>$Vd_{ss}$</td>
<td>6</td>
<td>0.5374</td>
<td>0.49 ± 0.19</td>
</tr>
<tr>
<td>Cefaloridine</td>
<td>$CL_{tot}$</td>
<td>3</td>
<td>0.9953</td>
<td>0.80 ± 0.06</td>
<td>$Vd_{ss}$</td>
<td>3</td>
<td>0.9969</td>
<td>0.97 ± 0.05</td>
</tr>
</tbody>
</table>
10.1.3. Prediction of PK of β-lactam antibiotics

10.1.3.1. One-species BW Scaling

10.1.3.1.1. One-species BW Scaling using rat PK

Table 10.6 shows the observed human PK parameters and predicted human PK parameters from rat PK. Table 10.7 and Figure 10.4-10.5 show that there was an overprediction from rat PK and PPB correction decreased % MPE and % RMSE for both, $\text{CL}_{\text{tot}}$ and $\text{Vd}_{\text{ss}}$. Table 10.8 shows the observed human PK parameters and predicted human PK parameters from dog PK. Table 10.9 and Figure 10.8-10.9 shows that dog gave better predictions than rat, in terms of both, the prediction errors and number of compounds in the 0.5-2.0 fold error range. PPB information for β-LAs in the dog was not available and hence, predictions could not be made for $\text{CL}_{\text{tot}}^{u}$ and $\text{Vd}_{\text{ss}}^{u}$ for humans using dog PK.
Table 10.6 One Species Scaling using Rat PK for β-LAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human $\text{CL}_{\text{tot}}$ [ml/min]</th>
<th>Observed Human $V_d^{ss}$ [L]</th>
<th>$\text{CL}_{\text{tot}}^{u}$ [ml/min]</th>
<th>$V_d^{ss}$ [L]</th>
<th>$\text{CL}_{\text{tot}}^{u}$ [ml/min]</th>
<th>$V_d^{ss}$ [L]</th>
<th>% Prediction error $\text{CL}_{\text{tot}}$</th>
<th>$V_d^{ss}$</th>
<th>% Prediction error $\text{CL}_{\text{tot}}^{u}$</th>
<th>$V_d^{ss}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>320.0</td>
<td>15.7</td>
<td>1400.0</td>
<td>49</td>
<td>338%</td>
<td>212%</td>
<td>338%</td>
<td>212%</td>
<td>338%</td>
<td>212%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>363.0</td>
<td>15.9</td>
<td>3108.0</td>
<td>39.9</td>
<td>756%</td>
<td>151%</td>
<td>756%</td>
<td>151%</td>
<td>756%</td>
<td>151%</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>351.3</td>
<td>15.4</td>
<td>540.5</td>
<td>23.7</td>
<td>896%</td>
<td>77%</td>
<td>896%</td>
<td>77%</td>
<td>896%</td>
<td>77%</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>131.0</td>
<td>14.0</td>
<td>910.0</td>
<td>22.4</td>
<td>595%</td>
<td>60%</td>
<td>595%</td>
<td>60%</td>
<td>595%</td>
<td>60%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>110.9</td>
<td>16.5</td>
<td>819.0</td>
<td>0.469</td>
<td>639%</td>
<td>-97%</td>
<td>639%</td>
<td>-97%</td>
<td>639%</td>
<td>-97%</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>82.0</td>
<td>18.7</td>
<td>214.8</td>
<td>48.9</td>
<td>663%</td>
<td>-21%</td>
<td>663%</td>
<td>-21%</td>
<td>663%</td>
<td>-21%</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>256.7</td>
<td>15.9</td>
<td>366.7</td>
<td>22.7</td>
<td>257%</td>
<td>-44%</td>
<td>257%</td>
<td>-44%</td>
<td>257%</td>
<td>-44%</td>
</tr>
<tr>
<td>Ceftriaxime</td>
<td>156.1</td>
<td>12.0</td>
<td>226.2</td>
<td>17.4</td>
<td>765%</td>
<td>156%</td>
<td>765%</td>
<td>156%</td>
<td>765%</td>
<td>156%</td>
</tr>
<tr>
<td>Cefalexine</td>
<td>331.8</td>
<td>12.6</td>
<td>378.8</td>
<td>14.4</td>
<td>143%</td>
<td>633%</td>
<td>143%</td>
<td>633%</td>
<td>143%</td>
<td>633%</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>160.1</td>
<td>10.3</td>
<td>333.5</td>
<td>21.4</td>
<td>1282%</td>
<td>-100%</td>
<td>1282%</td>
<td>-100%</td>
<td>1282%</td>
<td>-100%</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>64.0</td>
<td>8.7</td>
<td>621.2</td>
<td>84.8</td>
<td>503%</td>
<td>47%</td>
<td>503%</td>
<td>47%</td>
<td>503%</td>
<td>47%</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>255.9</td>
<td>20.2</td>
<td>462.8</td>
<td>36.6</td>
<td>-43%</td>
<td>3360%</td>
<td>-43%</td>
<td>3360%</td>
<td>-43%</td>
<td>3360%</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>106.4</td>
<td>10.5</td>
<td>639.1</td>
<td>22.4</td>
<td>501%</td>
<td>113%</td>
<td>501%</td>
<td>113%</td>
<td>501%</td>
<td>113%</td>
</tr>
<tr>
<td>Cephradine</td>
<td>298.9</td>
<td>15.6</td>
<td>346.8</td>
<td>18.1</td>
<td>44%</td>
<td>91%</td>
<td>44%</td>
<td>91%</td>
<td>44%</td>
<td>91%</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>157.7</td>
<td>11.5</td>
<td>1470.0</td>
<td>231</td>
<td>832%</td>
<td>1917%</td>
<td>832%</td>
<td>1917%</td>
<td>832%</td>
<td>1917%</td>
</tr>
<tr>
<td>Cefpiramide</td>
<td>57.4</td>
<td>10.5</td>
<td>665.7</td>
<td>18.2</td>
<td>1060%</td>
<td>73%</td>
<td>1060%</td>
<td>73%</td>
<td>1060%</td>
<td>73%</td>
</tr>
<tr>
<td>Cefalothin</td>
<td>330.0</td>
<td>7.4</td>
<td>1145.8</td>
<td>25.6</td>
<td>583%</td>
<td>43%</td>
<td>583%</td>
<td>43%</td>
<td>583%</td>
<td>43%</td>
</tr>
<tr>
<td>Cephalexidine</td>
<td>207.2</td>
<td>21.7</td>
<td>328.9</td>
<td>34.4</td>
<td>221%</td>
<td>32%</td>
<td>221%</td>
<td>32%</td>
<td>221%</td>
<td>32%</td>
</tr>
</tbody>
</table>
Table 10.7. One Species Scaling using Rat PK for β-LAs

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach (from rat data)</td>
<td>( C_{L_{tot}} )</td>
<td>18</td>
<td>557 (± 83 %)</td>
<td>655</td>
<td>4.72 (± 1.88)</td>
<td>0.28</td>
<td>2/18 (11 %)</td>
</tr>
<tr>
<td></td>
<td>( V_{d_{ss}} )</td>
<td>18</td>
<td>372 (± 206 %)</td>
<td>929</td>
<td>14.0 (± 10.5)</td>
<td>0.10</td>
<td>8/18 (44 %)</td>
</tr>
<tr>
<td></td>
<td>( C_{L_{tot}}^u )</td>
<td>9</td>
<td>435 (± 110 %)</td>
<td>535</td>
<td>3.34 (± 1.65)</td>
<td>0.37</td>
<td>1/9 (11 %)</td>
</tr>
<tr>
<td></td>
<td>( V_{d_{ss}}^u )</td>
<td>8</td>
<td>130 (± 82 %)</td>
<td>254</td>
<td>0.30 (± 0.54)</td>
<td>0.05</td>
<td>5/9 (55 %)</td>
</tr>
</tbody>
</table>

Figure 10.4. Predicted Human \( C_{L_{tot}} \) from Rat PK vs. Observed Human \( C_{L_{tot}} \)
Figure 10.5. Predicted Human Vd_{ss} from Rat PK vs. Observed Human Vd_{ss}.

Figure 10.6. Predicted human CL\textsubscript{tot}^{u} from rat PK vs. Observed human CL\textsubscript{tot}^{u}.
Figure 10.7. Predicted Human $V_{dss}^{u}$ from Rat PK vs. Observed Human $V_{dss}^{u}$
<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed</th>
<th>Predicted</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CL\text{tot}</td>
<td>CL\text{tot}</td>
<td>Vd\text{ss}</td>
</tr>
<tr>
<td></td>
<td>[ml/min]</td>
<td>[ml/min]</td>
<td>[L]</td>
</tr>
<tr>
<td>Azlocillin</td>
<td>138.3</td>
<td>412.8</td>
<td>18.9</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>207.0</td>
<td>226.2</td>
<td>17.4</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>226.7</td>
<td>226.2</td>
<td>17.4</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>156.1</td>
<td>15.1</td>
<td>15.1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>14.4</td>
<td>10.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Imipenem</td>
<td>674.8</td>
<td>328.9</td>
<td>34.4</td>
</tr>
<tr>
<td>Cefpiramid</td>
<td>57.4</td>
<td>359.1</td>
<td>34.3</td>
</tr>
<tr>
<td>Cephaloridine</td>
<td>207.2</td>
<td>328.9</td>
<td>34.4</td>
</tr>
<tr>
<td>Ceftarolizone</td>
<td>79.8</td>
<td>455</td>
<td>26.6</td>
</tr>
<tr>
<td>Cepharpirin</td>
<td>654.5</td>
<td>792.4</td>
<td>22.4</td>
</tr>
</tbody>
</table>
Table 10.9. One Species Scaling using Dog PK

<table>
<thead>
<tr>
<th>Method</th>
<th>PK variable</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>One species approach (from rat data)</td>
<td>CLₜot</td>
<td>13</td>
<td>252 (%)</td>
<td>517</td>
<td>0.34</td>
<td>0.07</td>
<td>5/13 (38 %)</td>
</tr>
<tr>
<td></td>
<td>Vdₜot</td>
<td>13</td>
<td>76 (%)</td>
<td>141</td>
<td>14.0 (±10.5)</td>
<td>0.10</td>
<td>8/13 (62 %)</td>
</tr>
</tbody>
</table>

Figure 10.8. Predicted Human CLₜot from Dog PK vs. Observed Human CLₜot
10.1.3.2. Two-species BW Scaling

10.1.3.2.1. Two-species BW Scaling for $CL_{tot}$

Table 10.10 and 10.11 shows the observed human PK parameters and predicted human PK parameters using two species BW scaling method. Table 10.12 and Figure 10.10-10.11 show that there was an overprediction from this method. The analysis was carried out for a very small number of compounds due to lack of information for $\beta$-LAs in both the species.
Table 10.10. Two Species Method using Rat and Dog PK for CL$_{tot}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\text{CL}_{tot}^{\text{rat}}$ (ml/min)</th>
<th>$\text{CL}_{tot}^{\text{dog}}$ (ml/min)</th>
<th>Intercept</th>
<th>Slope</th>
<th>Predicted $\text{CL}_{tot}$ human (ml/min)</th>
<th>Observed $\text{CL}_{tot}$ human (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftizoxime</td>
<td>4.83</td>
<td>36.56</td>
<td>1.00</td>
<td>0.53</td>
<td>96.6</td>
<td>156.10</td>
</tr>
<tr>
<td>Cefalexine</td>
<td>3.05</td>
<td>30.00</td>
<td>0.83</td>
<td>0.60</td>
<td>86.8</td>
<td>331.80</td>
</tr>
<tr>
<td>Cefpiramide</td>
<td>2.14</td>
<td>56.43</td>
<td>0.88</td>
<td>0.84</td>
<td>267.7</td>
<td>57.40</td>
</tr>
<tr>
<td>Cephaloridine</td>
<td>2.99</td>
<td>113.40</td>
<td>0.90</td>
<td>0.85</td>
<td>298.1</td>
<td>207.20</td>
</tr>
</tbody>
</table>

Figure 10.10. Predicted Human CL$_{tot}$ from Rat and Dog PK vs. Observed Human CL$_{tot}$
### Table 10.11. Two Species Method using Rat and Dog PK for Vd$_{ss}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd$_{ss}$ rat (l)</th>
<th>Vd$_{ss}$ dog (l)</th>
<th>Intercept</th>
<th>Slope</th>
<th>Predicted Vd$_{ss}$ human (l)</th>
<th>Observed Vd$_{ss}$ human (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefrizoxime</td>
<td>0.11</td>
<td>3.04</td>
<td>-0.43</td>
<td>0.87</td>
<td>15.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Cefalexine</td>
<td>0.35</td>
<td>2.58</td>
<td>-0.16</td>
<td>0.53</td>
<td>6.5</td>
<td>12.6</td>
</tr>
<tr>
<td>Cefpiramide</td>
<td>0.06</td>
<td>5.37</td>
<td>-0.47</td>
<td>1.16</td>
<td>45.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Cephaloridine</td>
<td>0.13</td>
<td>9.79</td>
<td>-0.38</td>
<td>1.02</td>
<td>31.0</td>
<td>21.7</td>
</tr>
</tbody>
</table>

**Figure 10.11. Predicted Human Vd$_{ss}$ from Rat and Dog PK vs. Observed Human Vd$_{ss}$**

![Graph showing predicted vs. observed Vd$_{ss}$](image-url)

- **Line of identity**
- **Line with slope = 0.5**
- **Line with slope = 2.0**
Table 10.12. Two Species Method using Rat and Dog PK

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope (±SE)</th>
<th>r²</th>
<th>No. of compounds in 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two species approach</td>
<td>CL_tot</td>
<td>4</td>
<td>75 (± 100)</td>
<td>189</td>
<td>-0.51 (± 0.59)</td>
<td>0.27</td>
<td>2/4 (50 %)</td>
</tr>
<tr>
<td>Vd ss</td>
<td>4</td>
<td>88 (± 84)</td>
<td>171</td>
<td>0.26 (± 2.41)</td>
<td>0.006</td>
<td>3/4 (75 %)</td>
<td></td>
</tr>
</tbody>
</table>

10.1.3.3. GFR ratio method

10.1.3.3.1. GFR ratio method using rat and dog PK

Table 10.13 and 10.14 shows the observed and predicted human CL_{ren} using GFR ratio method. Table 10.15 and Figure 10.12-10.13 show that there was an overall overprediction. In comparison with predictions using dog data, GFR ratio method using rat PK data showed lower prediction errors as well as more number of compounds in the 0.5-2.0 fold error range. The analysis gave was carried out for a very small number of compounds due to lack of information for β-LAs in both the species
### Table 10.13. GFR Ratio Method using Rat PK

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL(_{\text{ren}}) [ml/min/kg]</th>
<th>Observed Human CL(_{\text{ren}}^u) [ml/min/kg]</th>
<th>Predicted Human CL(_{\text{ren}}) [ml/min/kg]</th>
<th>Predicted Human CL(_{\text{ren}}^u) [ml/min/kg]</th>
<th>% Prediction error</th>
<th>CL(_{\text{ren}}) [ml/min/kg]</th>
<th>CL(_{\text{ren}}^u) [ml/min/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mezlocillin</td>
<td>3.2</td>
<td>4.92</td>
<td>2.92</td>
<td>4.2</td>
<td>-9%</td>
<td>-9%</td>
<td>-15%</td>
</tr>
<tr>
<td>Moxalactam</td>
<td>0.75</td>
<td></td>
<td>2.27</td>
<td></td>
<td></td>
<td>203%</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.87</td>
<td>8.7</td>
<td>1.68</td>
<td>9.9</td>
<td>93%</td>
<td>93%</td>
<td>14%</td>
</tr>
<tr>
<td>Cefpiramide</td>
<td>0.14</td>
<td></td>
<td>1.12</td>
<td></td>
<td></td>
<td>701%</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 10.12. Predicted Human CL\(_{\text{ren}}\) from Rat PK vs. Observed Human CL\(_{\text{ren}}\)**

Line of identity  
Line with slope = 0.5  
Line with slope = 2.0
Table 10.14. GFR Ratio Method using Dog PK

<table>
<thead>
<tr>
<th>Drug</th>
<th>Observed Human CL\textsubscript{ren} [ml/min/kg]</th>
<th>Predicted Human CL\textsubscript{ren} [ml/min/kg]</th>
<th>% Prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefprozil</td>
<td>2.1</td>
<td>0.4</td>
<td>-81%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1.4</td>
<td>0.9</td>
<td>-36%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.1</td>
<td>0.7</td>
<td>555%</td>
</tr>
<tr>
<td>Cefpiramide</td>
<td>0.14</td>
<td>1.0</td>
<td>646%</td>
</tr>
<tr>
<td>Ceforanide</td>
<td>0.8</td>
<td>14.5</td>
<td>1713%</td>
</tr>
<tr>
<td>Cephapirin</td>
<td>4.5</td>
<td>1.0</td>
<td>-77%</td>
</tr>
</tbody>
</table>

Figure 10.13. Predicted Human CL\textsubscript{ren} from Dog PK vs. Observed Human CL\textsubscript{tot}
### Table 10.15. GFR Ratio Method using Rat and Dog PK

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>n</th>
<th>%MPE (±SE)</th>
<th>%RMSE</th>
<th>Slope</th>
<th>( r^2 )</th>
<th>No. of compounds In the 0.5-2 fold error range</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR ratio method</td>
<td>CL(_{\text{ren}})</td>
<td>4</td>
<td>247 (± 157%)</td>
<td>368</td>
<td>0.51</td>
<td>0.78</td>
<td>2/4 (50 %)</td>
</tr>
<tr>
<td>(from rat PK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR ratio method</td>
<td>CL(_{\text{ren}})</td>
<td>6</td>
<td>453 (± 285%)</td>
<td>782</td>
<td>-0.69</td>
<td>0.04</td>
<td>1/6 (17 %)</td>
</tr>
<tr>
<td>(from dog PK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 10.2. Discussion

There were considerable differences in reported, BW-corrected, CL\(_{\text{tot}}\) and V\(_{\text{dss}}\) values across species (range: 1 to 80-fold, 1 to 25-fold, respectively) for β-LAs. PPB was not similar across different species, with rat \( f_u \) accounting for only 60 % variability in human \( f_u \). Sawada et al\(^99\) found a good correlation between \( f_c \) human and \( f_u \)-rats for weakly acidic and basic drugs (n = 14, Slope = 1.85, \( r^2 = 0.92 \)). β-LAs are acidic and hydrophilic drugs with log D (at pH 7.4) less than 1.0 and thus, most of the β-LAs showed \( f_c \) values > 50 % indicating that these drugs are mainly excreted by kidneys across different species. Most of the β-LAs showed intermediate PPB (30-70 %). Acidic drugs bind strongly to serum albumin.\(^{110}\) Based on the \( f_u \) and \( V_t/f_u \) values, Sawada et al\(^99\) showed that acidic drugs weakly bind to the tissues and a little difference with regards to \( V_t/f_u \) between rat and human. A good correlation was found between V or V\(_{\text{dss}}\) (rat) and V or V\(_{\text{dss}}\) (human) (n = 15, Slope = 0.848, \( r = 0.848 \)). The relationship between \((V_t/f_u)_{\text{human}}\) and \((V_t/f_u)_{\text{rat}}\) was found to be better (n = 15, Slope = 0.951, \( r = 0.958 \)). In-addition, Sawada attributed interspecies differences in t\(_{1/2}\), metabolic clearance
and $V_{dss}$ to differences in $f_u$. In the present analysis on $\beta$-LAs, $f_u$ correction lead to improvement $r^2$ values, decrease in prediction errors and resulted in more number of compounds in the 0.5-2.0 fold error range. Sawada et al.\textsuperscript{108} studied prediction of six $\beta$-LAs in humans from PK parameters in animals and showed that there was a positive relationship between $V_{ss}$ and $f_u$ (slope = 0.173-0.644, $r = 0.401-0.967$). Simple allometry showed that most of the $\beta$-LAs have low slopes ($< 0.70$) for $n = 3$ as well as for $n =$ all available animals for $CL_{tot}$. Renal blood flow (RBF) and GFR (ml/min/kg) decrease as the animal size increases in an allometric manner. The exponent values were 0.84 for RBF and 0.78 for GFR\textsuperscript{4} were steeper than the slopes obtained from allometric relationships for $CL_{tot}$ and $CL_{ren}$ for $\beta$-LAs. This might be due to the possible involvement of drug transporters in the disposition of $\beta$-LA. Mahmood et al.\textsuperscript{43} tried to predict $CL_{tot}$, $CL_{ren}$ and $V_{dss}$ in humans from animal data for ten drugs which were mainly renally secreted in humans. The slopes for simple allometry for $CL_{tot}$ ranged from 0.71-0.93, however, ofloxacin, a known OAT substrate, showed a lower slope of 0.583. Sawada et al.\textsuperscript{108} predicted the disposition of six $\beta$-lactam antibiotics using mouse, rat, rabbit, dog and human PK data. The log-log relationship between clearances ($CL_{tot}$ and $CL_{ren}$) and body weight showed low slopes, 0.405-0.662 ($n = 5$, mean: 0.574) for $CL_{tot}$ and 0.429-0.713 ($n = 5$, mean: 0.628) for $CL_{ren}$. It was also found that unbound intrinsic clearance ($CL_{int}^{u}$) was proportional to the 0.45-0.74 power of body weight. Literature studies show that $\beta$-lactam antibiotics like cephalosporins and penicillins show net secretion and it is has been reported that some cephalosporins interact with hOAT1, hOAT2 and hOAT3.\textsuperscript{22,93,94} Jariyawat et al.\textsuperscript{88} showed inhibition of p-aminohippurate transport via rat-OAT1 by penicillins and cephalosporins.
Various prediction methods like one-species BW scaling, two-species (rat, dog) BW scaling and GFR ratio methods were used to predict $\text{CL}_{\text{tot}}$, $\text{CL}_{\text{ren}}$, and $\text{Vd}_{\text{ss}}$. Due to lack of $f_u$ information available across different species, predictions for $\text{CL}_{\text{tot}}^u$ and $\text{Vd}_{\text{ss}}^u$ could be made only for few compounds using one-species method. Similar to the earlier findings from opioid and $\beta$-ARL interspecies scaling study, dog was found to be the best species using the one species method for prediction of $\text{CL}_{\text{tot}}$, $\text{Vd}_{\text{ss}}$, $\text{CL}_{\text{tot}}^u$ and $\text{Vd}_{\text{ss}}^u$ and plasma protein binding correction decreased prediction errors and resulted in more number of compounds in the 0.5-2.0 fold error range.

It is known that renal physiology has a good relationship with BW. Thus, renal excretion in humans can be extrapolated from animal PK. Ceftizoxime and aztreonam PK and plasma concentration profiles have been extrapolated from the animal data using allometric approach.\textsuperscript{111-113} GFR ratio method has been successfully used to predict $\text{CL}_{\text{ren}}$ of famotidine and ACE inhibitors like enalapril and lisinopril.\textsuperscript{114-116} In the present research on $\beta$-LAs, GFR ratio method using rat PK gave better predictions for human $\text{CL}_{\text{ren}}$ than those obtained using dog PK, however, these conclusions are based on a small number of drugs.

Like opioids and $\beta$-ARLs, body size accounted for most of the observed variability ($r^2>0.80$) in systemic PK variables in the animal species studied for $\beta$-LAs. Like hydrophilic $\beta$-ARLs, $\text{CL}_{\text{tot}}$ and $\text{CL}_{\text{ren}}$ for $\beta$-LAs showed good correlation with the BW, however, the slopes were shallow, which may be attributed to involvement of hepatobiliary and renal transporters. Dog was found to be the species giving the best prediction of $\text{CL}_{\text{tot}}$, $\text{Vd}_{\text{ss}}$, $\text{CL}_{\text{tot}}^u$, $\text{Vd}_{\text{ss}}^u$ using the one species methos while rat was the best species for prediction of $\text{CL}_{\text{ren}}$ using GFR ratio method.
CHAPTER 11

11. Comparative Analysis of Opioids, β-ARLs and β-LAs

11.1. Comparison of physicochemical properties of opioids, β-ARLs and β-LAs

Figure 11.1-11.7 shows the distribution for the molecular descriptors for opioids, β-ARLs and the β-LAs. Both opioids and β-ARLs, are basic compounds with molecular weights ranging from 200-500 Dalton. The opioid dataset is more skewed towards lipophilic compounds (log (D)\textsubscript{7,4} values ranging from -4.1 to 3.7), while the β-ARL dataset is a combination of hydrophilic as well as lipophilic compounds (log (D)\textsubscript{7,4} values ranging from -2.9 to 3.1). Morphine is a prototypical opioids, and most of the opioids in the dataset were found to be based on the typical morphine-like, rigid scaffold. Hence, the opioid dataset has smaller nRot values compared to the β-ARL dataset, which contains drugs with one or more aromatic rings and long side chains, making the structures more flexible. Since β-ARL dataset is a combination of hydrophilic and lipophilic compounds, they also show HBAs, HBDs and PSA values higher than for opioids. In contrast to the opioid and β-ARL datasets, β-LAs are acidic, hydrophilic molecules (log (D)\textsubscript{7,4} values ranging from -7.3 to 2.5) with larger MWs ranging from 199-700 Dalton, showing higher HBAs, HBDs and PSA values. Most of the β-LAs have structures which had fused rings as well as long side-chains, thus, nRot were the highest of the three classes. Overall, opioids and β-ARLs had a large diversity
in log (D)$_{7.4}$ values while β-LAs show less diversity in log (D)$_{7.4}$ values, but show slightly more diversity in MW, HBA, HBD and nRot values compared to opioids and β-ARLs.
Figure 11.1. MW Distribution by Drug Class
Figure 11.2. Log (D)\textsubscript{7.4} Distribution by Drug Class
Figure 11.3 Molar Volume Distribution by Drug Class
Figure 11.4. nRot Distribution by Drug Class

(A) Opioids

(B) β-ARLs

(C) β-LAs
Figure 11.5. HBA Distribution by Drug Class
Figure 11.6. HBD Distribution by Drug Class
Figure 11.7. PSA Distribution Drug Class
11.2. Comparison of PK Properties for Opioids, β-ARLs and β-LAs

Figure 11.8-11.16 shows the distribution for PK variables for opioids, β-ARLs and the β-LAs. On average, the opioid dataset has more lipophilic compounds; as a result, most of them were cleared by nonrenal elimination, i.e., hepatic and extrahepatic clearance. Glucuronidation and phase I metabolism are known to be the main metabolic pathways. Amongst them, UGT2B7, CYP2D6, CYP3A, CYP2C9, and CY2C19 play the major role in opioid metabolism. In addition, membrane transporters like P-glycoprotein (P-gp) determine the hepatic/renal/efflux of some opioids like morphine, alfentanil, fentanyl, loperamide and sufentanil. Out of 38 opioids, only two opioids, M3G and M6G, showed fe values above 50%, while all others were mainly non-renally cleared (fe < 50%); fourteen opioids showed CL\text{tot} or CL\text{nonren}^\text{blood} values exceeding LBF or even CO, indicating extrahepatic/nonrenal clearance, e.g., ester hydrolysis, in blood and other body tissues. Compared to the opioids, the β-ARL dataset was a combination of hydrophilic as well as lipophilic compounds. Out of 49 β-ARLs, 14 compounds showed fe values exceeding 50% while all others were mainly metabolized (fe < 50%), and seven compounds showed CL\text{tot} or CL\text{nonren}^\text{blood} values exceeding LBF or CO, indicating extrahepatic/nonrenal clearance. Thus, for most β-ARL, similar to opioids, CL\text{tot} was primarily due to nonrenal elimination, i.e., hepatic and extrahepatic clearance. For both the datasets, the median Vd\text{ss} and Vd\text{ss}^u values exceeded BW and total body water, indicating extensive tissue sequestration for most compounds.

Unlike opioids and β-ARLs, β-LAs are hydrophilic molecules with larger molecular weights, thus show lower Vd\text{ss} and Vd\text{ss}^u, indicating a low extent of tissue distribution. They also have lower values for CL\text{tot}, CL\text{tot}^u and CL\text{nonren} and more number of compounds.
showing $f_e$ above 50 %, indicating they are low ER$_{hep}$ drugs (with low CL$_{int}$, with the possibility of biliary excretion and involvement of hepatic drug transporters), mainly excreted unchanged by kidneys, again involving drug transporters. The median CL$_{ren}^u$ values for β-LA and β-ARL dataset was more than GFR, indicating net tubular secretion. Membrane transporters like P-gp, OCTs and MRP2 are involved in transport of some β-ARL$^{86, 87}$ while literature studies reports that β-LAs like cephalosporins and penicillins show net tubular secretion, and it is has been reported that some cephalosporins interact with hOAT1, hOAT2 and hOAT3.$^{22, 93, 94}$ Hydrophobicity and basicity have been indicated to be the major determinants of substrate interaction with OCTs, while hydrophobicity and acidity have been shown to be associated with OAT interactions. Furthermore, hydrogen bonding ability have also been shown to stabilize the substrate-transporter complex.$^{95}$ Thus, it is speculated that the involvement of drug transporters in the disposition of β-ARLs and β-LAs is due to the presence of higher number of HBAs and HBDs, which help in the interaction with drug transporters.
Figure 11.8. Vdss Distribution by Drug Class

(A) Opioids

(B) β-ARLs

(C) β-LAs
Figure 11.9. CL_{tot} Distribution by Drug Class
Figure 11.10. $CL_{\text{rea}}$ Distribution by Drug Class
Figure 11.11. CL<sub>nonren</sub> Distribution by Drug Class
Figure 11.12. $f_u$ Distribution by Drug Class

(A) Opioids

(B) β-ARLs

(C) β-LAs
Figure 11.13. $V_{dss}$ Distribution by Drug Class (Note: Log values plotted in the graphs for visual inspection)
Figure 11.14. CL$_{tot}^d$ Distribution by Drug Class (Note: Log values plotted in the graphs for visual inspection)
Figure 11.15. $\text{Cl}_{\text{monren}}$ Distribution by Drug Class
Figure 11.16. CL\textsubscript{rec}\textsuperscript{u} Distribution by Drug Class

(A) Opioids  (B) β-ARLs  (C) β-LAs

Prenalterol  Cefatrizine  Cefmenoxime
CHAPTER 12

12. Pooled Data Analysis for Opioids, β-ARLs and β-LAs

12.1. Characterization of molecular descriptor space

Figure 12.1 shows the relationship between log (D)\textsubscript{7.4} and other molecular descriptors such as MW, HBA, HBD and nRot across all three classes of drugs. The effect of log (D)\textsubscript{7.4} on the MW was studied by dividing the pooled dataset into number of MW bins. This allowed us to come up with average cut-offs. It was observed that when the log (D)\textsubscript{7.4} is less than approximately -2.0 and MW greater than the value of approximately 350 Dalton (D), MW decreases with increase log (D)\textsubscript{7.4} (Figure 12.1 (A)). Above log (D)\textsubscript{7.4} \approx -2.0 and MW < 350 D, there is no apparent relation between log (D)\textsubscript{7.4} and MW. The space below log (D)\textsubscript{7.4} < - 2.0 is occupied by β-LAs, mainly second and third cephalosporins and few penicillins like mezlocillin and furazlocillin. β-LA structures evolved over time in the quest of achieving better broad spectrum activity, or acid/β-lactamase stability and in doing so, long side chains were added with many HBAs and HBDs, giving rise to second and third cephalosporins and resulting in a increase in MW and a decrease in polarity. Figure 12.1 (B) shows that there is a significant relationship between log (D)\textsubscript{7.4} and HBA (n =146, r\textsuperscript{2} = 0.57, slope =-1.06 units). Hydrophilic β-LA show larger number of HBAs and lipophilic opioids show the least number of HBAs. There is also a significant relationship between log (D)\textsubscript{7.4} and HBD (n =146, r\textsuperscript{2} = 0.31, slope =-0.34 units) (Figure 12.1 (C)), though not as strong as
the relationship between HBA and log (D)_{7.4}, probably due to the smaller range of HBA values as compared to HBDs. For the pooled data, there was no trend observed between nRot and log (D)_{7.4} (Figure 12.1(D)), however, within the individual classes, nRot tends to increase with increase in log (D)_{7.4} for opioids while they decrease with increase in log (D)_{7.4} for β-LAs. Opioids with lower log (D)_{7.4} have morphine-like, rigid structure and less nRot, while more lipophilic opioids don’t have the morphine-like, rigid structure, instead, have long side chains, making those flexible. Hydrophilic β-LAs have long side chains as compared to the less hydrophilic β-LAs, resulting in β-LAs with low log (D)_{7.4} values with more flexibility.

The pooled dataset shows that there is a significant relation between MW and number of HBA (n = 146, r^2 = 0.74, slope = 0.03 units) and HBDs (n = 146, r^2 = 0.18, slope = 0.007 units) (Figure 12.2(A) and (B)). Larger MW β-LAs show higher HBA and HBD values while low MW opioids show least number of HBA and HBD values. For the pooled dataset, there is a significant relationship between MW and nRot (n =146, r^2 = 0.12, slope = 0.01 units) (Figure 12.2 (C)). To summarize the molecular descriptor space:

- MW and log (D)_{7.4} appear to be the most important properties. (see next chapter)
- The effect of log (D)_{7.4} on the MW was studied by dividing the pooled dataset into number of MW bins and the average cut offs are: When the log (D)_{7.4} < -2.0, MW decreases with increase in log (D)_{7.4}, while, when log (D)_{7.4} > -2.0, MW is independent of log (D)_{7.4}.
- HBA and HBD are related to MW and log (D)_{7.4}.
Figure 12.1. Effect of log (D)\textsubscript{7.4} on the Other Molecular Properties

Note: Ellipses represent 95% density ellipses
Figure 12.2. Effect of MW on the Other Molecular Properties

Note: Ellipses represent 95% density ellipses
12.2. Effect of Molecular Descriptors on the $f_u$ for the Pooled Dataset

Figure 12.3 (A-E) shows the effect of different molecular descriptors such as log $(D)_{7.4}$, MW, HBA, HBD and nRot on the $f_u$ values for the pooled dataset. Figure 12.3 (A) shows that below log $(D)_{7.4} \sim -2.0$, there is no relationship between $f_u$ and log $(D)_{7.4}$, however, as the log $(D)_{7.4}$ exceeds -2.0, there is an apparent decrease in $f_u$ with increase in log $(D)_{7.4}$. Figure 12.3 (B) shows that below MW $\sim 350$ D, there is no relationship between $f_u$ and MW, however, as the MW exceeds -350 D there is an apparent decrease in $f_u$ with increase in MW. The observed relationships between $f_u$ and the rest of the molecular descriptors such as HBA, HBD and nRot are a consequence of collinearity amongst the molecular descriptors (HBA-log $(D)_{7.4}$, HBA-MW and nRot-MW).

Thus, overall, it appears that log $(D)_{7.4}$ is an important determinant for $f_u$ of compounds with log $(D)_{7.4}$ values above -2.0 and MW less than 350 D, while MW is an important determinant for $f_u$ of compounds with log $(D)_{7.4}$ values below -2.0 and MW above 350 D.
Figure 12.3. Effect of Molecular Descriptors on $f_u$ for the Pooled Dataset

- **β-LAs**
- **β-ARLs**
- **Opioids**
12.3. Effect of log (D)_{7.4} on the PK variables for the Pooled Dataset

Figure 12.4 (A-D) shows the effect of log (D)_{7.4} on the biologically relevant PK variables $V_{dss}^u$, $CL_{tot}^u$, $CL_{ren}^u$ and $CL_{nonren}^u$.

Below log (D)_{7.4} values of -2.0, $V_{dss}^u$ is independent of log (D)_{7.4}, however, above log (D)_{7.4} values of -2.0, there is a strong relationship between the $V_{dss}^u$ and log (D)_{7.4}; as log (D)_{7.4} increases, $V_{dss}^u$ increases, indicating increase in tissue sequestration (Figure 12.4(A)). For the compounds with log (D)_{7.4} below -2.0, $V_{dss}^u$ is small, approaching to plasma volume values below 0.04 L/kg, indicating limited extravascular distribution.

Figure 12.4 (B) shows that for log (D)_{7.4} value below -2.0, $CL_{tot}^u$ is independent of log (D)_{7.4}, however, above a log (D)_{7.4} value of -2.0, there is a strong positive relationship between the $CL_{tot}^u$ and log (D)_{7.4}. Above a log (D)_{7.4} value of -2.0, $CL_{tot}^u$ depends on $CL_{ren}^u$ and $CL_{nonren}^u$. For these compounds with log (D)_{7.4} above -2.0, there is no change in $CL_{ren}^u$ with log (D)_{7.4} (Figure 12.4(C)), while $CL_{nonren}^u$ increases with log (D)_{7.4} (Figure 12.4(D)). For compounds with log (D)_{7.4} above -2.0, the $f_e$ declines with log (D)_{7.4} due to increased importance of metabolic clearance, making the estimates for $f_e$ or $CL_{ren}$ less accurate for those compounds. Thus, the relationship between $CL_{tot}^u$ and log (D)_{7.4} is dominated by $CL_{nonren}^u$, which, in turn, increases with log (D)_{7.4} due to increase in $CL_{int}$.

Figure 12.5 (A-D) shows the effect of log (D)_{7.4} on PK variables $V_{dss}$, $CL_{tot}$, $CL_{ren}$ and $CL_{nonren}$. As log (D)_{7.4} increases above -2.0, $V_{dss}$ increases, while below log (D)_{7.4}, $V_{dss}$ is independent of log (D)_{7.4} (Figure 12.5 (A)). Above log (D)_{7.4} value of -2.0, two opposing forces act on $V_{dss}$; $f_u$ decreasing with log (D)_{7.4} and $V_{dss}^u$ increasing with log (D)_{7.4} (Figure 12.3 (A), Figure 12.4(A)); however, the effect of $V_{dss}^u$ dominates the effect of $f_u$. 

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Similarly, as log(D)_{7.4} increases above -2.0, CL_{tot} increases, while below log(D)_{7.4}, CL_{tot} is independent of log(D)_{7.4} (Figure 12.5 (B)). Above log(D)_{7.4} value of -2.0, two opposing forces act on CL_{tot}; CL_{tot}^{u} increasing with log(D)_{7.4} and f_{u} decreasing with log(D)_{7.4}, however, the effect of CL_{tot}^{u} and in turn, the effect of CL_{int} dominates the effect of f_{u}. Below log(D)_{7.4} value of -2.0, f_{u} and CL_{tot}^{u} are independent of log(D)_{7.4} (Figure 12.3 (A), Figure 12.4 (B)). This may be due to the dominant effect of low ER_{hep} drugs below log(D)_{7.4} of -2.0 and high ER_{hep} drugs above log(D)_{7.4} of -2.0.

CL_{ren} is independent of log(D)_{7.4} below log(D)_{7.4} value of -2.0, however, above log(D)_{7.4} of -2.0, CL_{ren} decreases with log(D)_{7.4} (Figure 12.5 (C)). The CL_{ren} of the drugs above log(D)_{7.4} of -2.0 is dependent on f_{u} and CL_{ren}^{u}; f_{u} decreasing with log(D)_{7.4} (Figure 12.3 (A)) and CL_{ren}^{u} independent of log(D)_{7.4} (Figure 12.4 (C)), resulting in CL_{ren} decreasing with log(D)_{7.4}, due to the dominant effect of log(D)_{7.4} on f_{u}.

Figure 12.5 (D) shows that CL_{nonren} is independent of log(D)_{7.4} below log(D)_{7.4} value of -2.0, however, above log(D)_{7.4} value of -2.0, CL_{nonren} increases with log(D)_{7.4}. The CL_{nonren} of the drugs above log(D)_{7.4} value of -2.0 is dependent on f_{u} and CL_{nonren}^{u}; f_{u} decreasing with log(D)_{7.4} (Figure 12.3 (A)) and CL_{nonren}^{u} increasing with log(D)_{7.4} (Figure 12.4 (D)), resulting in CL_{nonren} increasing with log(D)_{7.4}, due to the dominant effect of CL_{nonren}^{u}. Below log(D)_{7.4} value of -2.0, the compounds have large MWs, are hydrophilic and have low CL_{nonren}^{u} (low ER_{hep}). In addition, their f_{u} is independent of log(D)_{7.4} ((Figure 12.3 (A)). Thus, their CL_{nonren} is independent of log(D)_{7.4}.
Figure 12.4. Effect of log \((D)_{7.4}\) on the Biologically Relevant Variables for the Pooled Dataset
Figure 12.5. Effect of log (D)\textsubscript{7.4} on the PK Variables for the Pooled Dataset

A) 

B) 

C) 

D) 

* β-LAs
x β-ARLs
● Opioids

log (D) at pH 7.4
12.4. Effect of MW on the PK variables for the Pooled Dataset

Figure 12.6 (A-D) shows the effect of MW on the biologically relevant PK variables like $V_{dss}$, $CL_{tot}$, $CL_{ren}$ and $CL_{nonren}$. There is no apparent effect of MW on $V_{dss}$, $CL_{tot}$, $CL_{ren}$ and $CL_{nonren}$.

Figure 12.7 (A-D) shows the effect of MW on the PK variables $V_{dss}$, $CL_{tot}$, $CL_{ren}$ and $CL_{nonren}$. For the entire dataset, there is a significant relation between $V_{dss}$ and MW ($n = 146$, $r^2 = 0.32$, slope $= -0.008$ units) (Figure 12.7(A)), the regression being governed by very high $V_{dss}$ values below MW~350 D and very low $V_{dss}$ values above MW~350 D. The $V_{dss}$ values are dependent on $V_{dss}$ and $f_u$, both of which are independent of MW for compounds below MW~350 D (Figure 12.3 (B), Figure 12.6 A), thus, there is no relation between $V_{dss}$ and MW for compounds below MW~350 D. Above MW~350 Da, the $V_{dss}$ values are dependent on $f_u$, which decreases with MW (Figure 12.3 (B)) and $V_{dss}$ independent of MW (Figure 12.6 A), thus, resulting in overall decrease in $V_{dss}$, due to the dominant effect of $f_u$.

For the entire dataset, there is a significant relation between $CL_{tot}$ and MW ($n = 145$, $r^2 = 0.23$, slope $= -0.006$ units) (Figure 12.7(B)), the regression being governed by very high $CL_{tot}$ values below MW~350 D and very low $CL_{tot}$ values above MW~350 D. The $CL_{tot}$ values are dependent on $CL_{tot}$ and $f_u$, both of which are independent of MW for compounds below MW~350 D (Figure 12.3 (B), Figure 12.6 B), thus, there is no relation between $CL_{tot}$ and MW for compounds below MW~350 D. Above MW~350 D, the $CL_{tot}$ values are dependent on $f_u$, which decreases with MW (Figure 12.3 (B)) and $CL_{tot}$ independent of MW (Figure 12.6 (B)), thus, resulting in a decrease in $CL_{tot}$ with MW, overall relation being dominated by the effect of MW on $f_u$. 

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The CL\textsubscript{ren} values are dependent on CL\textsubscript{ren} \textsuperscript{u} and f\textsubscript{u}, both of which are independent of MW for compounds below MW~ 350 D (Figure 12.3 (B), Figure 12.6(C)), thus, there is no relation between CL\textsubscript{ren} and MW for compounds below MW~ 350 D. Above MW~ 350 D, the CL\textsubscript{ren} values are dependent on f\textsubscript{u}, which decreases with MW (Figure 12.3 (B)) and CL\textsubscript{ren} \textsuperscript{u} independent of MW (Figure 12.6 (C)); resulting in CL\textsubscript{ren} decreasing with MW (Figure 12.7 (C)), the overall relation being dominated by effect of MW on f\textsubscript{u}.

For the entire dataset, there is a significant relation between CL\textsubscript{nonren} and MW (n = 119, r\textsuperscript{2} = 0.25, slope = -0.009 units) (Figure 12.7(D)), the regression being governed by very high CL\textsubscript{nonren} values below MW~ 350 D and very low CL\textsubscript{nonren} values above MW~ 350 D. The CL\textsubscript{nonren} values are dependent on CL\textsubscript{nonren} \textsuperscript{u} and f\textsubscript{u}, both of which are independent of MW for compounds below MW~ 350 D (Figure 12.3 (B), Figure 12.6 (D)), thus, there is no relation between CL\textsubscript{nonren} and MW for compounds below MW~ 350 D. Above MW~ 350 D, the CL\textsubscript{nonren} values are dependent on f\textsubscript{u}, which decreases with MW (Figure 12.3 (B)) and CL\textsubscript{nonren} \textsuperscript{u} independent of MW (Figure 12.6 (D)), thus, resulting in CL\textsubscript{nonren} independent of MW (Figure 12.7 (D)), the overall relation being dominated by effect of MW on CL\textsubscript{nonren} \textsuperscript{u}.

Thus, for the pooled dataset, log (D)\textsubscript{7.4} and MW are the only statistically significant and biologically plausible molecular descriptors affecting the biologically relevant PK properties and their effect is summarized in Chapter 13.
Figure 12.6. Effect of MW on the Biologically Relevant Variables for the Pooled Dataset

A) $V_{dss}(u)$ (L/kg)  
- β-LAs  
- β-ARLs  
- Opioids

B) $CL_{tot}(u)$ (ml/min/kg)

C) $CL_{ren}(u)$ (ml/min/kg)

D) $CL_{nore}(u)$ (ml/min/kg)

MW
Figure 12.7. Effect of MW on the PK Variables for the Pooled Dataset

A) 

B) 

C) 

D) 

Figure 12.7. Effect of MW on the PK Variables for the Pooled Dataset

- β-LAs
- β-ARLs
- Opioids

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12.5. Effect of Molecular descriptors on the AS-PK Slopes for CL\textsubscript{tot} for the Pooled Dataset

Figure 12.8 (A-E) shows the effect of different molecular descriptors like log (D)\textsubscript{7.4}, MW, HBA, HBD and nRot on the AS-PK CL\textsubscript{tot} slopes for the pooled dataset. There is no particular trend between the slopes for CL\textsubscript{tot} and the molecular descriptors for the pooled dataset. However, as the log (D)\textsubscript{7.4} increases, CL\textsubscript{tot} slopes for β-LAs show an upward trend (Figure 12.8 (A)), while as MW and HBA increases (Figure 12.8 (B) and (C)), CL\textsubscript{tot} slopes for β-LAs shows a downward trend, though not significant. As the nRot increases, there is a significant decrease in CL\textsubscript{tot} slope for opioids (n =18, r\textsuperscript{2} = 0.24, slope = -0.03 units) (Figure 12.8 (E)).

Figure 12.9 (A-E) shows the effect of different molecular descriptors like log (D)\textsubscript{7.4}, MW, HBA, HBD and nRot on the AS-PK Vd\textsubscript{ss} slopes for the pooled dataset. There is no particular trend between the Vd\textsubscript{ss} slopes and the molecular descriptors for the pooled dataset. However, as the MW and HBAs increase, Vd\textsubscript{ss} slope decreases for β-LAs, though not significant (Figure 12.9 (B) and (C)). As the nRot increases, there is a significant increase in Vd\textsubscript{ss} slope for β-LAs (n =11, r\textsuperscript{2} = 0.37, slope = 0.05 units) (Figure 12.8 (E)).
Figure 12.8. Effect of Molecular Descriptors on the PK-AS slope of $\text{CL}_{\text{tot}}$ for the Pooled Dataset
Figure 12.9. Effect of Molecular Descriptors on the PK-AS slope of Vd_{ss} for the Pooled Dataset

- **(A)** log(D) at pH 7.4
- **(B)** MW
- **(C)** HBA
- **(D)** HBD
- **(E)** nRot

- *β-LAs*
- *β-ARLs*
- Opioids

Figure 12.9. Effect of Molecular Descriptors on the PK-AS slope of Vd_{ss} for the Pooled Dataset
CHAPTER 13

13. Overall Conclusions

The majority of chemical drug candidates entering clinical testing for safety and efficacy ultimately fail to reach the market place, among other things due to the lack of better understanding of their ADME properties in early drug development.\textsuperscript{1, 2} The overall process of drug development is extremely time consuming and expensive, making early screening of drug candidates imperative. Human and animal PK databases have been used successfully to understand the relationship between chemical structure and PK behavior of the drugs.\textsuperscript{13, 19, 39, 40, 109} For such analyses, it is a prerequisite that the physicochemical and biological properties in the database should have a wide range, distribution, and published information on PK variables should be available for a sufficient number of analogs belonging to the same class of compounds. Most of the QSPKR studies in the literature are either on homologous series of compounds (resulting from systematic variation in the structure of the lead compounds) or on heterogenous datasets which have compounds from different structural and pharmacological classes.\textsuperscript{16, 21-23} The use of a homologous series, which enables to identify the contribution of each substituent-functional group, results in a narrow range of molecular properties, which makes identification of important molecular properties difficult; on the other hand, the widespread use of MLLR/univariate regression on heterogenous datasets may neglect major interaction(s) amongst the molecular properties. Furthermore, some QSPKR studies predict $\text{CL}_{\text{tot}}/F_{\text{oral}}$ and $V_d/\text{F}$.\textsuperscript{325}
F_{oral} since they used the systemic exposure data after oral administration in humans/animals.\textsuperscript{26, 30, 31} The involvement of a complex phenomenon such as oral absorption can make these predictions difficult, even more compared to systemic ADME. Therefore in the present research, the focus was on systemic PK properties (i.e., after IV administration) to get rid of the confounding effects of oral absorption, which may depend on different molecular properties. In the present research, a database of human PK parameters was gathered for 146 drugs. Each value was obtained after critical evaluation of study design, dosage regimen, sampling schedule, methods of sample analysis and PK analysis methods. Most of the databases in the literature built models for total PK properties, i.e., not corrected for PPB. However, it is assumed that only unbound drug is available for distribution, excretion and metabolism and interaction with the target drug receptors and hence, this research built QSPKR and AS-PK models using biologically relevant, i.e., unbound PK variables. In-addition, the selected drugs were structural analogs, acted on a common pharmacological target and, at the same time, showed considerable diversity in their physicochemical and PK properties. Moreover, the effect of more than one molecular property on the PK variables was studied at a time, thus, also exploring the possibility of interactions amongst the molecular properties. However, the following limitations of this database should also be acknowledged:

(i) The database was a “convenience sample” based on the available information in literature; not a result of systematic variation of structure. Each drug in the final database had human PK information after I.V. administration. Limited information was available on animal (rat and dog) PK and the dataset shrunk furthermore for unbound PK variables due to lack of information on PPB across different species.
Primary PK variables, obtained from literature references, varied from drug to drug with regard to dose level, number of subjects, sampling times, analytical methods and thus, were subject to potential bias and imprecision as a result of study design and methods.

The final values for PK variables were means of PK property values obtained from different studies, and the methods did not account for intersubject variability. Interspecies differences in the metabolic pathways and drug transporters could not taken into account in PK-AS methods other than a change in allometric relationship.

Dose-proportional systemic PK was assumed.

For some drugs, extrahepatic clearance could only be suspected based on high \( CL_{\text{nonren}}^{\text{blood}} \) values without mechanistic proof.

For some drugs, especially with high \( \log (D) \) \( f_{c} \) or \( CL_{\text{ren}} \) may have been poorly estimated due to its small value.

Nevertheless, this QSPKR database should be able to provide an insight into relationship between structure and PK and interspecies differences. Opioids were selected as the dataset for preliminary studies because they are structural analogs and, at the same time, show considerably diverse physicochemical and PK properties. To make this research project more generalizable in terms of types of compounds studied, this research was extended to two additional classes of compounds belonging to two different chemical and pharmacological classes: \( \beta \)-ARLs and \( \beta \)-LAs. The final dataset contains small MW (200-500 D), highly lipophilic, basic compounds which are primarily eliminated by liver as well as large MW (500-700 D), highly hydrophilic, acidic compounds which are primarily excreted by kidneys. Though the molecular property space of the present database is quite large, addition of neutral molecules, compounds having
MW more than 700 D and lesser than 200 D and compounds from other pharmacological classes will increase the diversity and generalizability of the database. QSPKR and AS-PK models were built for the datasets for the individual drug class; however, only trend/discriminatory analysis was done on the pooled dataset. Overall conclusions of the initial efforts towards predicting human PK using QSPKR and interspecies scaling are given below.

Using available information for the three pharmacological classes of drugs, namely opioids, β-ARLs and β-LAs, it was hypothesized that: 1) molecular properties can be used to quantitatively to predict systemic human PK; however, the molecular properties responsible for the biologically relevant PK properties differ by class of drugs. 2) Human PK can be successfully allometrically scaled from rat and dog PK; however, the allometric scaling coefficient depends on the molecular properties drug properties.

To prove the first hypothesis, the relationship between molecular properties and PK properties was studied. Chapter 11 compares the molecular and PK properties across the three different dataset: opioids, β-ARLs and β-LAs. It was found that opioids and β-ARLs have a large diversity in log (D)7.4 values, while β-LAs show less diversity in log (D)7.4 values, but show slightly more diversity in MW, HBA, HBD and nRot values compared to opioids and β-ARLs. For most β-ARL and opioids, CL\textsubscript{tot} was primarily due to nonrenal elimination, i.e., hepatic and extrahepatic clearance. For both β-ARL and opioid, the median Vd\textsubscript{ss} and Vd\textsubscript{ss\textsuperscript{u}} values exceeded BW and total body water, indicating extensive tissue sequestration for most compounds. In contrast, β-LAs show lower Vd\textsubscript{ss} and Vd\textsubscript{ss\textsuperscript{u}}, some approaching blood/plasma volume, indicating a low extent of tissue distribution. β-LAs also have lower values for CL\textsubscript{tot}, CL\textsubscript{tot\textsuperscript{u}} and CL\textsubscript{nonren}, their median CL\textsubscript{ren\textsuperscript{u}} was higher than GFR and a larger number of compounds showed f\textsubscript{e} above 50%; this indicates they are low ER\textsubscript{hep} drugs (with low CL\textsubscript{int}, and the possibility of biliary
excretion and involvement of hepatic drug transporters), mainly excreted unchanged by kidneys, undergoing tubular secretion, again involving drug transporters.\textsuperscript{22, 93, 94} Chapter 12 concentrates on defining the molecular property space for the pooled dataset; it was found that MW and log (D)\textsubscript{7.4} were the most important molecular properties. The pooled dataset was divided into different ranges of MW bins (e.g. 200-400 D, 400-700 D) and the effect of log (D)\textsubscript{7.4} was studied on those MW bins using a number of linear regressions to define the cut-off values. In the past, studies carrying out discriminatory/trend analysis have divided the QSPKR databases into different categories such as charge/ionization state, therapeutic area or into different range of MW bins.\textsuperscript{16, 21, 22} The present trend analysis showed that on average, when the log (D)\textsubscript{7.4} value was below -2.0 and MW value above 350 D, MW decreased with an increase in log (D)\textsubscript{7.4}, while, when log (D)\textsubscript{7.4} was above -2.0 and MW value below 350 Dalton, MW was independent of log (D)\textsubscript{7.4}. HBA and HBD showed collinearity with MW and log (D)\textsubscript{7.4}. Generally, it is observed that the transit of the drug in the body involves movement of drug across several biological membranes which are composed of phospholipids layers and interaction with membrane bound proteins such as transporters, enzymes or receptors in order to elicit pharmacological action. This transit is a result of interplay amongst the different molecular descriptors.\textsuperscript{15, 26, 73} Based on the \textit{in-vitro} solubility and permeability studies for 2245 compounds in United States Adopted Name (USAN) database, Lipinski came up with a ‘Rule of Five’ concept which utilizes cut offs of log (P), MW, HBA and HBD to classify oral absorption.\textsuperscript{17} The rule states that a compound is likely to have poor pral absorption if MW is more than 500 D, clog P > 5, there are more than five HBDs and more than 10 HBAs. The final dataset in this research contained 146 drugs (38 opioids, 48 β-ARLs and 60 β-LAs) with a wide range of molecular properties; median clog(P): 1.2 (-6.1 to 7.2), median clog (D)\textsubscript{7.4}: -0.95 (-7.3-3.7), median MW: 365 D (199-672), median:
nRot: 7 (1-15), median HBD: 3 (0-7) and median HBA: 6 (0-17). This database has a relatively small number of compounds and median values for clog(P), MW, HBD and HBAs are well below Lipinski’s ‘Rule of Five’, however, it contains information about compounds which have been approved by FDA or which were/are used in clinical settings.

In the present trend analysis, using the average cut-off of log (D)\(_{7.4}\) value of -2.0 and MW value of 350 D, it was found that log (D)\(_{7.4}\) was found to be the statistically, the most significant and biologically plausible molecular property affecting the biologically relevant, systemic PK properties, namely \(f_u\), \(V_{dsu}\), \(CL_{nonrenu}\) for compounds with log (D)\(_{7.4}\) values exceeding -2.0 and MW values below 350 Dalton. This cut-off included most of the opioids (n= 23) and β-ARLs (n= 34) but very few while β-LAs (n = 2); thus, it was biased towards basic compounds. Figure 13.1 shows the mechanistic paradigm, explaining the effect of log (D)\(_{7.4}\) on both biologically relevant and total PK variables. Table 13.1 shows the effect of log (D)\(_{7.4}\) on compounds with log (D)\(_{7.4}\) values above -2.0 and MW value below 350 D.

As log (D)\(_{7.4}\) increased, \(f_u\) decreased, while \(V_{dsu}\), \(CL_{totu}\), \(CL_{nonrenu}\) increased. Increasing lipophilicity resulted in increase in PPB due to hydrophobic interactions with plasma proteins. Basic compounds show high affinity towards α-acid glycoprotein due to an electrostatic interaction with the acidic residues. The unbound fraction in tissues is dependent on nonspecific hydrophobic interactions with lipids and tissue proteins. However, it is also speculated that bases show ion-pair interactions with the charged polar head groups of the phospholipids, resulting in increase in tissue binding and increase in \(V_{dss}\) and \(V_{dssu}\)\(^\text{20, 21, 92}\). By converting \(V_{dss}\), \(CL_{tot}\) and \(CL_{nonren}\) into \(V_{dssu}\), \(CL_{totu}\) and \(CL_{nonrenu}\), the confounding impact of PPB was removed. This led to improvement in the trend between log (D)\(_{7.4}\) and the unbound PK variables, as shown by the increased/steeper slopes for the unbound PK parameters. As log
(D)\textsubscript{7.4} increased, due to the dominating effect of increase in Vd\textsubscript{ss,u}, there was an increase in Vd\textsubscript{ss}, while the resultant increase in CL\textsubscript{int} lead to an increase in CL\textsubscript{tot} and CL\textsubscript{nonren}. CL\textsubscript{ren,u} is independent of log (D)\textsubscript{7.4}, however, due to the dominating effect of f\textsubscript{u}, CL\textsubscript{ren} decreases with log (D)\textsubscript{7.4}. These findings are corroborated by number of studies in the literature which studied the effect of log (D)\textsubscript{7.4} on the PK variables\textsuperscript{16, 20, 21}. The order of effect of log (D)\textsubscript{7.4} as indicated by the r\textsuperscript{2} on the PK variables is: Vd\textsubscript{ss,u} > CL\textsubscript{nonren,u} > CL\textsubscript{tot,u} > CL\textsubscript{nonren} > Vd\textsubscript{ss} > CL\textsubscript{tot}. Overall, PPB (which increases with log (D)\textsubscript{7.4} itself) tended to obscure the log (D)\textsubscript{7.4} dependence of Vd\textsubscript{ss}, CL\textsubscript{tot}, but was responsible for the decrease in CL\textsubscript{ren} with log (D)\textsubscript{7.4}.

Table 13.1: Effect of log (D)\textsubscript{7.4} on compounds with log (D)\textsubscript{7.4} >- 2.0 and MW < 350 D

<table>
<thead>
<tr>
<th>PK variable</th>
<th>n</th>
<th>Slope</th>
<th>r\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>f\textsubscript{u}</td>
<td>49</td>
<td>-0.15</td>
<td>0.37 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(Vd\textsubscript{ss}) (L/kg)</td>
<td>57</td>
<td>0.16</td>
<td>0.26 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(Vd\textsubscript{ss,u}) (L/kg)</td>
<td>48</td>
<td>0.35</td>
<td>0.54 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL\textsubscript{non}) (ml/min/kg)</td>
<td>59</td>
<td>0.14</td>
<td>0.15 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL\textsubscript{non,u}) (ml/min/kg)</td>
<td>49</td>
<td>0.29</td>
<td>0.38 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL\textsubscript{nonren}) (ml/min/kg)</td>
<td>46</td>
<td>0.28</td>
<td>0.34 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL\textsubscript{nonren,u}) (ml/min/kg)</td>
<td>38</td>
<td>0.44</td>
<td>0.52 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL\textsubscript{ren}) (ml/min/kg)</td>
<td>46</td>
<td>-0.18</td>
<td>0.14 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL\textsubscript{ren,u}) (ml/min/kg)</td>
<td>38</td>
<td>-0.07</td>
<td>0.05 (N.S.)</td>
</tr>
</tbody>
</table>
For compounds with log (D)_{7.4} less than -2.0 and MW more than 350 D, MW was found to be the statistically, the most significant and biologically plausible molecular property, affecting f_u. This cut-off included most of the β-LAs (n= 45) and very few β-ARLs (n= 2) and opioids (n = 3), and, thus, was biased towards acidic compounds. Figure 13.2 shows the mechanistic paradigm, explaining the effect of MW on both biologically relevant and total PK variables. Table 13.2 shows the effect of MW on the compounds with log (D)_{7.4} value less than -2.0 and MW value more than 350 D.

Figure 13.1. Effect of log (D)_{7.4} on PK variables of Compounds with log (D)_{7.4} > -2.0 and MW < 350 D
For these compounds, as the MW increased, $f_u$ decreased, indicating increased hydrogen bonding interaction, resulting due to higher number of HBAs and HBDs in these large and polar compounds. Gleeson\textsuperscript{21} determined structure-property guides for diverse molecules in the GSK database, which was divided into different ranges of MW bins. On an average, it was found that molecules with MW < 300 D were 72 \% bound, molecules with MW between 300 and 500 D were 54 \% bound while molecules with MW between 500-700 D were 98.2 \% bound. The multivariate PLS model results by Gleeson on the same dataset showed that MW had a significant, independent effect on PPB above lipophilicity.\textsuperscript{118} In the present research, MW does not show any apparent effect on $V_{dss}^u$, $CL_{tot}^u$, $CL_{nonren}^u$ and $CL_{ren}^u$. As the MW increased, due to the dominating effect of a decrease in $f_u$, there was a decrease in $V_{dss}$, $CL_{tot}$ and $CL_{ren}$. These compounds have small volumes of distribution, approaching blood/plasma volumes, as well as lower values for $CL_{tot}$, $CL_{tot}^u$ and $CL_{nonren}$ and $CL_{ren}^u$ greater than GFR. This indicates limited extravascular distribution, low ER\textsubscript{hep} ratio and net tubular secretion as the main mechanism at the kidneys, respectively. Varma et al\textsuperscript{22} studied the relationship between physicochemical properties and human renal clearance, which showed that in general, secreted compounds are hydrophilic, have higher MW, PSA, nRot and HBA/HBD count and and ionized at physiological pH. Thus, the small extent of distribution and elimination appears to be determined by interaction of HBAs and HBDs. Unlike the effect of log (D)\textsubscript{7.4}, effect of MW was significant on the total PK properties like $V_{dss}$, $CL_{tot}$ and $CL_{ren}$, due to the confounding significant effect of MW on $f_u$.

Figure 13.3 summarizes the overall QSPKR effects on the pooled dataset.
Table 13.2. Effect of MW on compounds with log(D)_{7.4} < -2.0 and MW > 350 D

<table>
<thead>
<tr>
<th>PK variable</th>
<th>n</th>
<th>Slope</th>
<th>r^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>f_u</td>
<td>47</td>
<td>-0.001</td>
<td>0.15 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(Vd_{ss}) (L/kg)</td>
<td>49</td>
<td>-0.002</td>
<td>0.19 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(Vd_{ss}^u) (L/kg)</td>
<td>47</td>
<td>0.0004</td>
<td>0.00006 (N.S.)</td>
</tr>
<tr>
<td>log(CL_{tot}) (ml/min/kg)</td>
<td>50</td>
<td>-0.003</td>
<td>0.29 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL_{tot}^u) (ml/min/kg)</td>
<td>47</td>
<td>-0.001</td>
<td>0.03 (N.S.)</td>
</tr>
<tr>
<td>log(CL_{nonren}) (ml/min/kg)</td>
<td>48</td>
<td>-0.002</td>
<td>0.06 (N.S.)</td>
</tr>
<tr>
<td>log(CL_{nonren}^u) (ml/min/kg)</td>
<td>46</td>
<td>0.0006</td>
<td>0.005 (N.S.)</td>
</tr>
<tr>
<td>log(CL_{ren}) (ml/min/kg)</td>
<td>48</td>
<td>-0.002</td>
<td>0.17 (p&lt;0.05)</td>
</tr>
<tr>
<td>log(CL_{ren}^u) (ml/min/kg)</td>
<td>46</td>
<td>-0.0006</td>
<td>0.02 (N.S.)</td>
</tr>
</tbody>
</table>

Figure 13.2. Effect of MW on PK Variables of Compounds with log(D)_{7.4} < -2.0 and MW > 350 D
Log \((D)_{7.4} < -2.0\) and \(MW > 350\)

- Yes
  - \(f_u \propto \frac{1}{MW}\)
  - No change in \(Vd_{ss}^u\)
  - No change in \(CL_{tot}^u\)
  - No change in \(CL_{nonren}^u\)
  - No change in \(CL_{ren}^u\)
  - MW is the most important molecular property

- No
  - \(f_u \propto \frac{1}{\log(D)_{7.4}}\)
  - \(Vd_{ss}^u \propto \log(D)_{7.4}\)
  - \(CL_{tot}^u \propto \log(D)_{7.4}\)
  - \(CL_{nonren}^u \propto \log(D)_{7.4}\)
  - \(CL_{ren}^u\) No change in CL
  - Log \((D)_{7.4}\) is the most important molecular property

Figure 13.3. Summary of QSPKR study on the Pooled Dataset
To prove the second hypothesis, human PK properties (CL\textsubscript{tot}, Vd\textsubscript{ss} and their unbound counterparts) were scaled from rat and dog PK properties for the three different datasets: opioids, β-ARLs and β-LAs. For most compounds, animal body size accounted for most of the observed variability ($r^2>0.80$) in systemic PK variables in the animal species studied. Single-animal (rat, dog) methods provided acceptable predictions for CL\textsubscript{tot}, Vd\textsubscript{ss}, CL\textsubscript{ren} and their unbound counterparts; thus, these findings suggest that the use of three or more species may not be necessary. Overall, the dog was found to be the species giving the best prediction of CL\textsubscript{tot}, Vd\textsubscript{ss}, CL\textsubscript{ren}, CL\textsubscript{tot}^u, CL\textsubscript{ren}^u and Vd\textsubscript{ss}^u. However, these predictions were based on the limited amount of data available in the literature. Prediction methodologies in the literature concentrate on more than one species because it is believed that high $r^2$ values among three species is an indication of achieving better prediction of human PK. However, Boxenbaum showed that human antipyrine CL\textsubscript{tot} was poorly predicted despite high $r^2$ values and use of multiple species.\textsuperscript{37} Similar observations have been made by Ward et al\textsuperscript{13} for a database of 103 marketed compounds. Studies have been published which have shown that $r^2$ is not a good measure of predictive ability of the allometric relationship.\textsuperscript{36, 46} In fact, allometry often leads to large overpredictions which can be reduced by incorporating PPB differences amongst different species.\textsuperscript{52, 119, 120} This corroborated our findings which showed that $f_u$ correction of CL\textsubscript{tot}, Vd\textsubscript{ss} and CL\textsubscript{ren} improved goodness of fit, lowered prediction errors and resulted in human predictions within acceptable range for a larger number of compounds. Hosea et al \textsuperscript{56} predicted human PK from rat, dog and monkey data for 50 proprietary compounds that had progressed to clinical studies; the database spanned several chemical
classes and therapeutic areas with a range of physicochemical properties and elimination routes by metabolism and non-metabolism processes. The findings were similar to the present research, wherein single species methods were found to be at least as accurate as in predicting human PK than allometric methods using multiple species, regardless of clearance mechanism. The use of unbound concentrations resulted in more accurate predictions. However, Hosea et al. obtained poor predictions for the class of compounds showing involvement of active transport and attributed this to the possible differences in drug transporters. The database in the present research has compounds which are substrates for drug transporters like P-gp, MRP2, OATs and OCT. The present research also showed that, in general, CL\textsubscript{nonren} and CL\textsubscript{nonren\textsuperscript{u}} were most difficult parameters to predict, possibly due the associated interspecies differences in the metabolic pathways and hepatobiliary drug transporters. Thus, with the objective of improving accuracy of interspecies predictions, associations between prediction errors and allometric coefficients were explored (Section 12.5). It was hypothesized that understanding of molecular properties for inliers or outliers for each species would increase the accuracy of the interspecies predictions. In the past, Jolivette et al. tried to determine whether calculated molecular properties may be used to predict the extrapolative success and failure of rat, dog and monkey data to predict human PK. It was found that extrapolation from rat and dog is more likely to accurately predict human CL\textsubscript{tot} for molecules that are relatively small and hydrophilic compared to larger, more lipophilic compounds. Jolivette et al. also found that rat CL\textsubscript{tot} will not be predictive of human for molecules that have a clog(P) value more than 0 and that molecules with high CL\textsubscript{tot} in rat but with clog(P) more than 3 will not have high CL\textsubscript{tot} in humans. However, in the present research, no apparent relationship was found.
between AS slopes/inter-species predictions across different classes and the molecular properties, although this conclusion was based on limited amount of data available from literature. For hydrophilic β-ARLs and β-LAs, CL<sub>tot</sub> and CL<sub>ren</sub> showed good correlation with BW; however, the allometric slopes were shallow, which may be attributed to involvement of hepatobiliary transporters. Irrespective of the species, high CL<sub>tot</sub> and Vd<sub>ss</sub> were found to be associated with high log (D)<sub>7.4</sub>, low MW, low number of HBA/HBDs and low nRot, while low CL<sub>tot</sub> and Vd<sub>ss</sub> were associated with low log (D)<sub>7.4</sub>, high MW, high number of HBA/HBD and high nRot. Thus, the effect of molecular descriptors such as log (D)<sub>7.4</sub>, MW, HBA, HBD and nRot on the PK properties of the pooled dataset for rat and dog were similar to humans, which may also a plausible reason for the lack of apparent relationship between AS slopes/inter-species predictions across different classes and the molecular properties.

Overall, QSPKR and Interspecies Scaling provided acceptable predictions for PK variables for individual datasets of opioids and β-ARLs. However, predicting human PK of large and polar β-LAs was found to be difficult due to the possible involvement of active transport. Overall, the results were based on relatively limited dataset and should be interpreted with caution. Though the molecular property space of the present database is quite large, addition of compounds from other pharmacological and chemical classes may increase the diversity and generalizability of the database. Despite the limitations, this research should be able to provide an initial insight into relationship between structure and PK and interspecies differences.
References

Appendix I (a)

Human PK Study Summaries of Opioids

Agonists

Morphine

Morphine is a basic drug and a potent analgesic used in severe acute and chronic pain. It is the most studied opioid. It is hydrophilic with log D (pH 7.4) of 0.14 (n-octanol-pH 7.4 buffer) and $pK_a$ of 7.9 (determined by microcalorimetric titration).\(^1\) At physiologic pH, 24% molecules are non-ionized. Morphine shows a lot of interindividual variability. It is widely distributed in the body. Morphine is highly extracted by liver\(^2\) and some studies show moderate to high clearance values. These clearance values are greater than the hepatic blood flow. It undergoes rapid glucuronidation to form two main metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine also undergoes extrahepatic metabolism, about 38% of the clearance of morphine maybe due to extrahepatic extraintestinal metabolism, probably in the kidney\(^3\).
### PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Stanski et al²</td>
<td>Healthy</td>
<td>74.1</td>
<td>0.099</td>
<td>Bolus</td>
<td>1-48 hr</td>
<td>RIA</td>
<td>Sensitivity – 1 ng/ml</td>
<td>Compartmental (2 and 3)</td>
<td>-</td>
<td>AUC (mg/min/ml) = 0.00675</td>
</tr>
<tr>
<td></td>
<td>n = 8</td>
<td>(±4.0)</td>
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<tr>
<td></td>
<td>28.2 yrs(± 0.8)</td>
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<td></td>
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</tr>
<tr>
<td>Owen et al³</td>
<td>Healthy</td>
<td>54-80</td>
<td>0.099</td>
<td>Bolus</td>
<td>5-480 min</td>
<td>GC or HPL C</td>
<td>-</td>
<td>Compartmental (2)</td>
<td>Fractionated</td>
<td>0.00294</td>
</tr>
<tr>
<td></td>
<td>n = 13</td>
<td></td>
<td></td>
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<td></td>
<td>24-28 yrs</td>
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<tr>
<td>Mazoit et al⁴</td>
<td>Healthy</td>
<td>57</td>
<td>0.14</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>RIA</td>
<td>Sensitivity-0.2 ng/ml</td>
<td>Compartmental (2)</td>
<td>Fractionated</td>
<td>0.00284</td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>(±13)</td>
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<td>46 yr (± 23)</td>
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<tr>
<td>Hasselstrom et al⁵</td>
<td>Healthy</td>
<td>65</td>
<td>0.06</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>HPL C</td>
<td>LOD -1 nmol/l</td>
<td>Compartmental (3)</td>
<td>Fractionated</td>
<td>0.00737</td>
</tr>
<tr>
<td></td>
<td>n = 7</td>
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<td>37 yr</td>
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<tr>
<td>Milne et al⁶</td>
<td>ICU subjects</td>
<td>44-75</td>
<td>0.020</td>
<td>Infusion</td>
<td>-</td>
<td>HPL C</td>
<td>3.8 ng/ml</td>
<td>-</td>
<td>Cumulative</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>n = 15</td>
<td></td>
<td>to 0.122 mg/kg/hr</td>
<td>Infusion</td>
<td>-</td>
<td>HPL C</td>
<td>3.8 ng/ml</td>
<td>-</td>
<td>Cumulative</td>
<td>-</td>
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<tr>
<td></td>
<td>17-78 yrs</td>
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</tr>
<tr>
<td>Lotsch et al⁷</td>
<td>Healthy</td>
<td>74.2</td>
<td>0.14</td>
<td>Bolus &amp; infusion</td>
<td>10 min-8 hrs</td>
<td>HPL C</td>
<td>10 ng/ml</td>
<td>Modeling</td>
<td>-</td>
<td>1.85 (± 0.31)</td>
</tr>
<tr>
<td></td>
<td>n = 20</td>
<td>(±6.5)</td>
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<td>24.6 yr (± 2.7)</td>
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</tr>
<tr>
<td>Osborne et al⁸</td>
<td>Healthy</td>
<td>63-83</td>
<td>0.07</td>
<td>Bolus</td>
<td>5 min-24 hrs</td>
<td>HPL C</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td>0.00249</td>
</tr>
<tr>
<td></td>
<td>n = 10</td>
<td></td>
<td></td>
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</tbody>
</table>
Urinary excretion study:
- Mazoit at al\(^4\) calculated urinary clearance by rate method –
  \[ CL_{\text{ren}} = \sum \frac{\Delta A_e}{\Delta t} / C \]^n/1.2 where \( n = \) number of data points (6) and 1.2 is blood/plasma conc. ratio. Urine samples were drawn every 30 mins for first 3 hrs and then each hr till 8 hrs.
- Hasselstrom et al\(^5\) calculated \( CL_{\text{ren}} \) by using \( CL_{\text{ren}} = A_e / \text{AUC} \) (Urine was collected 2 hr fractions for first 12 hrs and then in 12 hr fractions upto 72 hr)
- Milne et al\(^6\) calculated renal clearance as the urinary excretion rate divided by the mean of two plasma concentrations spanning the urine collection interval (mean = 0.048-0.33µmol/l)

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milne et al(^6)</td>
<td>( n = 5 ) (healthy), 25-39 yrs</td>
<td>Ultrafiltration</td>
<td>266 nmol/l</td>
<td>HPLC</td>
<td>fu =0.74 ± 0.01</td>
</tr>
<tr>
<td>Leow et al(^10)</td>
<td>( n = 5 ) (healthy), 25-42 yrs</td>
<td>Ultrafiltration (4000 rpm for 20 min, pH 7.4, 37°C)</td>
<td>20, 60, 100 ng/ml</td>
<td>HPLC LOQ = 4.5 ng/ml</td>
<td>Protein binding = 35.3% (± 0.2 %)</td>
</tr>
<tr>
<td>Hollt et al(^11)</td>
<td>( n = 4 )</td>
<td>Equilibrium Dialysis (equilibration time - 4 hrs, pH 7.4, 37°C)</td>
<td>( 10^{-7} ) M</td>
<td>RIA</td>
<td>Protein binding = 23.4 (± 1.1 %)</td>
</tr>
</tbody>
</table>
**Blood-to-plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazoit et al 9</td>
<td>n= 6</td>
<td>In-vitro</td>
<td>10 and 40 ng/ml</td>
<td>RIA</td>
<td>1.21 (± 0.08)</td>
</tr>
</tbody>
</table>

**Receptor binding studies:**

1. Emmerson et al 12 carried out studies in C6 glioma cells of the cloned rat µ-opioid receptor to determine binding affinities and activation of G-protein. Activation of G-protein by opioid agonists was examined by measuring the stimulation of GTP binding and intrinsic activity was expressed as the percent stimulation relative to DAMGO (100 %). The intrinsic activity of Morphine was 83 %. [3H]sufentanil (0.04nM) were used as high affinity ligand and [3H]naltrexone (0.5 nM) as low affinity ligand in the displacement studies to determine the affinity to receptors.

\[ K_i \text{ (high affinity)} = 0.16 \ (± 0.002) \]
\[ K_i \text{ (low affinity)} = 132 \ (± 6) \]

2. Chen et al 13 studied the binding affinity of opioids at µ-receptor in rat brain homogenates using [3H] DAMGO.

<table>
<thead>
<tr>
<th></th>
<th>Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1.2</td>
</tr>
<tr>
<td>M3G</td>
<td>37.1</td>
</tr>
<tr>
<td>M6G</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Morphine metabolites:**

Morphine undergoes variety of metabolic pathways, in particular glucuronidation of the 3-OH phenolic group and 6-OH alcoholic group to yield morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) resp. The pKₐ values for carboxylic acids for M3G and M6G are 2.83 (±0.05) and 3.23 (±0.05) determined by titrimetry. It has been suggested that M6G is a molecular chameleon that exists both in extended and folded forms, latter providing an unexpected liophilicity to it 14. Both the metabolites are highly hydrophilic, log D of M3G -1.12 and log D of M6G of -0.7915.
## PK studies of M6G:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Milne et al</td>
<td>ICU subjects</td>
<td>44-75</td>
<td>0.020 to 0.122 mg/kg/hr</td>
<td>Infusion</td>
<td></td>
<td>HPLC</td>
<td>18.9 ng/ml</td>
<td>-</td>
<td>Cummulative</td>
<td>AUC 2.18 (±0.40) CL_{tot} 0.12 (±0.02) CL_{ren} -</td>
</tr>
<tr>
<td>Lotsch et al</td>
<td>Healthy</td>
<td>74.2 (±6.5)</td>
<td>0.015 bolus, 0.007 2 for 4 hrs</td>
<td>Bolus &amp; infusion 10 min-8 hr</td>
<td>-</td>
<td>HPLC</td>
<td>10 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>2.4 (±0.2) 0.763 (calculated from MRT and CL)</td>
</tr>
<tr>
<td>Lotsch et al</td>
<td>Healthy</td>
<td>72.9 (±5.4)</td>
<td>0.06 bolus, 0.016 /hr infusion for 8 hrs</td>
<td>Bolus &amp; infusion 10 min-12 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>10 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Osborne et al</td>
<td>Cancer patients</td>
<td>37-100</td>
<td>0.007 -0.06 Infusion 5 min-12 hrs 24 hrs</td>
<td>HPLC 2 nmol/l</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Not mentioned</td>
<td>0.0244 1.37 (±0.54) - 0.51 (±0.36) n=16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penson et al</td>
<td>Healthy</td>
<td>71</td>
<td>0.028 Bolus 0-24 hrs</td>
<td>HPLC 2 nmol/l</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
<td>2.21 (±0.65) 0.23 (±0.062) -</td>
<td></td>
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</tr>
</tbody>
</table>

AUC = Area Under the Curve; CL_{tot} = Total Clearance; V_{dss} = Volume of Distribution; CL_{ren} = Renal Clearance.
**Urinary excretion study:**
- Milne et al\(^6\) calculated renal clearance as the urinary excretion rate divided by the mean of two plasma concentrations spanning the urine collection interval (mean = 0.093-11 µmol/l)
- Osborne et al\(^8\) collected urine samples for 24 hrs (time points not specified).

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milne et al(^6)</td>
<td>n = 5 (healthy), 25-39 yrs</td>
<td>Ultrafiltration</td>
<td>1020 nmol/l</td>
<td>HPLC</td>
<td>(f_u = 0.89 \pm 0.02)</td>
</tr>
</tbody>
</table>

**Blood –to –plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skopp et al(^8)</td>
<td>Healthy</td>
<td><em>In-vitro</em></td>
<td>250 ng/ml</td>
<td>HPLC</td>
<td>0.54</td>
</tr>
</tbody>
</table>

PGP substrates: Primary cultures of porcine brain capillary endothelial cells were used to study brain penetration of M6G. Uptake of M6G was significantly enhanced in presence of inhibitors of PGP, verapamil or vincristine\(^{19}\).
**PK study of M3G:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penson et al²⁰</td>
<td>Healthy, n = 3/dose group</td>
<td>70</td>
<td>0.107</td>
<td>Bolus</td>
<td>0-24 hr</td>
<td>HPLC</td>
<td>10 ng/ml</td>
<td>-</td>
<td>-</td>
<td>AUC (mg/min/ml)</td>
</tr>
<tr>
<td></td>
<td>Adult, 17-78 yrs</td>
<td>0.214</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt; (ml/min/kg)</td>
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<tr>
<td></td>
<td></td>
<td>0.428</td>
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<td></td>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt; (l/kg)</td>
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<td></td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt; (ml/min/kg)</td>
</tr>
</tbody>
</table>

- Milne et al<sup>6</sup> calculated renal clearance as the urinary excretion rate divided by the mean of two plasma concentrations spanning the urine collection interval (mean = 0.31-37 µmol/l)

**Urinary excretion study:**
- Milne et al<sup>6</sup> calculated renal clearance as the urinary excretion rate divided by the mean of two plasma concentrations spanning the urine collection interval (mean = 0.31-37 µmol/l)
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milne et al.⁶</td>
<td>n = 5 (healthy), 25-39 yrs</td>
<td>Ultrafiltration</td>
<td>2170 nmol/l</td>
<td>HPLC</td>
<td>fu =0.85 ± 0.02</td>
</tr>
</tbody>
</table>

Blood –to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skopp et al.¹⁸</td>
<td>Healthy</td>
<td>In-vitro</td>
<td>1000 ng/ml</td>
<td>HPLC</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Hydromorphone

Hydromorphone (HM) is a ketone of morphine. The log D of hydromorphone is -0.5 (± 0.027) (by shake flask method) and pkₐ of 8.01 (± 0.012) (by potentiometry). (Coyle et al. Anesthesiology. ASA abstracts 1984). Another study reports log D of 0.089.³¹ At physiological pH, 55.7 % molecules are non-ionized.
PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
<tbody>
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<tr>
<td>Parab et al22</td>
<td>Healthy n = 9 20-30 yrs</td>
<td>50-86</td>
<td>0.026</td>
<td>Bolus</td>
<td>0-12 hr</td>
<td>RIA</td>
<td>-</td>
<td>Compartmental (2)</td>
<td>-</td>
<td>0.00177</td>
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<td>14.64 (± 7.60)</td>
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<td>1.93 (from micro rate constant s)</td>
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<td>2.08 (from MRT)</td>
</tr>
<tr>
<td>Davis et al23</td>
<td>Allergic rhinitis patients n = 12 29.4 yrs</td>
<td>-</td>
<td>0.025</td>
<td>Bolus</td>
<td>0-16 hrs</td>
<td>LC-MS</td>
<td>0.020 ng/m</td>
<td>Non-compartental</td>
<td>-</td>
<td>0.00092</td>
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<td>26.9 (± 4.69)</td>
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<td>5.28 (± 0.44)</td>
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<tr>
<td>Hill et al24</td>
<td>Healthy n = 10 21-38 yrs</td>
<td>72.7</td>
<td>0.040</td>
<td>Bolus</td>
<td>1-300 mins</td>
<td>HPLC</td>
<td>LOD-0.1 ng/ml</td>
<td>Compartmental (3)</td>
<td>-</td>
<td>0.00175</td>
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<td>22.8 (± 1.78)</td>
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<td>4.05 (± 0.18)</td>
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</tbody>
</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coyle et al (Anesthesiology ASA abstracts)</td>
<td>Normal male</td>
<td>Ultrafiltration</td>
<td>2.5, 10, 20, 31, 41, 62, 72, and 80ng/m</td>
<td>Liquid scintillation</td>
<td>7.7 (± 1.1%)</td>
</tr>
</tbody>
</table>
Blood-to-plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coyle et al (Anesthesiology ASA abstracts)</td>
<td>Normal male</td>
<td>In-vitro</td>
<td>4, 10, 16, 20, 30, 40 ng/ml</td>
<td>Liquid scintillation</td>
<td>1.497 (± 0.096)</td>
</tr>
</tbody>
</table>

Metabolism: It is metabolized mainly in liver by glucuronidation at 3- and 6-position to form HM-3-gluconide (major) and HM-6-gluconide. At 6-position, HM also undergoes reduction to dihydromorphine and dihydroisomorphine via NADPH dihydromorphinone ketone reductases.25

Receptor binding studies:
Chen et al13 studied the binding affinity of opioids at µ-receptor in rat brain homogenates using [3H] DAMGO. Hydromorphone - Kᵢ (nM) = 0.6 (± 3.2)

Remifentanil

Remifentanil is a synthetic opioid. It has a log D of 1.226 and pKₐ of 7.327. An ester linkage in the chemical structure makes this compound susceptible to rapid metabolism by blood and tissue esterases. Approximately 98% of an administered dose is metabolized to the acid and is excreted in urine as the metabolite.28 Remifentanil is 92% plasma protein bound.26
### PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westmoreland et al 29</td>
<td>Healthy n = 24</td>
<td>81.1</td>
<td>0.002</td>
<td>Infusion For 10 min</td>
<td>1-360 min</td>
<td>GC-MS</td>
<td>0.1-250 ng/ml</td>
<td>-</td>
<td>-</td>
<td>AUC (mg/min/ml)</td>
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<tr>
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<td>42.2 yrs(± 6.4)</td>
<td>0.005</td>
<td>0.015</td>
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<td>0.030</td>
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<tr>
<td>Egan et al 30</td>
<td>Healthy n = 10</td>
<td>-</td>
<td>0.003 /min</td>
<td>Infusion</td>
<td>1-240 min</td>
<td>GC-MS</td>
<td>0.1 ng/ml</td>
<td>-</td>
<td>-</td>
<td>CL_{tot} (ml/min/kg)</td>
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<tr>
<td></td>
<td>18-40 yrs</td>
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<tr>
<td>Ross et al 31</td>
<td>Surgical n = 3</td>
<td>60.6</td>
<td>0.005</td>
<td>Bolus 2-60 min</td>
<td>-</td>
<td>GC-MS</td>
<td>ULQ-100 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Vd_{ss} (l/kg)</td>
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<tr>
<td></td>
<td>16-18 yrs</td>
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<tr>
<td>Dahaba et al 32</td>
<td>Healthy n = 13</td>
<td>69</td>
<td>0.000 1/min</td>
<td>Infusion For 20 min</td>
<td>5-60 min</td>
<td>HPLC</td>
<td>100 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>CL_{ren} (ml/min/kg)</td>
</tr>
<tr>
<td></td>
<td>58.2 yrs (± 11.5)</td>
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</tbody>
</table>

**Blood –to –plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
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</thead>
<tbody>
<tr>
<td>Duthie et al 33</td>
<td>By pass surgery</td>
<td>In-ivo</td>
<td>-</td>
<td>GC</td>
<td>B:P ratio calculated from blood and plasma</td>
</tr>
</tbody>
</table>
Metabolism: It is metabolized by rapidly by non-specific tissue and blood esterases to carboxylic acid metabolite which has 1/4600 the potency of remifentanil.²⁹, ³⁰, ³⁴-³⁷

Sufentanil
Sufentanil is a thienyl analogue of fentanyl. It is highly lipophilic with log D of 3.22 and pKₐ of 8.0 (Bovill et al. Baillere’s clinical anesthesiology 1991). At pH 7.4, 20 % of the molecules are non-ionized.

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>BW (kg)</th>
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<tr>
<td>Bovill et al ³⁸</td>
<td>Surgical n = 10 26-64 yrs</td>
<td>71.1</td>
<td>0.005</td>
<td>Bolus</td>
<td>1-60 min</td>
<td>RIA</td>
<td>Sensitivity- 0.06ng/ml</td>
<td>-</td>
<td>Comparative (2)</td>
<td>3.95x10³⁻⁴</td>
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<td>Lowest conc- 0.2-0.3 ng/ml</td>
<td>-</td>
<td></td>
<td>12.66 (±0.78)</td>
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<td>1.74 (± 0.19)</td>
</tr>
<tr>
<td>Scholz et al ³⁹</td>
<td>Brain injured n = 10 34 yrs</td>
<td>80</td>
<td>0.002 bolus and then 0.150 mg/h</td>
<td>Bolus and then Infusion For 48 hr</td>
<td>1 min-48 hr</td>
<td>RIA</td>
<td>5 ng/ml</td>
<td>-</td>
<td>Comparative (2)</td>
<td>0.01</td>
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<td>Median =15.2 (6.5-31.9)</td>
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<td>Median =10 (6.8-24.2)</td>
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<td>0.09 (0.02-0.478)</td>
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</table>

patients ng/ml plasma clearance 0.93
Urinary excretion study:
Scholz et al\textsuperscript{40} calculated renal clearance from the urinary recovery of sufentanil divided by the corresponding AUC value monitored over 72 hr. The renal clearance was found to be 0.6 % of the total clearance. The urine samples were collected for 72 hrs.

Plasma protein binding studies:

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<tr>
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<th>Method</th>
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<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meuldermans et al\textsuperscript{41}</td>
<td>n = 6 Healthy</td>
<td>Equilibrium dialysis (20 rpm at 37\textdegree C, 4hrs)</td>
<td>1 ng/ml</td>
<td>Liquid scintillation</td>
<td>$f_b = 0.925 (\pm 0.007)$</td>
</tr>
<tr>
<td>Meistelman et al\textsuperscript{42}</td>
<td>Adults n = 11</td>
<td>Equilibrium dialysis (20 rpm at 37\textdegree C, 4hrs)</td>
<td>1 ng/ml</td>
<td>HPLC</td>
<td>$f_u = 7.8 % (\pm 1.5%)$</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

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<tbody>
<tr>
<td>Meuldermans et al\textsuperscript{41}</td>
<td>Healthy n = 6</td>
<td>In-vitro</td>
<td>1 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.741 (\pm 0.049)</td>
</tr>
</tbody>
</table>

Metabolism: A study by Lavrijsen et al using liver microsomes demonstrates that the major metabolites formed were by oxidative N-dealkylation at the piperidine nitrogen, oxidative N-dealkylation of the piperidine ring from the phenylpropanamide nitrogen, oxidative O-demethylation and aromatic hydroxylation.\textsuperscript{43}
Receptor binding studies:

1. Emmerson et al\textsuperscript{12} carried out studies in C\textsubscript{6} glioma cells of the cloned \textbf{rat \textit{\textmu}-opioid receptor} to determine binding affinities and activation of G-protein. Activation of G-protein by opioid agonists was examined by measuring the stimulation of GTP binding and intrinsic activity was expressed as the percent stimulation relative to DAMGO (100\%). The intrinsic activity of sufentanil was 97\%. [\textsuperscript{3}H]sufentanil (0.04nM) were used as high affinity ligand and [\textsuperscript{3}H]naltrexone (0.5 nM) as low affinity ligand in the displacement studies to determine the affinity to receptors.

\[ K_i \text{ (high affinity)} = 0.034 \pm 0.009 \text{ nm} \]
\[ K_i \text{ (low affinity)} = 4.51 \pm 0.14 \text{ nm} \]

2. Leysen et al\textsuperscript{44} carried out receptor binding studies for different opioids using membrane preparations of \textbf{rat brain and spinal cord} and radiolabeled sufentanil. The equilibrium inhibition constant \( K_i \) was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37\(^\circ\)C.

\[ K_i \text{ (nm)} = 0.1 \]
Alfentanil
Alfentanil is a short acting analgesic. It is lipophilic with log D of 2.1\(^2\) and pK\(_a\) of 6.5.\(^2\) At physiological pH 7.4, 89% of the molecules are non-ionized. The renal clearance is reported to be 0.4 % of the total clearance.

PK studies:

<table>
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<tr>
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<tr>
<td>Egan et al(^3)(^0)</td>
<td>Healthy n = 10 18-40 yrs</td>
<td>-</td>
<td>1.5/m in</td>
<td>Infusion</td>
<td>1-600 min</td>
<td>GC-MS</td>
<td>1.0 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>7.0x10(^5)</td>
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<td>5.42 (± 1.28)</td>
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<td>0.56 (± 0.11)</td>
</tr>
<tr>
<td>Ferrier et al(^4)(^5)</td>
<td>Healthy n = 10 45(± 13 yrs</td>
<td>59 (±14)</td>
<td>0.050</td>
<td>Bolus</td>
<td>5-600 min</td>
<td>RIA</td>
<td>Sensitivity - 0.1 ng/ml Lowest conc- 2 ng/ml</td>
<td>-</td>
<td>Compartmental (2)</td>
<td>0.0161</td>
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<td>3.1(±1.6)</td>
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<td>0.281 (±0.097)</td>
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<tr>
<td>Meistelman et al(^4)(^6)</td>
<td>surgery n = 5 31.3(± 3.8) yrs</td>
<td>58 (± 6)</td>
<td>0.020</td>
<td>Bolus</td>
<td>1-360 min</td>
<td>RIA</td>
<td>Sensitivity -0.1 ng/ml Lowest conc- 0.18 ng/ml</td>
<td>-</td>
<td>Compartmental (2)</td>
<td>0.00476</td>
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<td>4.2 (± 1.7)</td>
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<td>0.457 (± 0.160)</td>
</tr>
<tr>
<td>Macfie et al(^4)(^7)</td>
<td>Healthy n = 6 38.2 yrs(18-</td>
<td>61.3 (± 8.1)</td>
<td>0.050</td>
<td>Bolus</td>
<td>0-90 min</td>
<td>RIA</td>
<td>-</td>
<td>-</td>
<td>Compartmental (2)</td>
<td>0.0112</td>
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<td>4.45 (± 0.55)</td>
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<td>0.398 (± 0.026)</td>
</tr>
</tbody>
</table>

363
<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belpaire et al</td>
<td>n =17, 36-74 yrs for adult</td>
<td>Equilibrium dialysis at 37°C for 4 hr</td>
<td>1-100 µg/ml</td>
<td>Liquid scintillation</td>
<td>% Free alfentanil: 5.5 (SEM = ± 0.2) (range = 4.2-7.4)</td>
</tr>
<tr>
<td>Meuldermans et al</td>
<td>n =6 Healthy</td>
<td>Equilibrium dialysis at 37°C for 4 hr</td>
<td>1 ng/ml</td>
<td>Liquid scintillation</td>
<td>$f_b = 0.921 (± 0.013)$</td>
</tr>
<tr>
<td>Ferrier et al</td>
<td>Healthy n =10 45(± 13) yrs</td>
<td>Equilibrium dialysis at 37°C for 4 hr</td>
<td>50 and 500 ng/ml</td>
<td>RIA</td>
<td>Free alfentanil: 11.5 (± 3.9) % at 50 ng/ml and 11.8 (± 4.1) % at 500 ng/ml</td>
</tr>
<tr>
<td>Meistelman et al</td>
<td>surgery n = 5</td>
<td>Equilibrium dialysis at 37°C for 4 hr</td>
<td>50 and 500 ng/ml</td>
<td>RIA</td>
<td>Binding: 92.3 (± 1.3) % at 50 ng/ml and 91.8 (± 1.5) % at 500 ng/ml</td>
</tr>
<tr>
<td>Macfie et al</td>
<td>Healthy n = 6 38.2 yrs (18-62)</td>
<td>Equilibrium dialysis at 37°C</td>
<td>Bolus dose 0.050 mg/kg</td>
<td>RIA</td>
<td>Binding: 90.7 (± 0.4) %</td>
</tr>
<tr>
<td>Study</td>
<td>Subjects</td>
<td>Method</td>
<td>Concentration range</td>
<td>Assay</td>
<td>B:P ratio</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Meuldermans et al 41</td>
<td>Healthy n =6</td>
<td>In-vitro</td>
<td>1 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.630 (± 0.021)</td>
</tr>
</tbody>
</table>

**Blood –to –plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hug et al88</td>
<td>Surgery n =3</td>
<td>Ultrafiltration</td>
<td>Bolus dose 0.125 mg/kg</td>
<td>RIA LOD – 0.25 ng/ml</td>
<td>Binding: 90.75%</td>
</tr>
</tbody>
</table>

**Metabolism:** Alfentanil is predominantly metabolized by the CYP3A4 and CYP 3A3. A study by Lavrijsen et al using liver microsomes demonstrates that the major metabolites formed were by oxidative N-dealkylation at the piperidine nitrogen, oxidative N-dealkylation of the piperidine ring from the phenylpropanamide nitrogen, oxidative O-demethylation and aromatic hydroxylation.

**Receptor binding study:**

1. Leysen et al44 carried out receptor binding studies for different opioids using membrane preparations of rat brain and spinal cord and radiolabeled sufentanil. The equilibrium inhibition constant $K_i$ was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37ºC. $K_i$(nm) for alfentanil = 19
Fentanyl

Fentanyl is a short acting analgesic. It is lipophilic with log D of 2.9 and pkₐ of 8.4. At physiological pH 7.4, 9.1% of the molecules are non-ionized.

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
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<th>PK Analysis</th>
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<tr>
<td>McClain et al</td>
<td>Healthy n = 7</td>
<td>65-85.5 (±14)</td>
<td>0.003-0.006</td>
<td>Bolus</td>
<td>-</td>
<td>Plasma, Urine</td>
<td>Plasma, Urine</td>
<td>-</td>
<td>Comparative (3)</td>
<td>4.4x10⁻⁴, 10.9 (Calculated)</td>
</tr>
<tr>
<td></td>
<td>22-29 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vdₚ₀ = 4.15</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.654</td>
</tr>
<tr>
<td>Singleton et al</td>
<td>Healthy adults n = 7</td>
<td>18-41 yrs</td>
<td>0.020/kg</td>
<td>IV infusion</td>
<td>1-240 min</td>
<td>RIA, Sensitivity = 0.5 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
<td>1.44x10⁻⁴, 13.9 (± 3.0)</td>
</tr>
</tbody>
</table>

Urinary excretion studies: Urine and stool were collected for 72 hrs. These were analyzed in duplicate or triplicate for ³H-fentanyl and for total ³H-radioactivity (³H-fentanyl and ³H-metabolite) and analyzed by paper chromatography. % dose excreted unchanged in urine = less than 8 %
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mclain et al(^2)</td>
<td>Healthy, n = 7, 22-29 yrs</td>
<td>Equilibrium dialysis (37°C for 24 hrs)</td>
<td>0.076-76 ng/ml</td>
<td>Liquid scintillation</td>
<td>Binding = 81 ± 2%</td>
</tr>
<tr>
<td>Meuldermans et al (^4)</td>
<td>Healthy, n = 6</td>
<td>Equilibrium dialysis (20 rpm at 37°C, 4hrs)</td>
<td>10 ng/ml</td>
<td>Liquid scintillation</td>
<td>(f_b = 0.844 \pm 0.019)</td>
</tr>
<tr>
<td>Hollt et al (^1)</td>
<td>Healthy, n = 4</td>
<td>Equilibrium Dialysis (equilibration time - 4 hrs, pH 7.4, 37°C)</td>
<td>10^-7 M</td>
<td>RIA</td>
<td>Protein binding = 69.5 (± 0.2 %)</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meuldermans et al (^4)</td>
<td>Healthy, n = 6</td>
<td>In-vitro</td>
<td>1 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.965 (± 0.055)</td>
</tr>
</tbody>
</table>

**Metabolism:** Fentanyl undergoes phase I metabolism by oxidative N-dealkylation and O-dealkylation. Other metabolites are phenylacetic acid, norfentanyl and p-OH (phenethyl) fentanyl.
Receptor binding studies:

1. Emmerson et al\textsuperscript{12} carried out studies in C\textsubscript{6} glioma cells of the cloned \textbf{rat \(\mu\)-opioid receptor} to determine binding affinities and activation of G-protein. Activation of G-protein by opioid agonists was examined by measuring the stimulation of GTP binding and intrinsic activity was expressed as the percent stimulation relative to DAMGO (100\%). The intrinsic activity of fentanyl was 97\%. \[^3\text{H}\]sufentanil (0.04nM) were used as high affinity ligand and \[^3\text{H}\]naltrexone (0.5 nM) as low affinity ligand in the displacement studies to determine the affinity to receptors.

\[K_i \text{ (high affinity)} = 0.16 \pm 0.002 \text{ nm}\]
\[K_i \text{ (low affinity)} = 157 \pm 7 \text{ nm}\]

2. Leysen et al\textsuperscript{44} carried out receptor binding studies for different opioids using membrane preparations of \textbf{rat brain and spinal cord} and radiolabeled sufentanil. The equilibrium inhibition constant \(K_i\) was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37\(^\circ\)C.

\[K_i \text{ (nm)} = 1.6\]

3. Cassel et al\textsuperscript{54} carried out an assay to measure binding to the \textbf{cloned human \(\mu\)-opioid receptor} contained \[^3\text{H}\]diprenorphine (0.4-1 nm) or \[^3\text{H}\]alvimopan (0.86-1.1 nm), test compounds at concentrations ranging 36 pM to 10 \(\mu\)M in 20 \(\mu\)g protein/well. After incubation of 90 mins, the bound radioactivity was determined. Ki values are the geometric means with confidence intervals in paranthesis.

\[\text{Using }[^3\text{H}]\text{diprenorphine, } K_i \text{ (nm)} = 14 \text{ (6.6-30)}\]

\[\text{Using }[^3\text{H}]\text{alvimopan, } K_i \text{ (nm)} = 34 \text{ (20-57)}\]

\hline

\textbf{Oxycodone}

Oxycodone is a synthetic derivative of thebaine. The log D (determined by shake flask method) of oxycodone is 0.21\textsuperscript{21} and another paper reports as -0.15\textsuperscript{55}. Lalovic et al\textsuperscript{56} reports the log D in the range of 1.2-1.7 (determined computationally or experimentally at pH 7-8). The pK\textsubscript{a} is reported as 8.53\textsuperscript{57}. 

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## PK Studies:

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirvela et al58</td>
<td>Control n = 10</td>
<td>NA</td>
<td>0.05</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>GC</td>
<td>AUC (mg/min/ml)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>0-24 hrs</td>
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<tr>
<td>Poyhia et al59</td>
<td>Surgery n = 9</td>
<td>71 (±11)</td>
<td>0.05</td>
<td>Bolus</td>
<td>5min-12 h</td>
<td>GC</td>
<td>3 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>3.18x10^{-3}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27(±5.3)</td>
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</tr>
<tr>
<td>Takala et al60</td>
<td>Healthy n = 10</td>
<td>67</td>
<td>0.044</td>
<td>Bolus</td>
<td>2 min-10hrs</td>
<td>GC</td>
<td>3 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>4.213 x 10^{-3} (CI-3.133 x10^{-3} - 5.292 x10^{-3})</td>
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<tr>
<td></td>
<td></td>
<td>19-28 yrs</td>
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</tr>
<tr>
<td>Leow et al61</td>
<td>Surgery n = 12</td>
<td>72.8 (±10.6)</td>
<td>0.11</td>
<td>Bolus</td>
<td>5 min-24 hr</td>
<td>HPLC</td>
<td>3 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>1.06 x 10^{-4}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68.8(±1.2)</td>
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</table>

### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poyhia et al58</td>
<td>(n = 8), healthy (25-30 yrs)</td>
<td>Ultrafiltration (24°C/20min) and then</td>
<td>200 ng/ml</td>
<td>GC</td>
<td>Binding : 38.3 % (± 18.1)</td>
</tr>
</tbody>
</table>
Urinary excretion studies:

1. Kirvela at al study⁵⁸:
Subjects: n =10, healthy
Urine samples were collected 0-3, 3-6, 6-12, 12-24 hrs. Urine samples were analysed using GC (LOQ-3 ng/ml). The urinary recovery of unconjugated oxycodone was 1% (0-5%).

Metabolism:
In a study done by Lalovic et al⁵⁶, it was found that oxycodone is metabolized via CYP3A-mediated N-demethylation (noroxycodone, noroxymorphone, and α- and β-noroxycodol) which accounted for 45 ± 21% of the dose There are other pathways mediated by CYP 2D6 as O-demethylation (Oxymorphone, and α- and β-oxymorphol), and 6-keto reduction (α- and β-oxycodol) which accounted for 11± 6% and 8± 6% dose.

Receptor binding studies:
Chen et al¹³ studied the binding affinity of opioids at μ-receptor in rat brain homogenates using [³H] DAMGO.
Oxycodone - Kᵢ (nM) = 47.4 (± 9.3)

Codeine
Codeine is a derivative of morphine. Kauffmann et al¹ reported log D of codeine is 0.35 (at pH 7.4 by shake-flask method) and its pKₐ 8.10 (determined potentiometrically). Avdeef at al¹⁵ reported the log D (shake flask method) as 0.22 and pKₐ as 8.22 (determined potentiometrically).
PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guay et al 62</td>
<td>Healthy n = 6</td>
<td>27.8 (±3.7) yrs</td>
<td>0.62</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>RIA</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
</tr>
<tr>
<td>Persson et al 63</td>
<td>Cholesytec- tomy patients n = 12</td>
<td>49-53 yrs</td>
<td>0.25</td>
<td>Bolus</td>
<td>0-12hr</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compart mental</td>
</tr>
</tbody>
</table>

Urinary excretion studies:

- Guay et al 62 determined urinary excretion of codeine. All the urine produced during 24 hrs was collected and analysed using RIA. The total renal clearance was calculated using the equation \( \text{CL}_{\text{ren}} = \frac{Ae_{t_1-t_2}}{\text{AUC}_{t_1-t_2}} \) where \( Ae_{t_1-t_2} \) is the codeine dose administered intravenously and \( \text{AUC}_{t_1-t_2} \) is the AUC during the urine collection interval \( t_1-t_2 \).
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vree at al(^{64})</td>
<td>n = 8</td>
<td>Centrifugation 4000g, 30 min</td>
<td>\textit{In-vivo} 0.1-1 µg/ml</td>
<td>HPLC LOQ-5 ng/ml</td>
<td>56.1 % (± 2.5)</td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>Centrifugation 4000g, 30 min</td>
<td>\textit{In-vitro} 0.1-1 µg/ml</td>
<td>HPLC LOQ-5 ng/ml</td>
<td>54.5 % (± 3.0)</td>
</tr>
<tr>
<td>Mohammed et al(^{65})</td>
<td>Ultrafiltration 15 min/1500g</td>
<td>After 60 mg oral dose \textit{In-vivo}</td>
<td></td>
<td>HPLC</td>
<td>29.2% (± 3.4)</td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration 15 min/1500g</td>
<td>100-400 ng/ml \textit{In-vitro}</td>
<td></td>
<td>HPLC</td>
<td>30.5% (± 2.7)</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Mohammed et al(^{65})</td>
<td>Healthy</td>
<td>\textit{In-vitro}</td>
<td>50-500 ng/ml</td>
<td>HPLC</td>
<td>0.96 (± 0.04)</td>
</tr>
</tbody>
</table>

Metabolism: Codeine is metabolized to 6 metabolites: Codeine-6-glucuronide (81.0 ±9.3%), Norcodeine (2.16 ± 1.44%), Morphine (0.56 ± 0.39%), M3G (2.10 ± 1.24%), M6G(0.80 ± 0.63%) and normorphine(2.44± 2.42%). It undergoes O-dealkylation to morphine by CYP2D6.\(^{64}\)

Receptor binding studies:
Chen et al\(^{13}\) studied the binding affinity of opioids at \textit{\(\mu\)-receptor in rat brain homogenates} using \(^3\text{H}\) DAMGO. Codeine - \(K_i\) (nM) = 248.3 (± 101.1)
Heroin

Diacetylmorphine is a semisynthetic derivative of morphine, it’s a prodrug and has active metabolites, 6-monoacetylmorphine and morphine which are responsible for analgesic effects. The heroin ester bonds undergo rapid hydrolysis in plasma. Rook et al reported $pK_a$ as 7.6. At physiological pH 38.7 % molecules are non-ionized. Avdeef at al have reported log D of 0.85 (determined by shake flask method) and $pK_a$ of 7.95 (determined potentiometrically). Plummer at al reports a log D (7.4) of 1.1.

PK studies:

<table>
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<tr>
<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>Assay</th>
<th>LOQ</th>
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<th>Urine Collection method</th>
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<tr>
<td>Rentsch et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Heroin addicted n = 8 35 yrs</td>
<td>69</td>
<td>3.47-6.1</td>
<td>Bolus</td>
<td>0-180 mins</td>
<td>-</td>
<td>LC-MS</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Girardin et al&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Opioid dependent n = 10 32 yrs</td>
<td>67</td>
<td>2.2</td>
<td>Bolus</td>
<td>0-60 mins</td>
<td>-</td>
<td>LC-MS</td>
<td>1 nmol/l</td>
<td>Non-compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Elliot at al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>n = 4, healthy narcotic use history</td>
<td>95.4</td>
<td>0.166 mg/hr</td>
<td>Infusion</td>
<td>0-8 hrs</td>
<td>0-40.5 hr</td>
<td>GC</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>
Urinary excretion study\(^{69}\):
All the urine was collected at 30 specified times for 40.5 hrs from the time heroin infusion. The bladder was emptied zero time and urine samples were collected at 0.5 hr intervals for 2.5 hr, then hourly until hour 24.5. The catheters were removed and accumulated urine is collected at 32.5 and 40.5 hrs.
% dose excreted in urine = 0.13

Metabolism: Heroin is rapidly metabolized to 6-monoacetylmorphine hydrolysis by nonspecific esterases and finally to morphine. Morphine is gluronidated and forms M3G and M6G. (Rook et al. Current Clin Pharmacology 2006)

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al(^{70})</td>
<td>n = 5, healthy</td>
<td>Equilibrium dialysis – Incubation at 37ºC for 20 hr with 9000dpm of heroin-(^{13})C</td>
<td>0.008-0.4 mg/ml</td>
<td>Liquid scintillation</td>
<td>protein binding = 20-39%</td>
</tr>
</tbody>
</table>

Receptor binding studies:  
Chen et al\(^{13}\) studied the binding affinity of opioids at \(\mu\)-receptor in rat brain homogenates using \([\text{H}]\text{DAMGO}\. Heroin - \(K_i\) (nM) = 9.6 (± 3.9)

Meperidine  
Meperidine (Pethidine) is a non-polar, lipophilic drug with a pk\(_a\) 8.68 (by potentiometry) and log D 1.6 (by shake flask method).\(^1\)\(^,\)\(^{71}\) Another study reports pk\(_a\) as 8.5 and log D as 1.59.\textbf{Error! Bookmark not defined.} Error! Bookmark not defined. At physiological pH 7.4, 7.4% is non-ionised.
### PK studies:

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Mather et al(^{72})</td>
<td>surgery n=33 40 (± 17 yrs)</td>
<td>72 (± 16 )</td>
<td>0.61</td>
<td>Bolus</td>
<td>0-360 mins</td>
<td>-</td>
<td>GLC</td>
<td>-</td>
<td>Compar tmental (2)</td>
<td>-</td>
</tr>
<tr>
<td>Koska et al(^{73})</td>
<td>Surgery n = 6 Age-NA</td>
<td>75.2 (± 14.3 )</td>
<td>5</td>
<td>Bolus</td>
<td>0-600 mins</td>
<td>-</td>
<td>GLC</td>
<td>-</td>
<td>Compar tmental (2)</td>
<td>-</td>
</tr>
<tr>
<td>Verbeek et al(^{74})</td>
<td>healthy n = 6 23-31 yrs</td>
<td>77.5 (± 14.3 )</td>
<td>0.28</td>
<td>Bolus</td>
<td>0-24 hr</td>
<td>-</td>
<td>GC-MS</td>
<td>LOD-2 ng/ml</td>
<td>Compar tmental (2)</td>
<td>-</td>
</tr>
<tr>
<td>Odar-Cederlo f et al(^{75})</td>
<td>minor hand surgery or cysitosc opy, mean urinary pH 6.6 (range -5.3-8)</td>
<td>-</td>
<td>1 mg/kg at rate 10mg /min</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>GC</td>
<td>-</td>
<td>-</td>
<td>Fraction ated</td>
<td>-</td>
</tr>
</tbody>
</table>
Urinary excretion study: Analysis: Urine was collected for periods of 0-6, 6-12, 12-24 hrs. For each sample creatinine and creatinine clearance was calculated. The urinary content of meperidine was measured by GC-MS. Renal clearance was calculated using midpoint values of individual plasma-concentration time curves. 

\[ CL_{\text{ren}} = 1.2 \text{ ml/min/kg (± 0.96)} \]

The renal clearance of meperidine is inversely correlated with urinary pH (\( r = -0.73, p<0.05 \))

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mather et al\textsuperscript{72}</td>
<td>surgery ( n = 19 )</td>
<td>Ultrafiltration</td>
<td>0.96 µg/ml</td>
<td>GLC</td>
<td>( f_a = 0.27 \pm 0.03 )</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mather et al\textsuperscript{72}</td>
<td>Healthy ( n = 5 ) 25-33 yrs</td>
<td>\textit{In-vitro}</td>
<td>0.2-20 µg/ml</td>
<td>GLC</td>
<td>1.33</td>
</tr>
<tr>
<td>Verbeeck et al\textsuperscript{74}</td>
<td>healthy ( n = 6 ) 23-31 yrs</td>
<td>\textit{In-vivo}</td>
<td>0.28 mg/kg as IV bolus</td>
<td>GC-MS</td>
<td>1.04 ± 0.03</td>
</tr>
</tbody>
</table>

Metabolism: The drug is metabolized to pethidinic acid, norpethidine, and norpethidinic acid. Norpethidine is an active metabolite.\textsuperscript{72, 75}

Receptor binding studies:
1. Emmerson et al\textsuperscript{12} carried out studies in C\textsubscript{6} glioma cells of the cloned \textbf{rat \( \mu \)-opioid receptor} to determine binding affinities and activation of G-protein. Activation of G-protein by opioid agonists was examined by measuring the stimulation of GTP binding and intrinsic activity was expressed as the percent stimulation relative to DAMGO (100\%). The intrinsic activity of meperidine was 64\%. \(^{[3]H}\)sufentanil (0.04nM) were used as high affinity ligand and \(^{[3]H}\)naltrexone (0.5 nM) as low affinity ligand in the displacement studies to determine the affinity to receptors.

\[
K_i \text{(high affinity)} = 38.1 (\pm 0.002) \\
K_i \text{(low affinity)} = 132 (\pm 6)
\]

2. Leysen et al\textsuperscript{44} carried out receptor binding studies for different opioids using membrane preparations of \textbf{rat brain and spinal cord} and radiolabeled sufentanil. The equilibrium inhibition constant \(K_i\) was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37ºC.

\(K_i\) (nm) for Meperidine = 193

\textbf{Methadone}

Methadone is a synthetic opioid, its structure being distinctly different than other opioids. It is a lipophilic drug with log D of 2.1 (by shake flask method) and \(pK_a\) 9.26 (determined by potentiometry).\textsuperscript{1} Another study reports \(pK_a\) 9.26 and log D as 2.06.\textsuperscript{44} At physiological pH 7.4, 1.2 \% is non-ionized.

\textbf{PK studies:}

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gourlay et al\textsuperscript{76}</td>
<td>Surgery n =19</td>
<td>67.8</td>
<td>0.29</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>-</td>
<td>GC</td>
<td>Sensitivity</td>
<td>-</td>
<td>Comparative (2)</td>
</tr>
<tr>
<td>Inturrisi</td>
<td>Chronic</td>
<td>66.1 ± 0.30</td>
<td>Bolus</td>
<td>5 -2880</td>
<td>0-24</td>
<td>RIA</td>
<td>Sensitivity</td>
<td>-</td>
<td>Comparative fraction</td>
<td>-</td>
</tr>
</tbody>
</table>

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Urinary excretion studies:\(^{77}\):

Urine samples were collected for 24 hrs. Renal clearance was calculated using the equation:

\[
\text{CL}_{\text{ren}} = \frac{X_u (0-24)}{\text{AUC} (0-24)}
\]

where \(X_u\) is amount of methadone excreted in the urine.

\[
\text{CL}_{\text{ren}} = 0.059 \text{ ml/min/kg}
\]

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inturrisi et al(^{77})</td>
<td>Chronic pain n = 5 50 ± 12</td>
<td>Equilibrium dialysis</td>
<td>0.073 µg/ml</td>
<td>Liquid scintillation</td>
<td>Binding – 89.4 ± 2.9%</td>
</tr>
<tr>
<td>Wilkins et al(^{78, 79})</td>
<td>Subjects n = 48</td>
<td>37°C for 20 mins followed by centrifugation for 30 mins</td>
<td>100-1000 µg/ml</td>
<td>GC</td>
<td>% Free methadone = 10.1% (± 3.4)</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inturrisi et al(^{77})</td>
<td>Chronic pain n = 5 50 ± 12</td>
<td>In-vitro</td>
<td>0.1, 0.2, 0.4 µg/ml</td>
<td>Liquid scintillation</td>
<td>0.75 ± 0.03</td>
</tr>
</tbody>
</table>
Metabolism: Methadone is demethylated by CYP3A4 to 2-ethylidene-1,5-dimethyl-3-3-dephenyl pyrrolidine (EDDP). It is also metabolized by other CYPs like CYP2D6, CYP1A2, CYP2C9 and CYP2C19.

Receptor binding studies:

1. Chen et al\textsuperscript{13} studied the binding affinity of opioids at $\mu$-receptor in rat brain homogenates using $[^3H]$ DAMGO. Methadone $K_i$ (nM) = 28.8(±10.4)

2. Leysen et al\textsuperscript{44} carried out receptor binding studies for different opioids using membrane preparations of rat brain and spinal cord and radiolabeled sufentanil. The equilibrium inhibition constant $K_i$ was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37ºC. $K_i$ (nm) for Methadone = 2.2

3. Cassel et al\textsuperscript{54} carried out an assay to measure binding to the cloned human $\mu$-opioid receptor contained $[^3H]$diprenorphine (0.4-1 nm) or $[^3H]$alvimopan (0.86-1.1 nm), test compounds at concentrations ranging 36 pM to 10 $\mu$m in 20 $\mu$g protein/well. After incubation of 90 mins, the bound radioactivity was determined. Ki values are the geometric means with confidence intervals in paranthesis.
   Using $[^3H]$ diprenorphine, $K_i$ (nm) = 14 (9.4-21)
   Using $[^3H]$ alvimopan, $K_i$ (nm) = 24 (15-36)

Dextropropoxyphene

Dextropropoxyphene is a synthetic opioid derived from methadone. It has a $p_{ka}$ 6.3 (Glare et al. Dextropropoxyphene. Opioids in cancer pain (ed: Mellar D, Glare P, Hardy J.) 2005, Oxford University Press, NY) and log $P$ of 4.81 obtained from Chemdraw software and the calculated log D (7.4) is 4.73 (using formula log D(7.4) = log P –log [1 + 10 $^{(p_{ka}-7.4)}$]).
PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram et al</td>
<td>Healthy n=8</td>
<td>71.6</td>
<td>0.91</td>
<td>Bolus</td>
<td>0-72 hrs</td>
<td>GC-MS</td>
<td>LOD</td>
<td>Non-compartmental</td>
<td>Fractionated</td>
<td>AUC (mg/min/ml)</td>
</tr>
<tr>
<td>Gram et al</td>
<td>Healthy n=8</td>
<td>71.6</td>
<td>0.92</td>
<td>Infusion over 0.5 hr</td>
<td>0-72 hrs</td>
<td>GLC-MS</td>
<td>LOD 8 and 5 nmol/l</td>
<td>Compartmental</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Urinary excretion studies: Urine was collected at intervals 3-9 hr during first day and then at 24 hrs intervals until end of day 7. The rate of urinary elimination of radioactivity was quantitated by calculating ratio between the excretion at 0-12 hr, 48-168 hr. The total urinary excretion of radioactivity at the end of day 7 was 55-75% of dose. Fraction excreted unchanged at the end of 7 days = 0.65

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giacomini et al</td>
<td>n = 8, healthy, 21-33 yrs.</td>
<td>Equilibrium dialysis (pH 7.4, 37°C, 12)</td>
<td>228, 510, 1046 ng/ml</td>
<td>GC</td>
<td>Free fraction of propoxyphene = 0.24 (± 0.02)</td>
</tr>
</tbody>
</table>
Metabolism: There are three metabolic pathways: N-demethylation (major), aromatic hydroxylation (minor) and ester hydrolysis (minor). N-desmethylpropoxyphene is the major metabolite formed by demethylation.

Tramadol

Tramadol is a centrally acting analgesic with dual mode of action comprising both µ-opioid and monoaminergic agonism. The $pK_a$ value is $9.44 \pm 0.03$ (determined by UV spectrophotometry at $25^\circ C$). The log P (from ChemDraw software) is 2.53 and the calculated log D (7.4) is 0.48 (using formula $\log D(7.4) = \log P - \log [1 + 10^{(pK_a-7.4)}]$).

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Lintz et al</td>
<td>Healthy n = 12</td>
<td>80.6 (± 9.5)</td>
<td>0.54</td>
<td>Bolus</td>
<td>0-30 hr</td>
<td>0-30hrs</td>
<td>GC-NFID</td>
<td>1.3 ng/ml</td>
<td>Non-compartmental</td>
<td>Fractionated</td>
</tr>
<tr>
<td>85</td>
<td>30.8(±6.4) yrs</td>
<td></td>
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</tr>
<tr>
<td>Lintz et al</td>
<td>Healthy n = 10</td>
<td>66.1 (± 8.2)</td>
<td>0.54</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>GC-MS</td>
<td>4.5 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
</tr>
<tr>
<td>86</td>
<td>48.7(±7.1) yrs</td>
<td></td>
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</tr>
<tr>
<td>Quetglas et al</td>
<td>Healthy n = 36</td>
<td>65</td>
<td>1.54</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>HPL C</td>
<td>0.5 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
</tr>
<tr>
<td>87</td>
<td>22-26</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
**Urinary excretion study**: Urine was collected in intervals 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-10, 10-12, 12-24, 24-27, 27-30 h to determine cumulative renal excretion. At the end of each period, volume and pH were determined. The cumulative excretion of unchanged tramadol was extrapolated to infinity \((Ae_\infty)\) was calculated by adding the amount determined experimentally until 30h \((Ae_{0-30})\) to the residual amount \(Ae_{30-\infty}\) which was computed from the renal excretion rate of the last sampling interval \((Ae_{27-30}/3)\) and the terminal rate constant \((\beta)\) determined by the equation

\[
Ae_{30-\infty} = (Ae_{27-30}/3)*e^{-1.5/\beta}
\]

For calculation of renal clearance, \(CL_{\text{ren}} = CL_{\text{tot}}*Ae_\infty\) (% dose)/100

\(CL_{\text{ren}} = 0.96\ \text{ml/min/kg (± 0.24)}\)

Gibson et al\(^{88}\) reports a \(CL_{\text{ren}}\) of 1.12 ml/min/kg.

**Plasma protein binding**: Gibson et al reports plasma protein binding of 20% \(^{88}\)

**Metabolism**: Biotransformation of tramadol in man and animals takes place via \(N\)- and \(O\)-demethylation (phase I reactions) and conjugation of \(O\)-demethylated compounds (phase II reactions). The phase metabolites are mono-\(O\)-demethyl-tramadol (M1), mono-\(N\)-demethyl-tramadol (M2), \(di-N\)-demethyl-tramadol (M3), \(tri-N,O\)-demethyl-tramadol (M4) and \(di-N,O\)-demethyl-tramadol (M5). M1-conjugates and M5-conjugates formed by glucuronidation and sulphation are the main phase II metabolites\(^{84}\)

**Receptor binding study**: Gillen et al\(^{84}\) determined affinity and efficacy of tramadol at the cloned human opioid receptor. The affinity of tramadol was determined by competitive inhibition of \(^3[H]\)-naloxone under high and low salt conditions. The agonist-induced (DAMGO) stimulation was used to determine relative intrinsic efficacy.

\(K_i\) (nm) low salt: 2400 ± 1100
\(K_i\) (nm) high salt: > 10000

Efficacy (%): DAMGO - 100 % ± 4
Tramadol - < 5

\(^{85}\) Urinary excretion study
\(^{88}\) Plasma protein binding
\(^{84}\) Metabolism

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Piritramide

Piritramide is a synthetic opioid analgesic, structurally related to meperidine.

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kietzmann et al²</td>
<td>Surgical n = 10 41(± 12 yrs)</td>
<td>79 (± 8)</td>
<td>0.2 Bolus</td>
<td>0-48 hrs</td>
<td>0-72 hrs</td>
<td>GC</td>
<td>1.5 µg/ml</td>
<td>-</td>
<td>Fractionated</td>
<td>AUC (mg/min/ml) = 0.0255</td>
</tr>
<tr>
<td>Bouillon et al³</td>
<td>Surgical n = 29 21-82 yrs</td>
<td>74</td>
<td>0.2 Bolus</td>
<td>2 min-48 hrs</td>
<td>-</td>
<td>GC</td>
<td>1.5 µg/ml</td>
<td>-</td>
<td>-</td>
<td>AUC (mg/min/ml) = 7.16</td>
</tr>
</tbody>
</table>

**Urinary excretion study:** (Kietzman et al²)
Urine was collected in 12 hr portions upto 72 hr. CL_{R} = A_{c}/AUC_{0-∞}, A_{c} = total amount excreted unchanged \( f_{c} = A_{c}/\text{Dose} \), \( f_{c} = 1.40 (± 0.76) \)
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
</table>
| Kietzman et al²        | n = 10 surgical patients and pooled plasma of healthy | Ultrafiltration   | 30-5000 ng/ml       | GC    | % Bound in patients - 94.5 (±1.3) % Bound in healthy - 93.8  
In the pH range 7.0-7.8, the free fraction was markedly influenced by pH. The unbound fraction was 4.7% at pH 7.4 and 6.4% at pH 7.0  
4% albumin solution - % bound – 70  
0% AAG solution - % bound – 90 |
| Wiesner et al¹         | n = 5 healthy patients                  | Equilibrium dialysis | 400 ng/ml          | GC    | % Bound – 88% (to 5% human albumin)                   |
Tilidine

Tilidine is a cyclohexane derivative. It is a prodrug which gets demethylated in the liver to give active metabolite nortilidine which is further metabolized to bisnortilidine and several polar metabolites.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vollmer et al⁴</td>
<td>Surgical</td>
<td>76 (± 5.8)</td>
<td>0.58</td>
<td>Infusion</td>
<td>2 min-28 hrs</td>
<td>GLC</td>
<td>1-2 ng/ml</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 10</td>
<td></td>
<td></td>
<td></td>
<td>0-48hrs</td>
<td></td>
<td></td>
<td>Plasma-Urine</td>
<td>Plasma-Urine Fractionated</td>
<td>0.0402 (± 0.008)</td>
</tr>
<tr>
<td>Hajda et al⁵</td>
<td>Healthy</td>
<td>76 (± 5.8)</td>
<td>0.66</td>
<td>Infusion</td>
<td>2 min-28 hrs</td>
<td>GLC</td>
<td>1 ng/ml</td>
<td>Non-compart</td>
<td>Non-compart</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-compart</td>
<td>- 0.0430 (± 0.008)</td>
<td>15.76 (± 2.99 )</td>
</tr>
</tbody>
</table>

**Urinary excretion study:** (Vollmer et al⁴)
Urine was collected in 0-2, 2-4, 8-12, 12-24, 24-36, 36-48 hr. CL_R = A_e/AUC, A_e = total amount excreted unchanged, AUC- area under the curve during one dosing interval under steady state conditions.
A_e = 1.6% (± 1.4)

**Blood –to–plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hajda et al⁵</td>
<td>Human</td>
<td>In-vivo</td>
<td>-</td>
<td>-</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Meptazinol

Meptazinol is a centrally acting agonist-antagonist.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
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<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al(^7)</td>
<td>Healthy n =14 yrs</td>
<td>63-81</td>
<td>0.35</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Plasma</td>
<td>Plasma LOD 1-2 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>AUC (mg*min/ml) 216.4 (± 9.6)</td>
</tr>
<tr>
<td>Birnie et al(^8)</td>
<td>Control n =13 yrs</td>
<td>-</td>
<td>0.36</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Plasma</td>
<td>LOD 10 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Norbury et al(^6)</td>
<td>Healthy male n =9 yrs</td>
<td>72.2</td>
<td>0.35</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>Plasma</td>
<td>Lower limit of sensitivity = 3 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>30.5 (± 1.24)</td>
</tr>
<tr>
<td>Gepts et al(^9)</td>
<td>Surgical patients</td>
<td>65 ± 8</td>
<td>3</td>
<td>Bolus</td>
<td>2-300 min</td>
<td>Plasma</td>
<td>Lower limit of sensitivity = 5 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>0.120 (± 6.374)</td>
</tr>
</tbody>
</table>

[^7]: Murray et al.
[^8]: Birnie et al.
[^9]: Gepts et al.
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norbury et al 6</td>
<td>Healthy human</td>
<td>Equilibrium dialysis</td>
<td>25-250 ng/ml</td>
<td>Liquid scintillation</td>
<td>Binding = 27.1%</td>
</tr>
</tbody>
</table>

Ketobemidone

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collectio n method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bondesson et al 10</td>
<td>Healthy n = 6 30.0 yrs (± 10.5 )</td>
<td>68.8</td>
<td>0.145</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>GC-MS</td>
<td>10 ng/ml</td>
<td>-</td>
<td>Compart mental (2)</td>
<td>AUC (mg*min/ml) 0.0183 (± 0.007 ) CL_{tot} (ml/min/kg) 9.16 (± 3.5 ) Vd_{ss} (l/kg) 0.48 (calculated )</td>
</tr>
<tr>
<td></td>
<td>ICU patients n = 17 64 yrs</td>
<td>81</td>
<td>0.04</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>LC-MS</td>
<td>3nmol/l</td>
<td>-</td>
<td>Compart mental (2)</td>
<td>-</td>
</tr>
<tr>
<td>Al Shurbaji et al 11</td>
<td>Healthy male n = 6 32.0 (± 4.4 )</td>
<td>72.7</td>
<td>0.137</td>
<td>Bolus</td>
<td>0-10 hrs</td>
<td>GC-MS</td>
<td>2 ng/ml</td>
<td>Compart mental</td>
<td>(2)</td>
<td>4.9</td>
</tr>
</tbody>
</table>

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### Levorphanol

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ (ng/ml)</th>
<th>PK Analysis</th>
<th>Urine Collection Method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al(^{13})</td>
<td>Healthy male n = 12 yrs</td>
<td>68.8 (± 11.8 yrs)</td>
<td>0.145</td>
<td>Bolus</td>
<td>0-10 hrs</td>
<td>-</td>
<td>GC-MS</td>
<td>-</td>
<td>Compartmental (2)</td>
<td>-</td>
</tr>
<tr>
<td>Dixon et al(^{14})</td>
<td>Patients with pain n =1/dose 20-60 yrs</td>
<td>50-95</td>
<td>0.052</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>RIA</td>
<td>0.5</td>
<td>Compartmental (3)</td>
<td>-</td>
</tr>
</tbody>
</table>

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</tbody>
</table>

**PK Parameters:**

- **AUC:**
  - 13.0 (mg*min/ml)
  - 18.4 (ml/min/kg)
  - 11.5 (l/kg)
  - 13.0 (ml/min/kg)

- **CL\(_{tot}\):**
  - 13.0 (ml/min/kg)
  - 10.1 (l/kg)
  - 11.5 (l/kg)
  - 13.0 (ml/min/kg)

- **Vd\(_{ss}\):**
  - 13.0 (l/kg)

- **CL\(_{ren}\):**
  - 13.0 (ml/min/kg)
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon et al 14</td>
<td>Cancer patients n= 10</td>
<td>Equilibrium dialysis</td>
<td>-</td>
<td>Liquid scintillation</td>
<td>Binding =40 ± 2.6%</td>
</tr>
</tbody>
</table>


Partial Agonists

Butorphanol
Butorphanol is a mixed agonist-antagonist opioid analgesic. It has a $pK_a$ of 8.6 and log P of 3.48 obtained from Chemdraw software and the calculated log D (7.4) is 2.25 (using formula log D(7.4) = log P – log [1 + 10 $(pK_a-7.4)$]).

Metabolism: Butorphanol undergoes metabolism to form hydroxybutorphanol and norbutorphanol, hydroxybutorphanol being the major urinary metabolite.¹

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analyses</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Vachharajani et al²</td>
<td>Healthy n = 12 41 yrs</td>
<td>70.3</td>
<td>0.014</td>
<td>Bolus</td>
<td>0-16 hrs</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Fractionated</td>
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<tr>
<td>Ramsey et al³</td>
<td>Healthy n = 8 27.9 (± 3.9 yrs)</td>
<td>76.25</td>
<td>0.018</td>
<td>Bolus</td>
<td>2min-24 hr</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Compartmental</td>
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<tr>
<td>Shyu et al⁴</td>
<td>Allergic rhinitis n = 18 34 yrs</td>
<td>78.5</td>
<td>0.025</td>
<td>Bolus</td>
<td>3 min-16 hrs</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Non-compartmental</td>
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</tr>
<tr>
<td>Shyu et al³</td>
<td>Healthy n = 12 20-40 yrs</td>
<td>NA</td>
<td>0.014</td>
<td>Bolus</td>
<td>3 min-16 hrs</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Non-compartmental</td>
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</tbody>
</table>

¹ Shyu et al. (2018)
Urinary excretion studies:

- Gaver et al\(^1\) collected urine samples at each hr for the first 4 hrs (after administration of IV dose of 1mg of \(^3\)H-butorphanol) and then at 4-6, 6-8, 8-10, 10-24, 24-32, 32-48, 48-72, 72-96 and 96-120. Volume was determined at the end of 120 hrs.

Analysis: Samples were counted in scintillation medium. Urinary butorphanol was extracted and analysed by HPLC, TLC, MS and GC. The concentrations of butorphanol were calculated from specific activities.

Results:
Urinary excretion of radioactivity- main route is renal. The mean cumulative percentage of tritium excreted in urine after IV was 72 ± 4 %. The percentage excreted in feces was 14 ± 2 %. 4-5 % butorphanol was excreted as unchanged drug in urine.

- In a study by Vachcharajani et al\(^2\), urine samples were collected at 0-2, 2-4, 4-6, 6-12, 12-16 hrs.

Analysis: HPLC
% dose excreted unchanged in urine = 1.94 ± 1.5

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaver et al(^1)</td>
<td>-</td>
<td>centrifuged at 5(^\circ)C for 10 min at 2000 rpm</td>
<td>1.2 mg/ml</td>
<td>Liquid scintillation</td>
<td>83%</td>
</tr>
</tbody>
</table>
Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsey et al³</td>
<td>Healthy n =8 27.9 (± 3.9 )yrs</td>
<td>In-vivo</td>
<td>0.018 mg/kg iv dose</td>
<td>RIA</td>
<td>1.14 (±0.17)</td>
</tr>
</tbody>
</table>

Receptor binding study:

Emmerson et al⁶ carried out studies in C₆ glioma cells of the cloned rat µ-opioid receptor to determine binding affinities and activation of G-protein. Activation of G-protein by opioid agonists was examined by measuring the stimulation of GTP binding and intrinsic activity was expressed as the percent stimulation relative to DAMGO (100%). The intrinsic activity of butorphanol was 12 %. [³H]sufentanil (0.04nM) were used as high affinity ligand and [³H]naltrexone (0.5 nM) as low affinity ligand in the displacement studies to determine the affinity to receptors.

\[ K_i \text{ (high affinity)} = 0.088 \pm 0.005 \text{ nm} \]
\[ K_i \text{ (low affinity)} = 2.46 \pm 0.4 \text{ nm} \]

Nalbuphine

Nalbuphine is agonist and antagonist opioid analgesic agent that is structurally related to naloxone, an antagonist and to oxymorphone, an analgesic agonist of opiate receptors. The log D of 0.26 (from Chemdraw software) and pKₐ 8.71 (obtained from prescribing information from Nubain-nalbuphine hydrochloride-Endo Pharmaceuticals).

Metabolism: Nalbuphine undergoes hepatic metabolism. The major metabolite is N-hydroxycetocyclobutyl-methylnor nalbuphine and undergoes hydroxylation to give other metabolites.

Error! Bookmark not defined.
PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaillon et al(^7)</td>
<td>Healthy n = 9 23-32 yrs</td>
<td>76</td>
<td>9.1</td>
<td>Infusion</td>
<td>0-48 hrs</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>Lower limit of sensitivity = 0.2 ng/ml</td>
<td>Lower limit of sensitivity = 5 ng/ml</td>
<td>Compartmental</td>
</tr>
<tr>
<td>Lo et al(^8,9)</td>
<td>Healthy n = 12 20-40 yrs</td>
<td>73.5</td>
<td>D1 = 0.14 D2 = 0.27</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>Lower limit of sensitivity = 0.1 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
</tr>
<tr>
<td>Lo et al(^10)</td>
<td>Healthy 23.5 yrs</td>
<td>NA</td>
<td>9.1</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>0.21 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
</tr>
</tbody>
</table>

**Urinary excretion study\(^7\):**
The renal clearance calculated using the equation: \(CL_{\text{ren}} = \frac{Ae_{\infty}}{AUC}\), in which \(Ae_{\infty}\) was the amount of unchanged nalbuphine excreted into 48 hr.
\(CL_{\text{ren}} = 1.26 \text{ ml/min/kg} \text{ (4.3\% of the } CL_{\text{tot}})\)

**Plasma protein binding:** 45 % (Drug information handbook), 50 % (Jaillon et al\(^7\))
Receptor binding study:

Emmerson et al\textsuperscript{6} carried out studies in C\textsubscript{6} glioma cells of the cloned rat \textmu- opioid receptor to determine binding affinities and activation of G-protein. Activation of G-protein by opioid agonists was examined by measuring the stimulation of GTP binding and intrinsic activity was expressed as the percent stimulation relative to DAMGO (100\%). The intrinsic activity of nalbuphine was 11\%.

\[^{3}\text{H}]\text{Sufentanil} (0.04\text{nM}) were used as high affinity ligand and \[^{3}\text{H}]\text{naltrexone} (0.5 \text{nM}) as low affinity ligand in the displacement studies to determine the affinity to receptors.

\[K_i \text{ (high affinity)} = 0.048 \pm 0.005 \text{ nm} \]
\[K_i \text{ (low affinity)} = 1.68 \pm 0.05 \text{ nm}\]

Pentazocine

Pentazocine is a strong analgesic and weak narcotic antagonist. It has a log D of 2.04 (determined by shake flask method) and \( pK_a \) 9.16 (determined potentiometry).\textsuperscript{11}

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Ehrnebo et al\textsuperscript{12}</td>
<td>Healthy, n = 5</td>
<td>71 (± 10)</td>
<td>0.42</td>
<td>Bolus</td>
<td>5 min - 6 hr</td>
<td>Ion-pair</td>
<td>Lower limit of sensitivity -15 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>AUC (mg.min/ml)</td>
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<td></td>
<td>Chromatography</td>
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<tr>
<td>Beckett et al\textsuperscript{13}</td>
<td>Healthy, n = 4, 23-42</td>
<td>-</td>
<td>0.34</td>
<td>Bolus</td>
<td>- 0-32 hrs Faece</td>
<td>GC</td>
<td>1.0 \mu g/ml</td>
<td>Fractionated</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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Urinary excretion study:\textsuperscript{13}:
Urine samples were collected half hourly for the first 4 hrs, hourly for next 4 hrs, 2 hourly for next 6 hrs, then at 24 hrs, and 4-hourly thereafter up to 32 hr. Faeces were also collected as passed for 48 hrs.
% dose excreted unchanged in 32 hr in urine: 8-24%
% dose excreted unchanged in 48 hr in faeces: 0.1-2%

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrnebo et al\textsuperscript{14}</td>
<td>Healthy, n = 20, 22-45 yrs</td>
<td>Equilibrium dialysis</td>
<td>220 ng/ml</td>
<td>Liquid scintillation</td>
<td>Protein binding = 56-66%</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrnebo et al\textsuperscript{14}</td>
<td>Healthy, n = 3, 22-45 yrs</td>
<td>\textit{In-vitro}</td>
<td>-</td>
<td>Liquid scintillation</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Metabolism: It is extensively metabolized. The dimethyl allyl side chain is oxidized to two isomeric alcohols and the phenolic hydroxyl is conjugated. Both alcohols maybe conjugated and the trans-isomer is oxidized to carboxylic acid. This acid is also conjugated but to a lesser extent.\textsuperscript{15}
Receptor binding study:
Leysen et al\textsuperscript{16} carried out receptor binding studies for different opioids using membrane preparations of rat brain and spinal cord and radiolabeled sufentanil. The equilibrium inhibition constant $K_i$ was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37\degree C. $K_i$ (nm) for Pentazocine = 26

Buprenorphine

Buprenorphine is a semisynthetic analgesic with mixed agonist-antagonist properties. It has a log $D$ of 3.93 (shake flask method) and $pK_a$ 8.31 (by potentiometry).\textsuperscript{17}

\textbf{PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullingham et al\textsuperscript{18}</td>
<td>Healthy n = 24 64.5 (± 1.6)</td>
<td>67.7 (± 2.4)</td>
<td>0.004 Bolus</td>
<td>2-180 min</td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
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<tr>
<td>Kuhlman et al\textsuperscript{19}</td>
<td>Healthy n = 6</td>
<td>68</td>
<td>0.018 Bolus</td>
<td>0-96 hrs</td>
<td>-</td>
<td>GC-MS-MS</td>
<td>0.2 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>AUC (mg.min/ml)</th>
<th>$\text{Cl}_{\text{tot}}$ (ml/min/kg)</th>
<th>$V_d_{ss}$ (l/kg)</th>
<th>$\text{Cl}_{\text{ren}}$ (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.13x10\textsuperscript{-4}</td>
<td>18.8 (± 1.31)</td>
<td>2.8 (± 0.52)</td>
<td>-</td>
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<td></td>
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<td>9.57x10\textsuperscript{-4}</td>
<td>18.8 (SEM ± 3.2)</td>
<td>4.9 (SEM ± 1.71)</td>
<td>-</td>
</tr>
</tbody>
</table>
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heel et al²⁰</td>
<td>-</td>
<td>-</td>
<td>0-7 ng/ml</td>
<td>-</td>
<td>96%</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullingham et al¹⁸</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
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</tbody>
</table>

Metabolism: Extensively metabolized by N-dealkylation to norbuprenorphine by CYP3A4. Norbuprenorphine is the active metabolite with potency 1/5 th pf the parent compound. Norbuprenorphine and buprenorphine, both, undergo glucuronidation.²¹

Receptor binding studies:

1. Leysen et al¹⁶ carried out receptor binding studies for different opioids using membrane preparations of rat brain and spinal cord and radiolabeled sufentanil. The equilibrium inhibition constant $K_i$ was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37°C. $K_i$ (nm) for Methadone = 26

2. Cassel et al²² carried out an assay to measure binding to the cloned human μ-opioid receptor contained $^3$[H]diprenorphine (0.4-1 nm) or $^3$[H]alvimopan (0.86-1.1 nm), test compounds at concentrations ranging 36 pM to 10 μm in 20 μg protein/well. After incubation of 90 mins, the bound radioactivity was determined. $K_i$ values are the geometric means with confidence intervals in parenthesis.

  Using $^3$[H] diprenorphine, $K_i$(nm) = 0.52 (0.41-0.67)
  Using $^3$[H] alvimopan, $K_i$(nm) = 0.74 (0.55-1.0)
Dezocine is a semisynthetic analgesic with mixed agonist-antagonist properties.

### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al(^2)</td>
<td>Healthy n = 5/group 33-66 yrs</td>
<td>59.1-123.6</td>
<td>5</td>
<td>Bolus</td>
<td>1min-8 hrs</td>
<td>HPLC</td>
<td>LOD</td>
<td>1 ng/ml</td>
<td>Compart-mental</td>
<td>-</td>
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<td>29.6 (SE ± 8.6)</td>
<td>5.8 (SE± 1.6)</td>
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<td></td>
<td>29.3 (SE±10.3)</td>
<td>7.8 (SE±1.8)</td>
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<td></td>
<td>23.6 (SE±3.0)</td>
<td>3.2 (SE±1.5)</td>
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<td></td>
<td>Mean – 27.5 (SE±4.3)</td>
<td>Mean- 5.6 (SE±1.0)</td>
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<tr>
<td>Locnisk</td>
<td>Healthy</td>
<td>-</td>
<td>5</td>
<td>Bolus</td>
<td>0-8hrs</td>
<td>GC</td>
<td>0.2</td>
<td>Compart-mental</td>
<td>-</td>
<td>23.7</td>
</tr>
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</table>

\(^2\) Wilson et al.
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al(^2)(^3)</td>
<td>n = 12 18-52 yrs</td>
<td>Ultrafiltration</td>
<td>12.8-522 ng/ml.</td>
<td>HPLC</td>
<td>% Bound – 88.3-94.0% (SE ± 0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>10</th>
<th>20</th>
<th>and HPLC</th>
<th>ng/ml</th>
<th>mental</th>
<th>(± 4.1)</th>
<th>(± 11.1)</th>
<th>11.8 (± 3.1)</th>
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<td></td>
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<td></td>
<td>49.3 (± 9.2)</td>
<td>11.2 (± 3.0)</td>
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<td></td>
<td>41.5 (± 8.2)</td>
<td>9.4 (± 2.4)</td>
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</tbody>
</table>
**Antagonist**

**Naltrexone**

Naltrexone is a narcotic antagonist. It has a $pK_a$ of 8.13 (determined potentiometrically) and log D of 1.12 (by shake flask method)$^1$.

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Wall et al$^2$</td>
<td>Healthy n =5</td>
<td>-</td>
<td>0.013</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-72 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>-</td>
<td>Fractionated</td>
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</tr>
<tr>
<td>Lictko et al$^3$</td>
<td>Healthy n =5</td>
<td>-</td>
<td>0.014</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-72 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>-</td>
<td>Fractionated</td>
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</tbody>
</table>

Urinary excretion study$^2$:  
Urine was collected at intervals: 0-3, 3-6, 6-12, 12-24, 24-48, 48-72 hr. The urine was analyzed by liquid scintillation spectrometry.  
Renal clearance calculated by $C_u = \frac{dC}{dt}/P_t$  
$CL_{\text{ren}} = 1.33 \text{ ml/min/kg (± 0.45)}$
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludden et al4</td>
<td>-</td>
<td>Equilibrium dialysis</td>
<td>0.1-500 ng/ml</td>
<td>Liquid scintillation</td>
<td>20.7%</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall et al2</td>
<td>Healthy n =5</td>
<td>In-vivo</td>
<td>IV Bolus 0.013 mg/kg</td>
<td>Liquid scintillation</td>
<td>~1.00</td>
</tr>
</tbody>
</table>

Metabolism: The major metabolite is unconjugated 6β-naltrexol. The other metabolites are 6α-naltrexol, 2-hydroxy-3-O-methylnaltrexone and 2-hydroxy-3-O-methyl-6β-naltrexol.2

Receptor binding studies:

1. Emmerson et al5 carried out studies in C6 glioma cells of the cloned rat µ-opioid receptor to determine binding affinities and activation of G-protein. Activation of G-protein by opioid agonists was examined by measuring the stimulation of GTP binding and intrinsic activity was expressed as the percent stimulation relative to DAMGO (100%). The intrinsic activity of naltrexone was 0.

   [$^3$H]sufentanil (0.04nM) were used as high affinity ligand and [$^3$H]naltrexone (0.5 nM) as low affinity ligand in the displacement studies to determine the affinity to receptors.

   Ki (high affinity) = 0.087 (± 0.002) nm
   Ki (low affinity) = 0.28 (± 0.01) nm

2. Cassel et al6 carried out an assay to measure binding to the cloned human µ-opioid receptor contained [$^3$H]diprenorphine (0.4-1 nm) or [$^3$H]alvimopan (0.86-1.1 nm), test compounds at concentrations ranging 36 pM to 10 µm in 20 µg protein/well. After
incubation of 90 mins, the bound radioactivity was determined. Ki values are the geometric means with confidence intervals in parenthesis.
Using \(^3\)H diprenorphine, \(K_i\) (nm) = 1.1 (0.74-1.5)
Using \(^3\)H alvimopan, \(K_i\) (nm) = 0.86 (0.61-1.2)

Naloxone

Naloxone is a narcotic antagonist. It has a \(pK_a\) 7.82 (determined potentiometrically) and log D 1.52 (by shake flask method).

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Ngai et al(^7)</td>
<td>Healthy n = 9</td>
<td>63.8</td>
<td>0.36</td>
<td>Bolus</td>
<td>2-120 mins</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.0127</td>
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<tr>
<td></td>
<td>25-54 yrs</td>
<td>SE = ± 2</td>
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<td>9.0 ng/ml</td>
<td></td>
<td>RIA</td>
<td></td>
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<td>Compar tmental</td>
<td>28.4 (calculated by data thief)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 µg/ml</td>
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<td></td>
<td></td>
<td>2.4 (calculated by data thief)</td>
</tr>
<tr>
<td></td>
<td>Aitken-head et al(^8)</td>
<td>68.4</td>
<td>0.012</td>
<td>Bolus</td>
<td>1-180 mins</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.37x10(^{-4})</td>
</tr>
<tr>
<td></td>
<td>Healthy n = 12</td>
<td>28.5</td>
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<tr>
<td></td>
<td>28.5 yrs</td>
<td>0.012</td>
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<td></td>
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<td>63.8</td>
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<td>2.5 µg/ml</td>
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</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asali et al.(^9)</td>
<td>n = 18</td>
<td>Healthy</td>
<td>Equilibrium dialysis</td>
<td>HPLC</td>
<td>% Free naloxone = 54.1 (± 4.4)</td>
</tr>
</tbody>
</table>
Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibata et al10</td>
<td>n = 3 Healthy</td>
<td>In-vitro</td>
<td>-</td>
<td>LC-MS/MS</td>
<td>1.22</td>
</tr>
</tbody>
</table>

Metabolism:11
7,8-dihydro-14-hydroxynormorphinone and N-allyl-7,8-dihydro-14-hydroxynrmorphine are the major metabolites identified in human urine.

Receptor binding studies:

1. Leysen et al12 carried out receptor binding studies for different opioids using membrane preparations of rat brain and spinal cord and radiolabeled sufentanil. The equilibrium inhibition constant $K_i$ was calculated with 0.5 nm of sufentanil in the binding assay run in sodium free Tris-HCl buffer at pH 7.4 at 37°C. $K_i$ (nm) = 3.1

2. Cassel et al6 carried out an assay to measure binding to the cloned human $\mu$-opioid receptor contained $^3$[H]diprenorphine (0.4-1 nm) or $^3$[H]alvimopan (0.86-1.1 nm), test compounds at concentrations ranging 36 pM to 10 µm in 20 µg protein/well. After incubation of 90 mins, the bound radioactivity was determined. Ki values are the geometric means with confidence intervals in paranthesis.
Using $^3$[H] diprenorphine, $K_i$ (nm) = 3.3 (2.7-4.1)
Using $^3$[H] alvimopan, $K_i$ (nm) = 5.4 (3.5-8.3)
### Nalmefene

#### PK Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg) ± SD</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Plasma</td>
<td>Plasma</td>
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</tr>
<tr>
<td>Frye et al(^15)</td>
<td>Healthy n = 18 23.8 yrs (± 4.2)</td>
<td>76.1 (± 8.3)</td>
<td>1.11</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>RIA</td>
<td>0.0625-2 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>0.000996 (± 0.00027)</td>
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<tr>
<td>Matzke et al(^14)</td>
<td>Healthy n = 8 44.4 (± 16.8)</td>
<td>78 (± 16)</td>
<td>1.82</td>
<td>Bolus</td>
<td>5 min-44 hrs</td>
<td>RIA</td>
<td>0.0625-2 ng/ml</td>
<td>Compartmental</td>
<td>Fractionated</td>
<td>0.00086 (± 0.000198)</td>
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</tr>
<tr>
<td>Frye et al(^15)</td>
<td>Healthy n = 12 47.5 (± 18.3)</td>
<td>81.8 (± 19.1)</td>
<td>2.00</td>
<td>Bolus</td>
<td>5 min-48 hrs</td>
<td>RIA</td>
<td>0.0625-2 ng/ml</td>
<td>Compartmental</td>
<td>Cumulative</td>
<td>0.001812 (± 0.000654)</td>
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<tr>
<td>Dixon et al(^16)</td>
<td>Healthy n = 24 29 yrs</td>
<td>68</td>
<td>0.029</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>RIA</td>
<td>Limit of sensitivity = 0.3 ng/ml</td>
<td>Noncompartmental</td>
<td>Fractionated</td>
<td>0.001014 (± 0.000156)</td>
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</tbody>
</table>

\(^{a}\) Calculated.
Urinary excretion studies:

1. Matzke et al\textsuperscript{14}
   Urine samples were collected: 0-4, 4-8, 8-12, 12-24, 24-36 hrs
   Analysis: RIA
   Range: 1.25-40 ng/ml
   Renal clearance was calculated as the quotient of total amount recovered in urine and AUC from 0-48 hrs.
   \[ CL_{\text{ren}} = 1.35 \pm 0.85 \text{ ml/min/kg} \]

2. Frye et al\textsuperscript{15}
   All urine was collected from 0-4, 4-8, 8-12, 12-24, 24-36, 36-48 hr
   The renal clearance of nalmefene was calculated as the quotient of the total amount recovered in urine and the AUC from 0-48 hrs.

3. Dixon et al\textsuperscript{16}
   Urine samples were collected over 0-6, 6-12, 12-24, 24-48 hrs
   % dose excreted unchanged in the urine: 3.8\% (± 2.0) – 2mg IV dose
   5.5\% (± 1.1) – 6 mg IV dose
   5.7\% (± 1.7) – 12 mg IV dose
   5.0\% (± 3.1) - 24 mg IV dose
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frye et al(^1^5)</td>
<td>Healthy n = 12</td>
<td>Ultrafiltration</td>
<td>IV Bolus 2 mg/kg</td>
<td>RIA</td>
<td>34.4% (± 13.6)</td>
</tr>
</tbody>
</table>

Blood –to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revex Package Insert</td>
<td>Humans</td>
<td>In-vitro</td>
<td>0.376 to 30 ng/mL</td>
<td>-</td>
<td>1.3 (CV-6.6%)</td>
</tr>
</tbody>
</table>
Methylnaltrexone

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Yuan et al(^{17})</td>
<td>Healthy n = 12</td>
<td>29.3 yrs (± 5.8)</td>
<td>-</td>
<td>0.3</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>0-72 hrs</td>
<td>LC/MS/MS</td>
<td>0.05 ng/ml</td>
<td>Non-compartmental</td>
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<tr>
<td>Foss et al(^{18})</td>
<td>Healthy n = 8</td>
<td>28 yrs</td>
<td>75.3</td>
<td>0.64</td>
<td>Infusion for 10 min</td>
<td>0-12 hrs</td>
<td>0-8 hrs</td>
<td>HPLC</td>
<td>Lower limit of sensitivity = 100 ng/ml</td>
<td>Compartmental Cumulative AUC (mg*min/ml)</td>
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416
## Appendix I (b)

### Human PK Study Summaries of β-ARLS

#### Nonselective beta-blockers

**Carteolol**

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
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<tr>
<td>Ishizaki et al(^1)</td>
<td>Healthy 22-30 yrs</td>
<td>62</td>
<td>0.21</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-48 hr</td>
<td>HPLC</td>
<td>5 ng/ml</td>
<td>0.1µg/ml</td>
<td>Cumulative 328.7 (SE±0.94)</td>
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</table>

### Plasma protein binding studies:

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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lang et al(^2)</td>
<td></td>
<td></td>
<td>3.3-66 µg/ml</td>
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<td>14.5-16.3%</td>
</tr>
</tbody>
</table>
Urine excretion study:
- Ishizaki et al\textsuperscript{1}:
  Urine collection: 0-2, 2-4, 4-8, 8-12, 12-24, 24-48 hr
  Renal clearance $\text{CL}_{\text{ren}} = \frac{\text{Ae}_{48}}{[\text{AUC}]_{0,48}}$, where $\text{Ae}_{48}$ is cumulative amount of drug excreted unchanged in urine upto 48 hrs

Bioavailability study:
Ishizaki et al\textsuperscript{1}: Formulation : Not mentioned (17.785 mg)
Sampling: 0-24 hrs
Analysis: HPLC
$F_{\text{oral}} = 83.7 \pm 8.0$ (55.7-111.3 %)

Propranolol

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
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<tr>
<td>Wilson\textsuperscript{3}</td>
<td>Healthy n =10</td>
<td>69</td>
<td>0.2</td>
<td>Bolus</td>
<td>0-8 hr</td>
<td>GLC</td>
<td>5 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>215 (SE±24)</td>
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<tr>
<td>Olanoff\textsuperscript{4}</td>
<td>Healthy n=5</td>
<td>77</td>
<td>0.1 (-)/(+)</td>
<td>Infusion</td>
<td>0-16 hr</td>
<td>GC-MS</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data from Wilson et al\textsuperscript{3} and Olanoff et al\textsuperscript{4}.*
## Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al(^5)</td>
<td>Healthy n = 6</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>GLC</td>
<td>Compartmental</td>
</tr>
<tr>
<td></td>
<td>45 yrs</td>
<td></td>
<td></td>
<td></td>
<td>15.7 (SE ± 1.95)</td>
</tr>
<tr>
<td>Fagan et al(^6)</td>
<td>Healthy n = 6</td>
<td>equilibrium dialysis</td>
<td>125 ng/ml of (+)-P and (-)-P</td>
<td>Liquid scintillation</td>
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<tr>
<td></td>
<td>20-31 yrs</td>
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<td>185 (± 84)</td>
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<td>13.6 (± 5.3)</td>
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<td>2.92 (± 6.55)</td>
</tr>
<tr>
<td>Sager et al(^9)</td>
<td>Females n = 5</td>
<td>equilibrium dialysis</td>
<td>5 nM</td>
<td>Liquid scintillation</td>
<td>89.0%</td>
</tr>
<tr>
<td></td>
<td>67-73 yrs</td>
<td></td>
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<tr>
<td>Cheymol et al(^7)</td>
<td>Healthy n = 9</td>
<td>bolus</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>Non-compartmental</td>
</tr>
<tr>
<td></td>
<td>32 ± 9 yrs</td>
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<td>161 (± 16.6)</td>
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<td>11.6 (± 1.9)</td>
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<td>3.1 (± 0.7)</td>
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<tr>
<td>Cid et al(^8)</td>
<td>Healthy n = 9</td>
<td>iv infusion for 20 mins</td>
<td>0-10 hrs</td>
<td>GC</td>
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<td></td>
<td>24 yrs (23-25 yrs)</td>
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<td>59.21 (± 2.09)</td>
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<td>8.83 (± 1.0)</td>
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<td>3.44 (± 0.42)</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Methodology</td>
<td>Concentration</td>
<td>Analysis Method</td>
<td>F\textsubscript{u} (+)</td>
</tr>
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<td>---------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Walle et al\textsuperscript{10}</td>
<td>7</td>
<td>Equilibrium dialysis</td>
<td>125 ng/ml (+)-P and (-)-P</td>
<td>GC-MS</td>
<td>( f\textsubscript{u} (+) = 25.3% (SE =1.9) )</td>
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<tr>
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<td></td>
<td>( f\textsubscript{u} (-) = 22.0% (SE =2.0) )</td>
</tr>
<tr>
<td>Bendayan et al\textsuperscript{11}</td>
<td>10</td>
<td>Equilibrium dialysis</td>
<td>93 ng/ml</td>
<td>Liquid scintillation</td>
<td>( f\textsubscript{u} = 5.9% ± 1.0 )</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
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<td></td>
<td>( f\textsubscript{u} = 7.6 ± 2.6 )</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>( f\textsubscript{u} = 5.9% ± 1.0 )</td>
</tr>
<tr>
<td>Belpaire et al\textsuperscript{12}</td>
<td>4</td>
<td>Equilibrium dialysis</td>
<td>5 ng/ml</td>
<td>Liquid scintillation</td>
<td>89.3% ± 1.0</td>
</tr>
<tr>
<td>Taylor et al\textsuperscript{13}</td>
<td>6</td>
<td>Equilibrium dialysis</td>
<td>Oral 80 mg dose twice daily for 14 days</td>
<td>Fluorimetry</td>
<td>88.6% ± 0.9</td>
</tr>
</tbody>
</table>
Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
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</thead>
<tbody>
<tr>
<td>Olanoff et al⁴</td>
<td>n = 5</td>
<td>-</td>
<td></td>
<td>For (+) = 0.99</td>
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<td>RBC/fu = 2.95 ± 0.39</td>
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<td>For (-) = 0.99</td>
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<td>RBC/fu = 2.83 ± 0.39</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(calculated using hematocrit and RBC/fu ratio)</td>
</tr>
<tr>
<td>Taylor et al¹³</td>
<td>Healthy n = 6</td>
<td>Ex-vivo</td>
<td>Fluorimetry</td>
<td>0.74 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>27.3 ± 5 yrs</td>
<td>Oral 80 mg dose twice daily for 14 days</td>
<td></td>
<td>RBC: Plasma - 0.36 ± 0.11</td>
</tr>
</tbody>
</table>

Bioavailability study:

Watson et al⁵: Formulation : Not mentioned (80 mg twice daily)
Sampling: 0-24 hrs
Analysis: GLC
F_{oral} = 54 ± 82 %

Cid et al⁸: Formulation : Tablets (40 mg twice daily)
Sampling: 0-12 hrs
Analysis: GC
F_{oral} = 17.80 ± 3.58 %

Wilson et al³: Formulation : Tablet (3.2 mg/kg)
Sampling: 0-8 hrs
Analysis: GLC
F_{oral} = 0.32 ± 0.04
Timolol

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>Wilson et al(^3)</td>
<td>Healthy n=10</td>
<td>69</td>
<td>0.025</td>
<td>Bolus</td>
<td>0-8 hr</td>
<td>GLC</td>
<td>2 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>AUC (ng.h/ml)</td>
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<td>CL$_{\text{tot}}$ (ml/min/kg)</td>
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<td>Vd$_{ss}$ (l/kg)</td>
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<td>CL$_{\text{ren}}$ (ml/min/kg)</td>
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<tr>
<td>Vedin et al(^14)</td>
<td>Healthy n=12 24-39 yrs</td>
<td>73.5 ± 8.1</td>
<td>0.02</td>
<td>Bolus</td>
<td>0-12 hr</td>
<td>GLC</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td>AUC (ng.h/ml)</td>
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<td>CL$_{\text{tot}}$ (ml/min/kg)</td>
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<td>Vd$_{ss}$ (l/kg)</td>
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<td>CL$_{\text{ren}}$ (ml/min/kg)</td>
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<tr>
<td>Kubota et al(^15)</td>
<td>Healthy Male n=4 22-25 yrs</td>
<td>54</td>
<td>0.067</td>
<td>IV infusion for 60 mins</td>
<td>0-24 hr 0-48 hrs</td>
<td>HPLC</td>
<td>LOD-0.5 ng/ml</td>
<td>LOD-0.5 ng/ml</td>
<td>Cumulative</td>
<td>130 (SE ± 14)</td>
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<td>Vd$_{ss}$ (l/kg)</td>
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<td>CL$_{\text{ren}}$ (ml/min/kg)</td>
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fe = 26.4% (SE ± 0.46)
Plasma protein binding studies:

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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belpaire et al(^\text{12})</td>
<td>Healthy n =11 (25-45 yrs)</td>
<td>Equilibrium dialysis</td>
<td>100 ng/ml</td>
<td>Liquid scintillation</td>
<td>59.7 % (53.2 – 64.1)</td>
</tr>
</tbody>
</table>

Urinary excretion study:

**Kubota et al\(^\text{15}\)**: Urine collection: 0-48 hr
Renal clearance $\text{CL}_{\text{ren}} = \frac{\text{Ae}(48)}{[\text{AUC}]_0^{48}}$ where $\text{Ae}^{48}$ is cumulative amount of drug excreted unchanged in urine upto 48 hrs

Bioavailability study:
Wilson et al\(^\text{3}\): Formulation : Tablet (0.4 mg/kg)
Sampling: 0-8 hrs
Analysis: GLC
$F_{\text{oral}} = 0.61 \pm 0.06$
Nadolol

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morriso n et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Healthy male</td>
<td>80.1</td>
<td>1 mg</td>
<td>Bolus</td>
<td>0.08-24 hrs</td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>AUC (ng.h/ml)</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt; (ml/min/kg)</td>
</tr>
<tr>
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<td></td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>Cumulative</td>
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<td></td>
<td>2 mg</td>
<td></td>
<td>Collected for 3 days</td>
<td>TLRC</td>
<td>-</td>
<td>78 (SE ± 4)</td>
<td>2.82 (SE ± 0.09)</td>
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<td>-</td>
<td>-</td>
<td>159 (SE ± 10)</td>
<td>2.78 (SE ± 0.14)</td>
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<td>4 mg</td>
<td>(14C)</td>
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<td>-</td>
<td>-</td>
<td>275 (SE ± 0.18)</td>
<td>3.22 (SE ± 0.09)</td>
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425
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al(^1)</td>
<td>Healthy n = 95 (47 male and 48 female)</td>
<td>Equilibrium dialysis</td>
<td>500 ng/ml</td>
<td>Liquid scintillation</td>
<td>14 ± 4%</td>
</tr>
</tbody>
</table>

Bioavailability study:

Dreyfuss et al\(^1\): Formulation : Capsules (80 mg)
Analysis: Liquid scintillation
Average amount absorbed = 28.4 ± 6.6% (SE)

Dreyfuss et al\(^1\): Formulation : Capsules (2 mg)
Analysis: Liquid scintillation
Average amount absorbed (from urinary excretion data) = 33.6 ± 2.4 % (SE)
Average amount absorbed (from AUC) = 43.2%
### Oxprenolol

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason et al20</td>
<td>Healthy n = 6 21-29 yrs</td>
<td>(51-81) 65.2</td>
<td>0.31</td>
<td>Bolus</td>
<td>0-8 hr</td>
<td>GC</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
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<td></td>
<td>5.87</td>
</tr>
<tr>
<td>Laethem et al21</td>
<td>Healthy n = 8 21-27 yrs</td>
<td>72.5</td>
<td>0.97</td>
<td>Oral Table</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
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**Plasma protein binding studies:**

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<tr>
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<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belpaire et al12</td>
<td>Healthy n =11 (25-45 yrs)</td>
<td>Equilibrium dialysis</td>
<td>500 ng/ml</td>
<td>Liquid scintillation</td>
<td>92.0 (89.1 – 94.9)</td>
</tr>
<tr>
<td>Laethem et al21</td>
<td>Healthy n = 8 21-27 yrs</td>
<td>Equilibrium dialysis</td>
<td>500 ng/ml</td>
<td>Liquid scintillation</td>
<td>fu – (R)- 0.22 ± 0.02 fu – (S)- 0.18 ± 0.01 R/S = 1.21 ± 0.03</td>
</tr>
</tbody>
</table>
Blood—to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason et al$^{20}$</td>
<td>-</td>
<td>In-vitro</td>
<td>-</td>
<td>-</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Bioavailability study:
Mason et al$^{20}$: Formulation : Capsule (20, 40, 80, 160 mg)
Sampling: 0-8 hrs
Analysis: GC
$F_{oral}$ (20 mg) = 0.38
$F_{oral}$ (40 mg) = 0.45
$F_{oral}$ (80 mg) = 0.42
$F_{oral}$ (160 mg) = 0.38
Pindolol

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Gugler et al\textsuperscript{22}</td>
<td>Healthy n = 17 19-30 yrs</td>
<td>65 (50-80)</td>
<td></td>
<td>0.08</td>
<td>Infusion 0-24 hrs</td>
<td>UV</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
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<td>Cumulative</td>
<td>7.43 (± 1.2)</td>
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<td>2.1 (± 0.49)</td>
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<td>3.32 (± 0.74)</td>
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<td>fe = 38.9 ± 0.9%</td>
</tr>
<tr>
<td>Guerret et al\textsuperscript{23}</td>
<td>Healthy n = 6 28 ± 2.3 yrs</td>
<td>63 ± 3</td>
<td></td>
<td>0.05</td>
<td>Infusion for 6 mins</td>
<td>UV</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
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<td>Cumulative</td>
<td>102 (± 13)</td>
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<td>8.92 (± 0.90)</td>
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<td>fe = 54.2 ± 9.4%</td>
</tr>
</tbody>
</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gugler et al\textsuperscript{22}</td>
<td>-</td>
<td>In-vitro Gel chromatography</td>
<td>60 ng/ml</td>
<td>UV</td>
<td>57.2%</td>
</tr>
<tr>
<td>Taylor et al\textsuperscript{13}</td>
<td>Neurological investigation subjects n = 7 42.0 ± 13.6 yrs</td>
<td>Ex-vivo</td>
<td>Oral 10 mg dose once/twice daily for 6-7 days</td>
<td>Fluorimetry</td>
<td>71.4% ± 8.6</td>
</tr>
<tr>
<td>Belpaire et al\textsuperscript{12}</td>
<td>Healthy n =11 (25-45 yrs)</td>
<td>Equilibrium dialysis</td>
<td>100 ng/ml</td>
<td>Liquid scintillation</td>
<td>59.3 (50.5-70.2)</td>
</tr>
</tbody>
</table>
Blood–to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al13</td>
<td>Neurological investigation subjects n = 7 42.0 ± 13.6 yrs</td>
<td>Ex-vivo Oral 10 mg dose once/twice daily for 6-7 days</td>
<td>Fluorimetry</td>
<td>0.69 ± 0.08 RBC: Plasma - 0.37 ± 0.14</td>
</tr>
</tbody>
</table>

Urinary excretion study:

Gugler et al22: Urine collection: 0-4, 4-8, 8-12, 12-24 hr
Renal clearance $CL_{ren} = Ae_{24}/[AUC]_{0}^{24}$ where $Ae_{24}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs

Guerret et al23: Urine collection: 0-48 hr

Bioavailability study:
Guerret et al23: Formulation: Not mentioned (5 mg)
Sampling: 0-10 hrs
Analysis: GLC-ECD
$F_{oral}$ (5 mg) =
Mepindalol

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
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<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Bonelli et al\textsuperscript{24}</td>
<td>Healthy male n = 5 21-36 yrs</td>
<td>70 (assumed)</td>
<td>0.007</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-96 hrs</td>
<td>Liquid scintillation</td>
<td>LOD 0.6 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
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<tr>
<td>Gugler et al\textsuperscript{25}</td>
<td>Healthy n = 5 19-32 yrs</td>
<td>63.5 (53-74)</td>
<td>0.063</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-24 hr</td>
<td>UV</td>
<td>LOD-2 ng/ml</td>
<td>LOD – 5 ng/ml</td>
<td>Compartmental</td>
</tr>
</tbody>
</table>

Plasma protein binding studies: Bonelli et al\textsuperscript{24}

Plasma protein binding was calculated by correlation of plasma and salivary data, the concentration in the saliva was taken to be identical to the concentration in plasma water. The concentration in the saliva was plotted against that of plasma concentration for all the volunteers and a straight line of slope \( \alpha \) was obtained. Plasma protein binding is then \( 1 - \alpha \).

Plasma protein binding = 57%
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gugler et al25</td>
<td>Healthy n = 3</td>
<td>gel chromatography</td>
<td>-</td>
<td>-</td>
<td>49 %</td>
</tr>
</tbody>
</table>

Urinary excretion study:
Bonelli et al24: Urine collection: 0-96 hr
Gugler et al25: Urine collection: 0-4, 4-8, 8-12, 12-24 hr
Renal clearance $CL_{\text{ren}} = \frac{Ae(\infty)}{[AUC]}$ where $Ae(\infty)$ is cumulative amount of drug excreted unchanged in urine

Bioavailability study:
Gugler et al25:
Formulation: Wafers (10mg)
Sampling: 0-24 hrs
Analysis: UV
$F_{oral} = 88.3\% \text{ (± 9.6)}$

Bonelli et al26: Formulation: Oral tablet (20 mg Mepindolol Sulphate)
Sampling: 0-24 hrs
Analysis: Liquid Scintillation
$F_{oral} = 82.1 \pm 11$
Penbutolol

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
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<td>Plasma</td>
<td>Urine</td>
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<tr>
<td>Vedin et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Healthy n = 12</td>
<td>-</td>
<td>0.042</td>
<td>Bolus</td>
<td>0-360 mins</td>
<td>-</td>
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<td>-</td>
<td>Noncompartmental</td>
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<tr>
<td>Jun et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Healthy n = 12 21-45 yrs</td>
<td>77.3</td>
<td>0.32</td>
<td>Oral</td>
<td>0-48 hrs</td>
<td>Fluorimetry</td>
<td>24 ng/ml</td>
<td>-</td>
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<td>Cumulative</td>
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</table>

AUC (ng·h/ml)

CL<sub>tot</sub> (ml/min/kg)

V<sub>dss</sub> (l/kg)

CL<sub>res</sub> (ml/min/kg)

- 0.042
- 0.085
- 0.171
- 2.44 (calculated)
- 2.46 (calculated)
- 2.10 (calculated)
- 0.22 (calculated)
- 0.14 (calculated)
- 0.12 (calculated)
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottschalk et al 29</td>
<td>-</td>
<td>Equilibrium dialysis</td>
<td>1-20 µg/ml</td>
<td>quantitative TLC</td>
<td>88 ± 4 %</td>
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</tbody>
</table>

Urinary excretion study:

Bernard et al 30: Urine collection: 0-4, 4-10, 10-24, 24-48 hr
Renal clearance $C_{L_{ren}} = \frac{Ae(48)}{[AUC]_0^{48}}$ where $Ae^{48}$ is cumulative amount of drug excreted unchanged in urine upto 48 hrs

Jun et al 28: Urine collection: 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, 60-72 hrs
Renal clearance $C_{L_{ren}} = \frac{Ae(48)}{[AUC]_0^{48}}$ where $Ae^{48}$ is cumulative amount of drug excreted unchanged in urine upto 48 hrs
Sotalol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poirier et al$^{31}$</td>
<td>Healthy male n = 6 22-25 yrs</td>
<td>69.5 (59-77)</td>
<td>1</td>
<td>0-48 hrs</td>
<td>Infusion for 5 min</td>
<td>HPLC</td>
<td>25 ng/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml)</td>
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<td></td>
<td></td>
<td>500 ng/ml</td>
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Plasma protein binding studies:

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<th>Assay</th>
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</thead>
<tbody>
<tr>
<td>Belpaire et al$^{12}$</td>
<td>Healthy n =11 (25-45 yrs)</td>
<td>Equilibrium dialysis</td>
<td>2000 ng/ml</td>
<td>Liquid scintillation</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Urinary excretion study:

Poirier et al$^{31}$: Urine collection: 0-48 hr
Renal clearance $CL_{ren} = Ae(\infty) / [AUC]$ where $Ae^\infty$ is cumulative amount of drug excreted unchanged in urine

Bioavailability study:

Deneer et al$^{32}$:
Formulation: Solution (80mg)
Sampling: 0-48 hrs
Analysis: HPLC
$F_{oral} = 100\% \pm 15.0$
Alpranolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
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<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson et al(^{34})</td>
<td>Healthy male (n = 5), 22-33 yr</td>
<td>69-75</td>
<td>0.07</td>
<td>IV infusion for 5 min</td>
<td>0-10 hrs</td>
<td>-</td>
<td>GC</td>
<td>1 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Belpaire et al(^{12})</td>
<td>Healthy (n = 11), (25-45 yrs)</td>
<td></td>
<td></td>
<td>Equilibrium dialysis</td>
<td>100 ng/ml</td>
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Plasma protein binding studies:

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</thead>
<tbody>
<tr>
<td>Johansson et al(^{34})</td>
<td>Healthy (n = 5)</td>
<td>Ultrafiltration</td>
<td>1.98 x 10^{-7} M</td>
<td>Liquid scintillation</td>
<td>85%</td>
</tr>
<tr>
<td>Belpaire et al(^{12})</td>
<td>Healthy (n = 11)</td>
<td>Equilibrium dialysis</td>
<td>100 ng/ml</td>
<td>Liquid scintillation</td>
<td>76.1%</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvan et al(^{33})</td>
<td>Healthy (n = 4)</td>
<td>In-vitro</td>
<td>60 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.98 ± 0.10</td>
</tr>
</tbody>
</table>

Bioavailability study:
Alvan et al\(^{33}\): Formulation: Oral tablet (200 mg Alpranolol)
Sampling: 0-10 hrs
Analysis: GC
\(F_{oral} = 26.3\% \) (calculated)
Tertatolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
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<td>AUC (ng.h/ml)</td>
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<td>CL_{tot} (ml/min/kg)</td>
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<td></td>
<td>V_{dss} (l/kg)</td>
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<td>CL_{ren} (ml/min/kg)</td>
</tr>
<tr>
<td>Campbe l et al 35</td>
<td>Healthy n = 10</td>
<td>70 (assumed)</td>
<td>0.036</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>not mentioned</td>
<td>GC-MS</td>
<td>1-1000 ng/ml</td>
<td>-</td>
<td>Noncompartmental</td>
</tr>
</tbody>
</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urien et al 36</td>
<td>Healthy n = 24</td>
<td>Equilibrium dialysis</td>
<td>50-400 ng/ml</td>
<td>Liquid scintillation</td>
<td>f_{e} = 7.4 % ± 1.6</td>
</tr>
</tbody>
</table>

Bioavailability study:
Campbell et al 35: Formulation: Not mentioned (2.5 mg)
Sampling: 0-12 hrs
Analysis: GC-MS
F_{oral} = 60%
**Flestolol**

**PK studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achari et al[37]</td>
<td>Healthy</td>
<td>76.7 ± 9.4</td>
<td>0.005 mg/kg/min</td>
<td>Infusion</td>
<td>0-90 mins</td>
<td>HPLC</td>
<td>2-200 ng/ml</td>
<td>-</td>
<td>-</td>
<td>AUC (ng.h/ml) 0.00223 (± 0.00086)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion 0-90 mins</td>
<td>HPLC</td>
<td>2-200 ng/ml</td>
<td>-</td>
<td>Compart-mental</td>
<td>AUC (ng.h/ml) 0.00223 (± 0.00086)</td>
</tr>
</tbody>
</table>
### Dilevalol

#### PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
</table>
| Tenero et al\(^\text{38}\) | Healthy  
  n = 9  
  26.2 yrs | 78.5    | 0.57  | Bolus       | 0-24 hrs | HPLC              | limit of sensitivity  
  2 ng/ml | -        | Compartmental | -          | 29.8  
  (± 5.7) | 16.6  
  (± 4.1) | -        |
| Kramer et al\(^\text{39}\) | Healthy  
  n = 12  
  25 yrs | 75      | 0.57  | Infusion    | 0-60 hrs  
  0-60 hrs | HPLC              | LOD-2 ng/ml  
  LOD-8 ng/ml | Compart-mental   | Cumulative  
  536  
  (± 66.8) | 23.2  
  (± 3.2) | 11.2  
  (± 4.2) | 0.69  
  (± 0.14)  
  \(\text{fe} = 3.00 \%  
  (± 0.67)\) |

#### Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenero et al(^\text{38})</td>
<td>Healthy</td>
<td><em>In-vitro</em></td>
<td>5-500 ng/ml</td>
<td>HPLC</td>
<td>1.24 ± 0.10</td>
</tr>
</tbody>
</table>
Urinary excretion study:

Kramer et al\textsuperscript{39}: Urine collection: 0-60 hr
Renal clearance $\text{CL}_{\text{ren}} = \frac{\text{Ae}(\infty)}{\text{[AUC]}}$ where $\text{Ae}(\infty)$ is cumulative amount of drug excreted unchanged in urine

Bioavailability study:

Tenero et al\textsuperscript{38}: Formulation: Oral – formulation not mentioned (360 mg Dilevalol)
Sampling: 0-72 hrs
Analysis: HPLC
$F_{\text{oral}} = 29.6 \pm 14.3$ %

Kramer et al\textsuperscript{39}: Formulation: Oral tablets (200 mg Dilevalol)
Sampling: 0-60 hrs
Analysis: HPLC
$F_{\text{oral}} = 11.3 \pm 3.97$ %
**Tolamolol**

**PK studies**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Dose (mg/kg)</th>
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<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faulkner et al(^{40})</td>
<td>Healthy n = 4 19-32 yrs</td>
<td>70.5 (65-76)</td>
<td>0.28</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>-</td>
<td>-</td>
<td>sensitivity – 2 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
</tr>
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<td>AUC (ng.h/ml) (\pm 108.00)</td>
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<td>CL(_{tot}) (ml/min/kg) (\pm 4.11)</td>
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<td>V(_{dss}) (l/kg) (\pm 1.72)</td>
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<td>CL(_{ren}) (ml/min/kg)</td>
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</table>

**Plasma protein binding studies:**

<table>
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<tr>
<th>Study</th>
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<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faulkner et al(^{40})</td>
<td>Healthy n = 4</td>
<td>Ultrafiltration</td>
<td>100-1000 ng/ml</td>
<td>Liquid scintillation</td>
<td>91.1 %</td>
</tr>
</tbody>
</table>

**Blood –to –plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faulkner et al(^{40})</td>
<td>Healthy n = 4</td>
<td>In-vitro</td>
<td>100-1000 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.55 (calculated)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>RBC: Plasma – 0.46</td>
</tr>
</tbody>
</table>
**Bioavailability study:**
Faulkner et al\(^{[40]}\): Formulation: Oral Tablet(100 mg)
Sampling: 0-8 hrs
Analysis:
\[ F_{\text{oral}} = 32.4\pm18.8\% \]
Bornaprolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
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</tr>
<tr>
<td>Cheymo et al41</td>
<td>Healthy n = 6</td>
<td>70</td>
<td>0.28</td>
<td>Bolus</td>
<td>0-167 hr</td>
<td>GLC</td>
<td>sensitivity-1 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26-34 yrs</td>
<td></td>
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</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shastri et al42</td>
<td>Healthy n = 1</td>
<td>Equilibrium dialysis</td>
<td>0.28-147 μM</td>
<td>Liquid scintillation</td>
<td>90.8 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In-vitro</td>
<td></td>
<td></td>
<td>RBC binding = 20% (0.1-170 μM)</td>
</tr>
</tbody>
</table>

Bioavailability study:
Bastain et al43: Formulation : Suspension (120, 240, 480, 960 mg)
Sampling: 0-167 hrs
Analysis: GLC
\[ F_{oral} (120 \text{ mg}) = 0.46 \pm 0.09 \]
\[ F_{oral} (240 \text{ mg}) = 0.40 \pm 0.08 \]
\[ F_{oral} (480 \text{ mg}) = 0.29 \pm 0.06 \]
\[ F_{oral} (960 \text{ mg}) = 0.22 \pm 0.02 \]
Levobunolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolle et al\textsuperscript{44}</td>
<td>Healthy n = 6</td>
<td>-</td>
<td>0.11</td>
<td>Infusion</td>
<td>Plasma Urine</td>
<td>Plasma Urine HPLC</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Bioavailability study:
Kolle et al\textsuperscript{44}: Formulation: Tablets (4 mg x 3)
Analysis: HPLC
F\textsubscript{oral} = 75 ± 22%
Adimolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiedemann et al(^{45})</td>
<td>Healthy n = 6</td>
<td>82.8 ± 8.1</td>
<td>0.06 Infusion</td>
<td>0-12 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td>9735 (± 5461)</td>
</tr>
</tbody>
</table>

Bioavailability study:
Wiedemann et al\(^{45}\):

Formulation: Tablet (100, 200 mg)
Sampling: 0-48 hrs
Analysis: HPLC

F\(_{oral}\) (100 mg) = 42.9 ± 10.8%
F\(_{oral}\) (200 mg) = 52.3 ± 18.6%

Formulation: Capsule (200 mg)
Sampling: 0-48 hrs
Analysis: HPLC

F\(_{oral}\) (200 mg) = 44.9 ± 13.2 %
**Bufuralol**

**PK studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
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</tr>
<tr>
<td>Balant et al(^46)</td>
<td>Healthy n = 3</td>
<td>-</td>
<td>0.07</td>
<td>Infusion for 2 mins</td>
<td>0-24 hrs</td>
<td>-</td>
<td>GC-MS</td>
<td>sensitivity 1 ng/ml</td>
<td>-</td>
<td>900</td>
</tr>
<tr>
<td>Balant et al(^47)</td>
<td>Healthy n = 3 25-30 yrs</td>
<td>70 (assumed)</td>
<td>0.07</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>GC-MS</td>
<td>-</td>
<td>Compart mental</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foti et al(^48)</td>
<td>Healthy n = 1</td>
<td>Equilibrium dialysis</td>
<td>20 μM</td>
<td>HPLC</td>
<td>(f_u = 0.19 \pm 0.06)</td>
</tr>
</tbody>
</table>

**Bioavailability study:**

Balant et al\(^46\):
Formulation: Capsule (20mg)
Sampling: 0-24 hrs
Analysis: GC-MS
\(F_{oral} = 0.71\)
Balant et al\textsuperscript{47} 
Formulation: Capsule (20mg) 
Sampling: 0-24 hrs 
Analysis: GC-MS 
$F_{oral} = 0.65$
Pamatolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
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<tr>
<td>Carruthers et al(^{49})</td>
<td>Healthy n = 4 18-29 yr</td>
<td>70 (assumed)</td>
<td>0.71</td>
<td>Bolus</td>
<td>0-16</td>
<td>-</td>
<td>GLC</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
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</tbody>
</table>

Bioavailability study:
Carruthers et al\(^{49}\):
Formulation: Not mentioned (50mg)
Sampling: 0-24 hrs
Analysis: GLC
\(F_{oral} = 87.8\%\)
Deacetyl Metipranolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abshagen et al</td>
<td>Healthy n = 17 31.4 yrs</td>
<td>79.1</td>
<td>0.25</td>
<td>Infusion for 48 mins</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>GC-MS</td>
<td>LOD = 1 ng/ml</td>
<td>Cumulative</td>
<td>15.63 ± 5.24 (calculated)</td>
</tr>
</tbody>
</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
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<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abshagen et al</td>
<td>Pooled human samples</td>
<td>Ultrafiltration</td>
<td>70, 140, 200 ng/ml</td>
<td>GC-MS</td>
<td>69.7 ± 2.3 %</td>
</tr>
</tbody>
</table>

Urinary excretion study:
Abshagen et al: Urine collection: 0-4, 4-8, 8-12, 12-24 hr
Renal clearance $CL_{ren} = Ae(\infty)/[AUC]$ where $Ae^\infty$ is cumulative amount of drug excreted unchanged in urine
β₁-selective beta-blockers

Bisoprolol

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
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<tr>
<td>Leopold et al</td>
<td>Healthy male</td>
<td>70</td>
<td>0.14</td>
<td>Bolus</td>
<td>0-96 hrs</td>
<td>Liquid scintillation</td>
<td>5 ng/ml</td>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 12</td>
<td>(assumed)</td>
<td></td>
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<td>0-48 hrs</td>
<td></td>
<td>5 ng/ml</td>
<td>Urine</td>
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<tr>
<td></td>
<td>53 ± 3 yrs</td>
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</tr>
<tr>
<td>Jeunne et al</td>
<td>Control</td>
<td>51 ± 4</td>
<td>0.16</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>1 ng/ml</td>
<td>Plasma</td>
<td></td>
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<tr>
<td></td>
<td>n = 8</td>
<td></td>
<td></td>
<td></td>
<td>0-48 hrs</td>
<td></td>
<td>1 ng/ml</td>
<td>Urine</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>25 ± 3 yrs</td>
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</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buhring et al</td>
<td>-</td>
<td>Ultrafiltration</td>
<td>0.01-5 µg/ml</td>
<td>Liquid scintillation</td>
<td>26-33%</td>
</tr>
<tr>
<td>Horikiri et al</td>
<td>Healthy n = 4</td>
<td>Ultrafiltration</td>
<td>20 ng/ml</td>
<td>HPLC</td>
<td>S (-) – 34.5 % (± 6 %) R (+) – 36.4 % (± 6.7 %) S/R ratio : 0.95</td>
</tr>
</tbody>
</table>
**Urinary excretion study:** Kubota et al \(^{15}\)

Urine collection: 0-48 hr (0-6, 6-12, 12-24, 24-48 h)

Renal clearance $CL_{\text{ren}} = CL \times \frac{Ae^\infty}{\text{dose}}$, where $Ae^\infty$ is cumulative amount of drug excreted unchanged in urine upto 48 hrs

**Oral Bioavailability:** Monocor (Bisoprolol Fumarate) (Biovail Pharmaceuticals prescription information) - 80%

**Esmolol**

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Yacobi et al(^{55})</td>
<td>Healthy male 21-27 yrs</td>
<td>62.4-76.2</td>
<td>0.05/min</td>
<td>Infusion</td>
<td>-</td>
<td>GC-MS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15/min</td>
<td></td>
<td>-</td>
<td>R-(+) 35.58%</td>
<td>S-(-) 41.69%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sum et al(^{56})</td>
<td>Healthy n = 8 yrs</td>
<td>65.8</td>
<td>0.4 mg/kg/min</td>
<td>Infusion</td>
<td>0-1110 mins</td>
<td>-</td>
<td>GC-MS</td>
<td>-</td>
<td>Compart mental</td>
<td>-</td>
</tr>
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</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al(^{57})</td>
<td>-</td>
<td>Equilibrium dialysis</td>
<td>0-6 µg/ml</td>
<td>HPLC</td>
<td>R-(+) 35.58% S-(-) 41.69%</td>
</tr>
</tbody>
</table>

Mean S(-)/R(+) for bound drug = 1.16

Thus, average of S and R form is taken as the mean protein binding of racemic esmolol.
Urinary excretion study: Flaherty et al\textsuperscript{58}.
Subjects: Healthy (n = 6), Age - 41 yrs, Weight – 82.3 yrs (normal CLcr – 114 ml/min)
Rate: Infusion (150 µg/kg/ml)
Urine collection: 0-4, 4-8, 8-12, 12-24 hr
Analysis: HPLC
LOD: 0.05 µg/ml
$f_e = < 0.5\%$

Atenolol

PK Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Kirch et al\textsuperscript{59}</td>
<td>Healthy n = 12 31.3 ± 4 yrs</td>
<td>61.7 ± 4.2</td>
<td>1.62</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>0-48 hrs</td>
<td>-</td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>-</td>
</tr>
<tr>
<td>Mason et al\textsuperscript{60}</td>
<td>Healthy n = 12 21-28 yrs</td>
<td>74.1</td>
<td>0.699 for 12 mins</td>
<td>Infusion</td>
<td>0-24 hrs</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>10 ng/ml</td>
<td>-</td>
<td>Compartamental Cummulative</td>
</tr>
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</tr>
</tbody>
</table>

$f_e = 94.1\%$ (± 8)
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belpaire et al(^{12})</td>
<td>Healthy n =11 (25-45 yrs)</td>
<td>Equilibrium dialysis</td>
<td>1000 ng/ml</td>
<td>Liquid scintillation</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al(^{13})</td>
<td>Healthy subjects n =4 25-31 yrs</td>
<td>Ex-vivo Oral 200 mg dose</td>
<td>Fluorimetry</td>
<td>1.07 ± 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RBC: Plasma –</td>
</tr>
</tbody>
</table>

**Urinary excretion study:** Mason et al\(^{60}\)
Urine collection: 0-48 hr (0-2, 2-4, 4-8, 8-12, 12-24, 24-48 h)
Renal clearance \(CL_{ren} = CL \times Ae^\infty/dose\), where \(Ae^\infty\) is cumulative amount of drug excreted unchanged in urine upto 48 hrs

**Bioavailability study:**
Mason et al\(^{60}\):
Formulation : Solution (25, 50, 100 mg)
Sampling: 0-24 hrs
Analysis: HPLC
\(F_{oral} (25mg) = 0.52 ± 0.18\)
\(F_{oral} (50 mg) = 0.54 ± 0.12\)
\(F_{oral} (100 mg) = 0.58 ± 0.16\)
### Betaxolol

#### PK Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints (calculate)</th>
<th>CL_{ren} (ml/min/kg)</th>
<th>AUC (ng.h/ml)</th>
<th>V_{ss} (l/kg)</th>
<th>CL_{tot} (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrandes et al 65</td>
<td>Healthy n = 12 45.2 yrs</td>
<td>71.7 ± 2.8</td>
<td>0.14</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>-</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>586 (± 37)</td>
<td>4.66 (± 0.33)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Warring</td>
<td>Healthy</td>
<td>67</td>
<td>0.15</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>GLC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3150000</td>
<td>3.80</td>
<td>5.95</td>
<td>-</td>
</tr>
<tr>
<td>Stagni et al 61</td>
<td>Healthy n = 12 24.8 ± 2.6 yrs</td>
<td>73.6 ± 7.5</td>
<td>0.12</td>
<td>IV infusion</td>
<td>0-48 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>0.7-70 ng/ml</td>
<td>-</td>
<td>Compart mental</td>
<td>-</td>
<td>610 (± 122)</td>
<td>3.42 (± 0.66)</td>
<td>-</td>
</tr>
<tr>
<td>Bianchetti et al 62</td>
<td>Healthy n = 8 46-59 yrs</td>
<td>55-85</td>
<td>0.14</td>
<td>Bolus</td>
<td>0-72 hrs</td>
<td>0-72 hrs</td>
<td>GC</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative 206 (± 122) (Stdev 4.16) (Stdev 0.4)</td>
<td>(calculated)</td>
<td>0.75 (SE ± 0.15)</td>
<td>fe = 18.4%</td>
</tr>
<tr>
<td>Morselli et al 67</td>
<td>Healthy controls</td>
<td>-</td>
<td>0.28</td>
<td>Bolus</td>
<td>0-72 hrs</td>
<td>0-72 hrs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.66 (± 0.33)</td>
<td>-</td>
</tr>
<tr>
<td>Ludden et al 63</td>
<td>Healthy n = 50.62 ± 4.8 (±286) yrs</td>
<td>73.6 (± 7.5)</td>
<td>0.12</td>
<td>Infusion</td>
<td>0-48 hrs</td>
<td>0-48 hrs</td>
<td>GC</td>
<td>Std curve range 2-200</td>
<td>Std curve range 200-</td>
<td>Non-compartmental</td>
<td>Cumulative 610 (± 122)</td>
<td>3.28 (calculated)</td>
<td>-</td>
<td>0.700 (± 0.288)</td>
</tr>
<tr>
<td>Bianchetti et al 64</td>
<td>Healthy n = 4 21-45 yrs</td>
<td>-</td>
<td>0.150</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>GLC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>fe = 11.6 (± 2.1%)</td>
<td>-</td>
</tr>
</tbody>
</table>
**Plasma protein binding studies:** Just mentioned as 50% (Warrington et al66)

**Bioavailability study:**

Stagni et al61: Formulation: Oral capsules (40 mg Betaxalol HCl)
Sampling: 0-48 hrs
Analysis: HPLC
\[ F_{oral} = 84 \pm 6\% \]

Bianchetti et al62: Formulation: Oral tablet (20 mg Betaxalol HCl)
Sampling: 0-72 hrs
Analysis: HPLC
\[ F_{oral} = 75.8 \pm 7.3\% \]

Ludden et al63: Formulation: Oral capsules (10, 20, 40 mg)
Sampling: 0-72 hrs
Analysis: GC
\[ F_{oral} = 87.5 \pm 7.9\% \text{ (for 10 mg dose)} \]
\[ 82.3 \pm 6.0\% \text{ (for 20 mg dose)} \]
\[ 83.9 \pm 6.6\% \text{ (for 40 mg dose)} \]

Bianchetti et al64: Formulation: Not mentioned (0.150 mg/kg)
Analysis: GLC
\[ F_{oral} = 89 \pm 5\% \]

Morselli et al67: Formulation: Not mentioned (20 mg)
\[ F_{oral} = 76 \pm 7\% \]

**Urinary excretion study: (Bianchetti et al62)**

Urine was collected from 012, 12-24, 24-48, 48-72 hrs
Analysis: GC
\[ CL_{ren} = Ae \text{ (72 hr)/ AUC (72 hr)} \]
Landiolol

PK Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Murakami et al</td>
<td>Healthy male</td>
<td>50-80</td>
<td>0.03 mg/kg/min followed by 0.01 mg/kg/min for 10 min</td>
<td>Infusion</td>
<td>0-32 0-24 hrs</td>
<td>HPLC</td>
<td>0.05-10 µg/ml</td>
<td>0.5-25 µg/ml</td>
<td>Noncompartmental</td>
<td>Cumulative</td>
</tr>
<tr>
<td></td>
<td>n = 16</td>
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Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsunekawa et al</td>
<td>Healthy human serum</td>
<td>Ultracentrifugation</td>
<td>0.1-50 ng/ml</td>
<td>Liquid scintillation</td>
<td>1.6-7.0% Average = 4.3%</td>
</tr>
<tr>
<td></td>
<td>HAS (43.2 ng/ml)</td>
<td>Ultracentrifugation</td>
<td>0.1-50 ng/ml</td>
<td>Liquid scintillation</td>
<td>2.4-11.0%</td>
</tr>
</tbody>
</table>

**Urinary excretion study:** (Murakami et al 68)

Urine was collected from 0-4, 4-8, 8-12, 12-24, 24 hrs
Analysis: HPLC
### Amusulalol

**PK studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakashima et al&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Healthy n = 7 33.3±1 yr</td>
<td>62.1 ± 1.36</td>
<td>0.16</td>
<td>Bolus</td>
<td>0-480 min</td>
<td>0-24 hrs</td>
<td>HPLC GC</td>
<td>Sensitivity 20 ng/ml</td>
<td>Sensitivity 0.2 µg/ml</td>
<td>Compart mental Cumulative</td>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>PK Analysis</td>
<td>Urine Collection method</td>
<td>PK endpoints</td>
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</table>

**Bioavailability study:**

Nakashima et al<sup>70</sup>: Formulation: (12.5, 25, 50, 100, 150 mg Amusulalol)
Sampling: 0-24 hrs
Analysis: HPLC and GC
F<sub>oral</sub> = 100 %

f<sub>0</sub> = 34.1 %
# Metoprolol

## PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ Assay</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regardh et al</td>
<td>Healthy n = 5 23-28 yrs</td>
<td>66 (62-70)</td>
<td>0.03</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative</td>
<td>-</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0-72 hrs</td>
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</tr>
<tr>
<td>Regardh et al</td>
<td>Healthy n = 10 73.1 yrs</td>
<td>67.3 (53-81)</td>
<td>0.002</td>
<td>Bolus</td>
<td>0-30 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>15.75 (± 1.19)</td>
</tr>
<tr>
<td>Jordo et al</td>
<td>Healthy n = 6 22-28 yrs</td>
<td>74</td>
<td>0.270</td>
<td>Bolus</td>
<td>0-480 min</td>
<td>GC-MS</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative</td>
<td>10.81 (SE ± 1.49)</td>
</tr>
<tr>
<td>Schaaef et al</td>
<td>Healthy non-smokers n = 8</td>
<td>70</td>
<td>0.28</td>
<td>Infusion for</td>
<td>0-10 hrs</td>
<td>HPLC range 5-250 ng/ml</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>11.6 (± 3.7)</td>
</tr>
</tbody>
</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belpaire et al</td>
<td>Healthy n =11 (25-45 yrs)</td>
<td>Equilibrium dialysis</td>
<td>100 ng/ml</td>
<td>Liquid scintillation</td>
<td>8.2%</td>
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</tbody>
</table>
**Blood-to-plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regardh et al(^{71})</td>
<td>Healthy n = 3</td>
<td>In-vitro</td>
<td>10 ng/ml</td>
<td>Liquid scintillation</td>
<td>1.23 ± 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23 ng/ml</td>
<td></td>
<td>1.09 ± 0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>77 ng/ml</td>
<td></td>
<td>1.08 ± 0.02</td>
</tr>
</tbody>
</table>

**Bioavailability study:**

- **Regardh et al\(^{71}\):** Formulation: Solution (1.95 mg Metoprolol)
  Sampling: 0-12 hrs
  Analysis: Liquid Scintillation
  \(F_{oral} = 40\%\)

- **Regardh et al\(^{72}\):** Formulation: Tablet (50 mg b.i.d Metoprolol)
  Sampling: 0-30 hrs
  Analysis: GC-MS
  \(F_{oral} = 55\%\)

- **Jordo et al\(^{73}\):** Formulation: Tablets (50 mg Metoprolol orally twice daily for 5 days)
  Sampling: 0-430 mins
  Analysis: GC-MS
  \(F_{oral (single dose)} = 0.50 (± 0.11)\)
  \(F_{oral (at steady state)} = 0.55 (± 0.07)\)

- **Schaaf et al\(^{74}\):** Formulation: Not mentioned (100 mg and 200 mg)
  Sampling: 0-10 hrs
  Analysis: HPLC
  \(F_{oral (100 mg)} = 0.454 (± 0.182)\)
  \(F_{oral (at steady state)} = 0.573 (± 0.195)\)
## Talinolol

### PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Populations</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trausch et al(^{75})</td>
<td>Healthy 26 ± 2 yrs (23-32 yrs)</td>
<td>72 ± 8</td>
<td>0.42</td>
<td>IV infusion</td>
<td>0-36 hrs</td>
<td>0-36 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>AUC (ng.h/ml)</td>
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<td>Plasma</td>
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<td>Urine</td>
<td>Cl(_{tot})</td>
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<td>Vd(_{ss})</td>
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<td>Cl(_{ren})</td>
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<td>(ml/min/kg)</td>
</tr>
<tr>
<td>Trausch et al(^{77})</td>
<td>n = 6</td>
<td></td>
<td></td>
<td></td>
<td>Ultrafiltration</td>
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</table>

### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zschiesche et al(^{76})</td>
<td>Healthy n = 8 (22-26 yrs)</td>
<td>Ultrafiltration</td>
<td>30 mg by IV</td>
<td>HPLC</td>
<td>(S)-(+) -78.2 ± 1.2 %</td>
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<td>(R)-(+) -79.0 ± 3.1 %</td>
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<tr>
<td>Trausch et al(^{77})</td>
<td>n = 6</td>
<td>Ultrafiltration</td>
<td>30 mg IV infusion</td>
<td>HPLC</td>
<td>60.9 ± 7.5 %</td>
</tr>
</tbody>
</table>

### Urinary excretion study: \footnotesize{(Trausch et al\(^{75}\)}

Urine was collected from 0-4, 4-8, 8-12, 12-24, 24-36 hrs
Analysis: HPLC
\[ CL\(_{\text{ren}}\) = \frac{A_{\text{e}}}{AUC_\infty} \]

### Bioavailability study:

\footnotesize{Trausch et al\(^{75}\): Formulation : Dragee (50 mg Talinolol)}
Sampling: 0-36 hrs
Analysis: HPLC
\[ F_{\text{oral}} = 55\% (± 16) \]
Bevantolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
<tbody>
<tr>
<td>MacNeil et al78</td>
<td>Healthy</td>
<td>70.5 (61-80)</td>
<td>0.71</td>
<td>IV infusion</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>GC</td>
<td>sensitivity</td>
<td>-</td>
<td>Compart mental</td>
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<tr>
<td></td>
<td>n = 6</td>
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</tr>
</tbody>
</table>

Plasma protein binding studies:
MacNeil et al78: just mentioned as 98%

Urinary excretion study: (MacNeil et al78)
Subjects: n = 4
Urine was collected from 0-24 hrs
Analysis: GC
f_e = 0.2-1.4%

Bioavailability study:
MacNeil et al78: Formulation: Capsules (50 mg Bevantolol)
Sampling: 0-12 hrs
Analysis: GC
F_oral = 57% (26-98%)
### Nebivolol

**PK studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheymol et al⁷⁹</td>
<td>Healthy control n=9 (32 ± 9 yrs)</td>
<td>60 ± 11</td>
<td>0.073</td>
<td>IV infusion for 5-8 min</td>
<td>0-48 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>0.2-1000 ng/ml LOD-0.1 ng/ml</td>
<td>Noncompartimental</td>
<td>-</td>
</tr>
</tbody>
</table>

**Plasma protein binding studies:** (Public assessment report – Glenmark Generics (Europe) Limited.)

% protein binding = 98.1%
Acebutolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Meffin et al(^{80})</td>
<td>Healthy n = 9 20-26 yrs</td>
<td>80</td>
<td>1</td>
<td>IV infusion for 15 mins</td>
<td>0-1440 min 0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative</td>
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<tr>
<td>Roux et al(^{81})</td>
<td>Healthy n = 5 29-46 yrs</td>
<td>65-82</td>
<td>0.35</td>
<td>Bolus</td>
<td>0-24 hrs 0-72 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative</td>
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<tr>
<td>Roux et al(^{82})</td>
<td>Healthy n = 5 23.4 ± 0.7 yrs</td>
<td>75.9 ± 1.7</td>
<td>0.35</td>
<td>Bolus</td>
<td>0-8 hrs 0-72 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>Fractionated</td>
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Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meffin et al.80</td>
<td>Healthy n = 5</td>
<td>In-vitro Equilibrium dialysis</td>
<td>0.02 - 9 µg/ml</td>
<td>Liquid scintillation</td>
<td>$f_a = 0.743$ COV - 10.5%</td>
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<tr>
<td>Coombs et al.83</td>
<td>Healthy</td>
<td>In-vitro Ultrafiltration</td>
<td>10-1000 ng/ml</td>
<td>Liquid scintillation</td>
<td>15%</td>
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</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meffin et al.80</td>
<td>Healthy n = 3</td>
<td>In-vitro</td>
<td>0.05 – 5 µg/ml</td>
<td>Liquid scintillation</td>
<td>0.617 COV – 2.8%</td>
</tr>
<tr>
<td>Roux et al.84</td>
<td>Healthy n = 9</td>
<td>In-vitro</td>
<td>1.0-10 mg/l</td>
<td>Flurorimetry</td>
<td>0.50 ± 0.04</td>
</tr>
</tbody>
</table>

Urinary excretion study:

Meffin et al.80
Subjects: n = 9
Urine was collected from 0-24 hrs
Analysis: HPLC
$f_a = 0.405$
Renal clearance calculated from measured acebutolol urinary excretion rates and mean blood concentrations

Roux et al.82:
Urine was collected from 0-2, 2-4, 4-6, 6-8, 8--24, 24-48, 48-72 hrs
Analysis: HPLC

Bioavailability study:
MacNeil et al.78: Formulation : Tablet (400 mg)
Sampling: 0-48 hrs
Analysis: HPLC
$F_{oral} = 0.34 (± 0.07)$
**Diacetolol (metabolite of acebutolol)**

**PK studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flouvat et al(^{85})</td>
<td>Healthy n = 6 35 ± 5.7 yrs</td>
<td>70 ± 7.5</td>
<td>1.43</td>
<td>Bolus</td>
<td>0-30 hrs, 0-96 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative AUC 6453 (SE ± 468)</td>
</tr>
</tbody>
</table>

**Urinary excretion study:** (Flouvat et al\(^{85}\))

Urine was collected from 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96 hrs
Analysis: HPLC
CL\(_{\text{ren}}\) = \(\text{Ae}_\infty / \text{AUC}_\infty\)

**Bioavailability study:**

Flouvat et al\(^{85}\): Formulation: Tablets (100, 400, 800 mg)
Sampling: 0-48 hrs
Analysis: HPLC
\(F_{\text{oral}} = 0.302\ (\text{SE} = \pm 0.052)\) after 100 mg dose
0.363 (SE = ± 0.052) after 400 mg dose
0.426 (SE = ± 0.068) after 800 mg dose
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coombs et al 83</td>
<td>Healthy</td>
<td>In-vitro Ultrafiltration</td>
<td>10-1000 ng/ml</td>
<td>Liquid scintillation</td>
<td>7.5 %</td>
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</table>

Pafenolol

PK studies

<table>
<thead>
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<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Regardh et al 86</td>
<td>Healthy male n = 8</td>
<td>73.5</td>
<td>0.14</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>GC</td>
<td>15</td>
<td>Noncompartental</td>
<td>Cumulative</td>
<td>4.00 (± 0.77)</td>
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<tr>
<td>Regardh et al 87</td>
<td>Healthy n =6</td>
<td>73.7 (68-84)</td>
<td>0.07</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>GC</td>
<td>-</td>
<td>Compartental</td>
<td>Cumulative</td>
<td>4.32 (± 0.14)</td>
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</table>
Urinary excretion study:

Regardh et al (86):
Urine was collected from 0-72 hrs
Analysis: GC
\( CL_{ren} = \frac{A_{e\infty}}{AUC_{\infty}} \)

Regardh et al (87):
Urine was collected from 0-24 hrs
Analysis: GC
\( CL_{ren} = \frac{A_{e\infty}}{AUC_{\infty}} \)

Bioavailability study:

Regardh et al (86): Formulation: Solution (40 mg)
Sampling: 0-24 hrs
Analysis: GC
\( F_{oral} = 27.5 \) (SD = ± 15.5)

Regardh et al (87): Formulation: Solution (25, 50, 100 mg)
Sampling: 0-24 hrs
Analysis: GC
\( F_{oral} = 27.0 \) (SD = ± 4.9)
\( F_{oral} = 30.4 \) (SD = ± 7.6)
\( F_{oral} = 46.2 \) (SD = ± 4.9)
### Nafetolol (K 5407)

#### PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
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<td></td>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
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</tr>
<tr>
<td>Goldaniga et al(^{88})</td>
<td>Healthy males</td>
<td>18, 61 yrs</td>
<td>52 and 65</td>
<td>0.017</td>
<td>Bolus 0-8 hrs</td>
<td>-</td>
<td>liquid scintillation</td>
<td>-</td>
<td>Noncompartamental</td>
<td>0-8 hr</td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldaniga et al(^{88})</td>
<td>Healthy males</td>
<td>In-vitro</td>
<td>40 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.82</td>
</tr>
</tbody>
</table>
Urinary excretion study:

Goldaniga et al\textsuperscript{88}:
Urine was collected from 0-120 hrs
Analysis: Liquid scintillation
$CL_{\text{ren}} = \frac{Ae_{\infty}}{AUC_{\infty}}$
Mixed $\alpha_1$ agonist/$\beta$ antagonist

**Carvedilol**

**PK Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mollendorf et al&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Healthy male $n = 20$ 19-45 yrs</td>
<td>-</td>
<td>0.18 over 1 hr</td>
<td>IV infusion</td>
<td>-</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Non-compart mental</td>
</tr>
<tr>
<td>Varin et al&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Healthy $n = 3$</td>
<td>0.07</td>
<td>0.14</td>
<td>0.21</td>
<td>IV infusion for 15 mins</td>
<td>0-32 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>Std curve</td>
<td>Compart mental</td>
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</tbody>
</table>
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujimaki et al$^{92}$</td>
<td>Healthy</td>
<td>Equilibrium dialysis</td>
<td>20 µg/ml</td>
<td>HPLC</td>
<td>S (-)- carvedilol</td>
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<tr>
<td></td>
<td>n = 5</td>
<td>In-vitro</td>
<td></td>
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<td>fu = 0.0063 ± 0.007</td>
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<td>R (+)- carvedilol</td>
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<td>fu = 0.0045 ± 0.002</td>
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</table>

### Blood–to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
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<tr>
<td>Fujimaki et al$^{92}$</td>
<td>Healthy</td>
<td>Equilibrium dialysis</td>
<td>40 ng/ml</td>
<td>Liquid scintillation</td>
<td>S (-)- carvedilol 0.74</td>
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<tr>
<td></td>
<td>males</td>
<td>In-vitro</td>
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<td></td>
<td>R (+)- carvedilol 0.67</td>
</tr>
<tr>
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<td>n = 5</td>
<td></td>
<td></td>
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<td>Racemic 0.69</td>
</tr>
</tbody>
</table>

Fe = 12.7%
Urinary excretion study:

Giesmann et al\textsuperscript{91}:
Urine was collected from 0-72 hrs
Analysis: HPLC
\( \text{CL}_{\text{ren}} = \frac{A_{e\infty}}{\text{AUC}_{\infty}} \)

Bioavailability study:

Giesmann et al\textsuperscript{91}: Formulation: not mentioned (12.5 mg)
Sampling: 0-24 hrs
Analysis: HPLC
PM \( F_{\text{oral}} = 36.0 \) (SD = ± 7.66)
EM \( F_{\text{oral}} = 21.5 \) (SD = ± 6.25)
Significant difference between PM and EM

Mollendorf et al\textsuperscript{89}:
Formulation: Capsule (25 mg and 50 mg), Suspension (50 mg)
Analysis: HPLC
\( F_{\text{oral}} = 22\% \) (25 mg capsule)
\( F_{\text{oral}} = 24\% \) (50 mg capsule)
\( F_{\text{oral}} = 22\% \) (suspension)
# Labetalol

## PK Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lalonde et al 94</td>
<td>Healthy male n = 9 22-32 (25.9) yrs</td>
<td>76.5</td>
<td>1.2</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>HPL C</td>
<td>Limit of sensitivity = 5 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Cheymol et al 7</td>
<td>Healthy n = 9 32 ± 9 yrs</td>
<td>60 ± 11</td>
<td>0.99</td>
<td>IV infusion for 5-10 mins</td>
<td>0-48 hrs</td>
<td>HPL C</td>
<td>LOD – 5 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>777.0 (± 88.4)</td>
</tr>
<tr>
<td>Daneshmund et al 94</td>
<td>Healthy n = 6 2-24 yrs</td>
<td>-</td>
<td>0.5</td>
<td>Bolus</td>
<td>0-360 mins</td>
<td>UV</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>399.8 (± 71.8)</td>
</tr>
<tr>
<td>Wood et al 95</td>
<td>Healthy n = 3 31.6 yrs</td>
<td>63.7</td>
<td>1</td>
<td>Bolus</td>
<td>0-10 hrs</td>
<td>HPL C</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Kanto et al 96</td>
<td>Healthy n = 4 28-42 yrs</td>
<td>63 (50-76)</td>
<td>1.5</td>
<td>Bolus</td>
<td>0-720 mins</td>
<td>UV</td>
<td>20-200 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Nyberg et al 97</td>
<td>Healthy n = 5 39 yrs</td>
<td>83 (SE ± 9)</td>
<td>2.4</td>
<td>Bolus</td>
<td>0-480 mins</td>
<td>Fluorimetry</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Luke et al</td>
<td>Normal</td>
<td>80</td>
<td>0.5</td>
<td>Infusion</td>
<td>0-48 hrs</td>
<td>HPL</td>
<td>1 ng/ml</td>
<td>-</td>
<td>Non-</td>
<td>331</td>
</tr>
</tbody>
</table>

AUC: Area under the curve; BW: Body weight; CL_{tot}: Total clearance; CL_{ren}: Renal clearance; HPL C: High performance liquid chromatography; LOD: Limit of detection; UV: Ultraviolet; Vd_{ss}: Volume of distribution; PK: Pharmacokinetics; Non-compartmental: Non-compartmental; Compartmental: Compartmental; SE: Standard error.
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al99</td>
<td>Human plasma</td>
<td>In-vitro Ultrafiltration</td>
<td>100-50000 ng/ml</td>
<td>Liquid scintillation</td>
<td>50 %</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lalonde et al 93</td>
<td>-</td>
<td>In-vitro</td>
<td>30-120 ng/ml</td>
<td>HPLC</td>
<td>1.36 ± 0.18</td>
</tr>
</tbody>
</table>

Bioavailability study:

**Lalonde et al93**: Formulation: Not mentioned
Sampling: 0-24 hrs
Analysis: HPLC
F<sub>oral</sub>: 44 ± 14 %

**Nyberg et al97**: Formulation: Tablets (200 and 400 mg)
Sampling: 0-480 mins
Analysis: Fluorimetry
F<sub>oral</sub>: 9 % (200 mg)
F<sub>oral</sub>: 16 % (400 mg)

**Luke et al98**: Formulation: Capsules (200 mg)
Sampling: 0-48 hrs
Analysis: HPLC
F<sub>oral</sub>: 0.26 ± 0.15 (200 mg)
Xamoterol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Bastain et al(^{43})</td>
<td>Healthy male n = 12</td>
<td>75</td>
<td>0.19</td>
<td>Bolus</td>
<td>0-55 hrs</td>
<td>0-72 hrs</td>
<td>RIA</td>
<td>LOD 4-0.5 ng/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>

**Urinary excretion study: (Bastain et al\(^{43}\))**

Urine was collected from 0-3, 3-6, 6-12, 12-24, 24-36, 36-48, 48-60, 60-72 hrs

Analysis: RIA

\(CL_{\text{ren}} = \text{Ae}(72\text{ hr})/\text{AUC}(72\text{ hr})\)

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastain et al(^{43})</td>
<td>Healthy n = 12 (pooled)</td>
<td>Equilibrium dialysis</td>
<td>50, 125 and 500 ng/ml</td>
<td>Liquid Scintillation</td>
<td>3.0 ± 0.4 % (0.1-5.9%)</td>
</tr>
</tbody>
</table>

**Bioavailability study:**

Bastain et al\(^{43}\): Formulation : Oral Tablet (50 mg and 200 mg) and solution (200 mg)

Sampling: 0-48 hrs

Analysis: RIA

\(F_{\text{oral}}\) (50 mg tablet) = 4.5 ± 0.4 %

\(F_{\text{oral}}\) (200 mg tablet) = 4.8 ± 0.3 %

\(F_{\text{oral}}\) (200 mg solution) = 4.5 ± 0.3 %
Medroxalol

PK studies

Table: PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>LOQ</th>
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<tr>
<td>Haegele et al100</td>
<td>Healthy n = 8</td>
<td>50-90</td>
<td>1</td>
<td>Bolus</td>
<td>0-25 hr</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Cumulative</td>
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</tbody>
</table>

Bioavailability study:

Haegele et al100: Formulation: Capsules (400, 800 and 1200 mg)
Sampling: 0-25 hrs
Analysis: HPLC
F_oral: 27.2 ± 9.1 (400 mg)
31.3 ± 13.6 (800 mg)
37.4 ± 9.1 (1200 mg)

Urinary excretion study: (Haegele et al100)
Urine was collected from 0-48 hrs
Analysis: HPLC
CL_ren = Ae (48 hr)/ AUC (48 hr)
Bopindolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
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<tbody>
<tr>
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<td>Plasma</td>
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<tr>
<td>Aellig et al\textsuperscript{101}</td>
<td>Healthy n = 9 29 ± 3 yrs</td>
<td>74 ±4</td>
<td>0.013</td>
<td>Bolus</td>
<td>0-72 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>LOD = 0.5 ng/ml</td>
<td>-</td>
<td>Compart mental</td>
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<td>Plasma</td>
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<td>Urine</td>
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</tbody>
</table>

Bioavailability study:

Aellig et al\textsuperscript{101}: Formulation: not mentioned (4 mg)
Sampling: 0-72 hrs
Analysis: HPLC
$F_{oral}$: 69.8 ± 19.9 %
Epanolol

PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Cockshott et al^{102}</td>
<td>Healthy n = 12 21-45 yrs</td>
<td>78.4 (64.4-92.3)</td>
<td>0.06</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>0-96 hrs</td>
<td>LOD – 0.18 ng/ml</td>
<td>LOD – 70 ng/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>

**Plasma protein binding studies:** 50% (Cockshott et al^{102}) – just mentioned, no details provided

**Urinary excretion study:** (Cockshott et al^{102})
Urine was collected from 0-96 hrs
Analysis: HPLC

**Bioavailability study:**
Cockshott et al^{102};
Formulation: solution (200 mg)
Sampling: 0-72 hrs
Analysis: RIA
F_{oral}: 7.06 %

Formulation: tablet (200 mg)
Sampling: 0-72 hrs
Analysis: RIA
F_{oral}: 7.89 %
### PK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor et al.</td>
<td>Healthy n = 5</td>
<td>67.2 ± 6.2</td>
<td>20</td>
<td>Bolus 0-48 hrs</td>
<td>-</td>
<td>GC sensitivity -1 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>AUC (ng.h/ml)</td>
<td>CLtot (ml/min/kg)</td>
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<td></td>
<td>5.70 (4.2-6.4)</td>
<td>8.96 (calculated)</td>
</tr>
</tbody>
</table>
**Celiprolol**

**PK studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy n = 4</td>
<td>69 ± 6</td>
<td>Bolus 0.14</td>
<td>0-72 hrs 0.72 hrs</td>
<td>Liquid Scintillation</td>
<td>Plasma</td>
<td>1 ng/ml</td>
<td>-</td>
<td>Fractionated</td>
<td>AUC (ng.h/ml) 4.55 (calculated)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Plasma</td>
<td></td>
<td>Urine</td>
<td></td>
<td>fe =50.65 % (± 3.93%)</td>
</tr>
</tbody>
</table>
**β_2_ adrenoceptor agonists**

**Bambuterol**

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nyberg et al^{104}</td>
<td>Healthy n = 8 36 yrs</td>
<td>69</td>
<td>73.4 nmol/kg</td>
<td>Infusion 0-60 hrs</td>
<td>0-72 hrs</td>
<td>GC-MS 0.5 nmol/l</td>
<td>4 nmol/l</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml)</td>
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<td>67.5 nmol*h/l</td>
</tr>
</tbody>
</table>

**Urinary excretion study: (Nyberg et al^{104})**
Urine was collected from 0-4, 4-12, 12-18, 18-24 hrs
Analysis: GC-MS
CL_{ren} = Ae (24 hr)/ AUC (24 hr)

**Bioavailability study:**

Nyberg et al^{104}: Formulation : Solution (668 nmol/kg)
Sampling: 0-48 hrs
Analysis: GC-MS
F_{oral} = 8.93 % (6.09-13.2)
Albuterol

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boulton et al[^105]</td>
<td>Healthy male n = 7 24 ± 2 yrs</td>
<td>75 ± 12 (62-96)</td>
<td>0.002 Bolus</td>
<td>0-8 hr</td>
<td>0-8 hr</td>
<td>HPLC</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml)</td>
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<td>CL\textsubscript{tot} (ml/min/ kg)</td>
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<td>(+) (S)-6.5 (± 2)</td>
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<td>-(R)-10.3 (± 3)</td>
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<td>Total-7.8 (± 2.3)</td>
</tr>
</tbody>
</table>

**Urinary excretion study: (Boulton et al[^105])**

Urine was collected every hour from 0-8 hrs
Analysis: HPLC
CL\textsubscript{ren} = Ae (8 hr)/ AUC (8 hr)

**Bioavailability study:**

Boulton et al[^105]: Formulation : Salbutamol sulphate elixir Solution (4 mg)
Sampling: 0-8 hrs
Analysis: HPLC
(+)-S F\textsubscript{oral} = 0.71 ± 0.09
(-)-R F\textsubscript{oral} = 0.30 ± 0.07 Total F\textsubscript{oral} = 0.53 ± 0.08
Terbutaline

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
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<tr>
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<td></td>
<td></td>
<td>AUC</td>
<td>CLtot</td>
<td>Vdss</td>
<td>CLren</td>
</tr>
<tr>
<td>Fagerstrom et al\textsuperscript{107}</td>
<td>Healthy n = 19</td>
<td>70 (assumed)</td>
<td>0.002 9</td>
<td>Study A-3 subjects - IV bolus</td>
<td>0-42 hrs</td>
<td>0-24 hrs</td>
<td>Liquid scintillation</td>
<td>GC-MS</td>
<td>-</td>
<td>20 ng/ml - HPL C</td>
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<td>Study B -5 subjects - IV infusion</td>
<td></td>
<td></td>
<td>GC-MS</td>
<td>-</td>
<td>HPL C - urine</td>
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<td>Study C - 11 subjects – IV infusion</td>
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<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Borgstrom et al</td>
<td>Healthy n = 6</td>
<td>64</td>
<td>0.004</td>
<td>IV infusion</td>
<td>0-24 hrs</td>
<td>0-72 hrs</td>
<td>GC-MS</td>
<td>2 pmol</td>
<td>-</td>
<td>Noncompartmental</td>
</tr>
</tbody>
</table>

483
Plasma protein binding studies:

Borga et al\textsuperscript{110}: 14-25\% (just mentioned)

Blood-to-plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borga et al\textsuperscript{110}</td>
<td>healthy n = 3</td>
<td>\textit{In-vivo}</td>
<td>5 mg terbutaline sulfate 3 times daily for 4 days</td>
<td>GC-MS</td>
<td>1.44</td>
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<td></td>
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<td>RBC: Plasma – 2.27</td>
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</tbody>
</table>

Urinary excretion study: (Borgstrom et al\textsuperscript{108})

Urine was collected every hour from 0-8 hrs
Analysis: HPLC
CL\textsubscript{ren} = Ae (8 hr)/ AUC (8 hr)
Fenoterol

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>AUC (ng.h/ml)</th>
<th>CL_{tot} (ml/min/kg)</th>
<th>Vd_{ss} (l/kg)</th>
<th>CL_{ren} (ml/min/kg)</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hildebrandt et al (^{111})</td>
<td>Healthy women n = 5 30 yrs</td>
<td>56</td>
<td>0.03</td>
<td>Infusion</td>
<td>0-120 mins</td>
<td>-</td>
<td>RIA</td>
<td>10-1000 pg/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
<td>37.9 (Q25-Q75: 34.2-38.03)</td>
<td>0.73 (Q25-Q75: 0.63-1.12)</td>
<td>-</td>
</tr>
</tbody>
</table>
**β₁ adrenoceptor agonists**

**Prenalterol**

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graffner et al¹¹²</td>
<td>Healthy male n = 6</td>
<td>78</td>
<td>0.032</td>
<td>Bolus</td>
<td>0-8 hr 0-24 hr</td>
<td>GC-MS</td>
<td>-</td>
<td>-</td>
<td>Compart mental Cumulative</td>
<td>27.34 AUC (ng.h/ml) 19.6 CL₉₀ (ml/min/kg) Vₐss (l/kg) 11.9 ± 0.79 fe = 60 ± 3%</td>
</tr>
</tbody>
</table>

**Blood-to-plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graffner et al¹¹²</td>
<td>Healthy n = 3</td>
<td>In-vitro</td>
<td>37 nmol/l 160 nmol/l 280 nmol/l</td>
<td>Liquid Scintillation</td>
<td>1.14 ± 0.01 RBC: Plasma: 1.30 ± 0.03</td>
</tr>
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<td></td>
<td>1.09 ± 0.10 RBC: Plasma: 1.19 ± 0.10</td>
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<td></td>
<td>0.98 ± 0.01 RBC: Plasma: 0.96 ± 0.03</td>
</tr>
</tbody>
</table>
**Urinary excretion study:** (Graffner et al\textsuperscript{112})
Urine was collected every hour from 0-24 hrs
Analysis: GC-MS
\[ \text{CL}_{\text{ren}} = \frac{Ae}{AUC} \]

**Bioavailability study:**
Graffner et al\textsuperscript{112}: Formulation : Solution (2.5, 5.0, 10.0 mg)
Sampling: 0-8 hrs
Analysis: GC-MS
\[ F_{\text{oral}} = 0.26 \pm 0.02 \text{ (2.5 mg)} \]
\[ F_{\text{oral}} = 0.23 \pm 0.04 \text{ (5.0 mg)} \]
\[ F_{\text{oral}} = 0.27 \pm 0.04 \text{ (10.0 mg)} \]
References:


**Appendix I (c)**

Human PK Study Summaries for β-LAs

**Penicillins**

Amoxicillin

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spyker et al (1977)¹</td>
<td>Healthy n = 8 18-32 yrs</td>
<td>77.5 (57-98)</td>
<td>3.03</td>
<td>Bolus</td>
<td>0-6 hr</td>
<td>0-6 hr</td>
<td>Plate assay</td>
<td>sensitivit y – 0.5 µg/ml</td>
<td>-</td>
<td>Compart-mental</td>
</tr>
</tbody>
</table>

---

¹Data from Spyker et al. (1977)
### Urinary excretion study:

Spyker et al.\(^1\)
Urine collection: 0-1, 1-2, 2-3, 3-4, 4-6 hr
\(f_e = 56.4\% \) (SD = ± 26.9%)

Sjovall et al. (1985)\(^2\):
Urine collection: 0-0.05, 0.5-1, 1-1.5, 1.5-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10 10-11, 11-12 hr
Renal clearance \(\text{CL}_{\text{ren}} = \frac{\text{d}X_u}{\text{d}t} / C_p\)

### Bioavailability study:

Spyker et al.\(^1\)
Healthy (\(n = 8\))
Formulation: Not mentioned (250, 500, 1000 mg sodium amoxicillin)
Sampling: 0-6 hrs
Analysis: Plate assay
\(F_{\text{oral}} = 93\%\)

<table>
<thead>
<tr>
<th>Sjovall et al (1985)(^2)</th>
<th>Healthy</th>
<th>74.7 ± 8.5</th>
<th>26.8</th>
<th>Bolus</th>
<th>0-10.5 hrs</th>
<th>0-12 hrs</th>
<th>HPLC</th>
<th>100 ng/ml</th>
<th>50 ng/ml</th>
<th>Compartmental</th>
<th>Fractionated</th>
<th>4.28 (± 0.68)</th>
<th>0.210 (± 0.028)</th>
<th>3.64 (± 0.46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 9</td>
<td>29.4 ± 5.81 yrs</td>
<td>496</td>
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</table>
Azlocillin
PK studies:

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<th>BW</th>
<th>Dose</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tion</td>
<td>(kg)</td>
<td>(mg/</td>
<td>kg)</td>
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</tr>
<tr>
<td>Barriere et al (1990)</td>
<td>Healthy</td>
<td>77</td>
<td>60</td>
<td>Bolus</td>
<td>0-14 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Noncompartmental</td>
<td>Cumulative</td>
<td>2.06 (± 0.52)</td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>±13</td>
<td></td>
<td></td>
<td>0-24 hrs</td>
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<td></td>
<td>22 ± 3  yrs</td>
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<tr>
<td>Leroy et al (1980)</td>
<td>Healthy</td>
<td>68.2</td>
<td>30</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>Agar Diffusion method</td>
<td>-</td>
<td>Compartmenental</td>
<td>-</td>
<td>5.45 (± 1.28)</td>
</tr>
<tr>
<td></td>
<td>n = 5</td>
<td>±10.6</td>
<td></td>
<td></td>
<td>0-24 hrs</td>
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<td></td>
<td>23.6 ± 2.6 yrs</td>
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</tr>
<tr>
<td>Tartaglione et al</td>
<td>Healthy</td>
<td>71.3</td>
<td>57.4</td>
<td>Infusion</td>
<td>0- 6 hrs</td>
<td>HPLC 0.5 µg/ml</td>
<td>-</td>
<td>Compartmenental</td>
<td>Cumulative</td>
<td>1.94 (± 0.31)</td>
</tr>
<tr>
<td></td>
<td>n = 12</td>
<td>±11.9</td>
<td></td>
<td></td>
<td>0-12 hrs</td>
<td></td>
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<tr>
<td></td>
<td>23 ± 2.2 yrs</td>
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</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiegel et al (1978)</td>
<td>Healthy</td>
<td>-</td>
<td>-</td>
<td>Agar diffusion test</td>
<td>27.9 % (± 6.1)</td>
</tr>
<tr>
<td></td>
<td>n = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenkranz</td>
<td>Healthy</td>
<td>Equilibrium</td>
<td>20 µg/ml</td>
<td>Circular</td>
<td>39 %</td>
</tr>
</tbody>
</table>
**et al et al** dialysis dichroism

**Urine excretion study:**
Urine collection: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(12)\text{AUC}_{0\text{12}}$ here $\text{Ae}^{12}$ is cumulative amount of drug excreted unchanged in urine upto 12 hrs

**Ampicillin**

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Bergan et al (1978) $^8$</td>
<td>Healthy n=10 22.5 ± 2.1 yrs</td>
<td>70.6 ± 4.7</td>
<td>7.88</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Ehrnebo et al (1979)$^9$</td>
<td>Healthy 23-28 yrs n=5</td>
<td>68 (58-78)</td>
<td>6.92</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>0-12 hrs Microbiological assay: Plasma</td>
<td>lower limit of sensitivity – 0.05 µg/ml</td>
<td>lower limit of sensitivity – 0.03 µg/ml</td>
<td>Compartmental</td>
<td>Cumulative</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Sjovall et al (1985)$^2$</td>
<td>Healthy n = 9 29.4 ± 5.81 yrs</td>
<td>74.7 ± 8.51</td>
<td>40.2</td>
<td>Bolus</td>
<td>0-10.5 hrs</td>
<td>0-12 hrs HPLC</td>
<td>100 ng/ml</td>
<td>300 ng/ml</td>
<td>Compartmental</td>
<td>Fractionated</td>
</tr>
</tbody>
</table>

fe = 72.9% (± 10.3) fe = 0.80
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kunin et al</td>
<td>Healthy n = 6</td>
<td>In-vivo Equilibrium dialysis</td>
<td>Therapeutic dose</td>
<td>Cup Plate method</td>
<td>22.5 ± 13.7 %</td>
</tr>
<tr>
<td>Ehrnebo et al</td>
<td>Healthy n = 5</td>
<td>In-vitro Equilibrium dialysis</td>
<td>-</td>
<td>Liquid scintillation</td>
<td>fraction bound = 0.178 (± 0.020)</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrnebo et al</td>
<td>Healthy n = 5</td>
<td>In-vitro</td>
<td>Liquid scintillation</td>
<td>fraction in RBC – 0.016 (± 0.038)</td>
</tr>
</tbody>
</table>

Urine excretion study:
Ehrnebo et al (1979)²:
Urine collection: 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-8, 8-10, 10-12 hr
Renal clearance $CL_{\text{ren}} = Ae(12)AUC_{0}^{6}$ here $Ae^{6}$ is cumulative amount of drug excreted unchanged in urine upto 6 hrs

Sjovall et al (1985)²:
Urine collection: 0-0.05, 0.5-1, 1-1.5, 1.5-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-9, 9-10 10-11,11-12 hr
Renal clearance $CL_{\text{ren}} = (dXu/dt)/Cp$

Bioavailability study: Ehrnebo et al (1979)⁹
Healthy (n = 8)
Formulation : Tablets (495 mg ampicillin)
Sampling: 0-6 hrs
Analysis: Microbiological assay
$F_{\text{oral}} = 55.3 ± 17.8 \%$
Piperacillin

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyers et al (1980)</td>
<td>Healthy n = 10 25-64 yrs</td>
<td>70.85 ± 13.94</td>
<td>28.22</td>
<td>Infusion for 30 mins</td>
<td>0-24 hrs</td>
<td>Cup plate method</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-24 hrs</td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td>AUC: 8.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70.4 (SE ± 1.41)</td>
<td>0.014</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>0-24 hrs</td>
<td>Agar well method</td>
<td>sensitivity 0.4 µg/ml</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;: 21.76</td>
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<tr>
<td></td>
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<td>0.028</td>
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<td>0.057</td>
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<td>0.085</td>
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<td>-</td>
</tr>
<tr>
<td>Tjandramaga et al (1978)</td>
<td>Healthy n = 5 22 yrs</td>
<td>70.4</td>
<td>0.014</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>Agar well method</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.028</td>
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<td></td>
<td>AUC: 10.04</td>
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<tr>
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<td>0.057</td>
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<td>CL&lt;sub&gt;tot&lt;/sub&gt;: 0.47</td>
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<td>0.085</td>
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<td></td>
<td></td>
<td>V&lt;sub&gt;dss&lt;/sub&gt;: 7.42</td>
</tr>
<tr>
<td>Aronoff et al (1980)</td>
<td>Healthy n = 7 30.1 ± 4.1 yrs</td>
<td>73.5 ± 8.8</td>
<td>15</td>
<td>Infusion for 2-4 mins</td>
<td>0-48 hrs</td>
<td>Agar well diffusion</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
<td>Cumulative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-48 hrs</td>
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<td></td>
<td></td>
<td></td>
<td>AUC: 3.05</td>
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<td></td>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;: 2.07</td>
</tr>
</tbody>
</table>

**PK endpoints:**

- **AUC (ng.h/ml):**
  - Aronoff et al: 3.05

- **CL<sub>tot</sub> (ml/min/kg):**
  - Tjandramaga et al (1978): 0.47 (± 0.03)
  - Aronoff et al: 2.07 (± 0.71)

- **V<sub>dss</sub> (l/kg):**
  - Meyers et al (1980): 6.04 (± 0.47)
  - Tjandramaga et al (1978): 5.46 (± 0.03)
  - Aronoff et al: 4.59 (± 0.43)

- **CL<sub>ren</sub> (ml/min/kg):**
  - Meyers et al (1980): 7.46 (± 0.72)
  - Tjandramaga et al (1978): 6.04 (± 0.48)
  - Aronoff et al: 5.50 (± 0.43)

- **fe:**
  - Meyers et al (1980): 67.5%
  - Tjandramaga et al (1978): 69%
  - Aronoff et al: 69% (± 15)
Urine excretion study:

Tjandramaga et al\textsuperscript{1}:
Urine collection: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(24)\text{AUC}_{\text{0-24}}$ where $\text{Ae}_{24}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs

Aronoff et al\textsuperscript{14}:
Urine collection: 0-2, 2-4, 4-6, 6-12, 12-24, 24-36, 36-48 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(48)\text{AUC}_{\text{0-48}}$ where $\text{Ae}_{48}$ is cumulative amount of drug excreted unchanged in urine upto 48 hrs

Tartaglione et al\textsuperscript{5}:
Urine collection: 0-12 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{fe} \times \text{CL}_{\text{tot}}$

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Age (years)</th>
<th>Infusion</th>
<th>0-6 hrs (h)</th>
<th>0-12 hrs (h)</th>
<th>HPLC</th>
<th>Cumulative</th>
<th>Compartental</th>
<th>Renal clearance</th>
<th>fe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tartaglione et al\textsuperscript{5}</td>
<td>Healthy</td>
<td>71.3±11.9</td>
<td>53.6</td>
<td>0-6 hrs</td>
<td>0-12 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Cumulative</td>
<td>307000 (±83000)</td>
<td>3.13 (±0.50)</td>
</tr>
<tr>
<td>Aronoff et al\textsuperscript{14}</td>
<td>Healthy</td>
<td>23±2.2</td>
<td>58% (±15)</td>
<td>2.25 μg/ml</td>
<td>30-36</td>
<td>HPLC</td>
<td>-</td>
<td>Cumulative</td>
<td>32000 (±8000)</td>
<td>3.13 (±0.50)</td>
</tr>
<tr>
<td>Tjandramaga et al\textsuperscript{1}</td>
<td>Healthy</td>
<td>58% (±15)</td>
<td>2.25 μg/ml</td>
<td>30-36</td>
<td>HPLC</td>
<td>-</td>
<td>Cumulative</td>
<td>32000 (±8000)</td>
<td>3.13 (±0.50)</td>
<td>0.17 (±0.03)</td>
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Ticarcillin

PK studies:

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<tr>
<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
<tbody>
<tr>
<td>Meyers et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Healthy n = 10 25-64 yrs</td>
<td>70.85 ± 13.94</td>
<td>28.22</td>
<td>Infusion for 30 mins</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>Cup plate method</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
</tr>
<tr>
<td>Davies et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Healthy n = 6 28-48 yrs</td>
<td>77.5 (60-95)</td>
<td>64.5</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>0-24 hrs</td>
<td>UV</td>
<td></td>
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<tr>
<td>Hoffken et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Healthy n = 10 32.5 yrs</td>
<td>69.8 (59.9-79.2)</td>
<td>64.2</td>
<td>Infusion for 15 mins</td>
<td>0-10 hrs</td>
<td>0-24 hrs</td>
<td>Agar diffusion</td>
<td>LOD 0.06 mg/l</td>
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Plasma protein binding studies:

<table>
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<tr>
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<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Li et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Healthy n = 2</td>
<td>Ultrafiltration</td>
<td>2 gm IV bolus</td>
<td>HPLC</td>
<td>f&lt;sub&gt;u&lt;/sub&gt; = 0.335</td>
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</table>
## Carbenicillin

### PK studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
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<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
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<tr>
<td>Meyers et al(^{15})</td>
<td>Healthy n = 10 25-64 yrs</td>
<td>70.85 ± 13.94</td>
<td>28.22</td>
<td>Infusion for 30 mins</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>Cup plate method</td>
<td>-</td>
<td>-</td>
<td>Compart-mental</td>
</tr>
<tr>
<td>Bergan et al(^{18})</td>
<td>Healthy n = 10 22-29 yrs</td>
<td>73.5</td>
<td>27.2</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>0-8 hrs</td>
<td>Agar well</td>
<td>-</td>
<td>-</td>
<td>Compart-mental</td>
</tr>
<tr>
<td>Hansen et al(^{19})</td>
<td>Healthy n = 5 52-84 yrs</td>
<td>70 (assumed)</td>
<td>57.1</td>
<td>Bolus</td>
<td>0-4 hrs</td>
<td>0-24 hrs</td>
<td>Plasma- Agar cup diffusion Urine - TLC</td>
<td>-</td>
<td>-</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Pancoast et al(^{20})</td>
<td>Healthy n = 8 30 yrs</td>
<td>69.6</td>
<td>57.5</td>
<td>Infusion for 5 mins</td>
<td>0-360 mins</td>
<td>0-12 hrs</td>
<td>LOD - 1 µg/ml LOD - 1 µg/ml</td>
<td>Compart-mental</td>
<td>Cumulative</td>
<td>-</td>
</tr>
<tr>
<td>Itoh et al(^{21})</td>
<td>Healthy n = 4 23-26 yrs</td>
<td>59.7 (± 3.8)</td>
<td>33.5</td>
<td>Bolus</td>
<td>0-5 hrs</td>
<td>0-12 hrs</td>
<td>HPLC LOD- 5 µg/ml</td>
<td>LOD- 5 µg/ml</td>
<td>Compart-mental</td>
<td>Fractionated</td>
</tr>
</tbody>
</table>
Urine excretion study:

Itoh et al\textsuperscript{21},
Urine collection: 0-0.5, 0.5-1, 1-2, 2-3, 3-4, 4-6, 6-12, 12-24 hr
Renal clearance $\text{CL}_\text{ren} = \frac{(dU/dt)}{C(\text{mid-point of urine collection interval})}$

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen et al\textsuperscript{19}</td>
<td>Healthy n = 6</td>
<td>4% HSA on sephadex column</td>
<td>50 – 400 µg/ml</td>
<td>UV</td>
<td>70 %</td>
</tr>
<tr>
<td>Rosenkranz et al\textsuperscript{7}</td>
<td>Healthy</td>
<td>Equilbrium dialysis</td>
<td>2 µg/ml</td>
<td>Circular dichroism</td>
<td>46 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 µg/ml</td>
<td></td>
<td>37 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200 µg/ml</td>
<td></td>
<td>29 %</td>
</tr>
<tr>
<td>HSA (4%)</td>
<td></td>
<td>2 µg/ml</td>
<td></td>
<td></td>
<td>43 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 µg/ml</td>
<td></td>
<td></td>
<td>34 %</td>
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<tr>
<td></td>
<td></td>
<td>200 µg/ml</td>
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<td>26 %</td>
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$S = 2.16 \ (\pm \ 0.22) \quad fe = 84\%$
## Sulbenicillin

### PK studies:

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<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
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<td></td>
</tr>
<tr>
<td>Hansen et al(^{19})</td>
<td>Healthy n = 5</td>
<td>70 (assumed)</td>
<td>57.1</td>
<td>Bolus</td>
<td>0-4 hrs</td>
<td>0-24 hrs</td>
<td>Plasma - Agar cup diffusion Urine - TLC</td>
<td>-</td>
<td>-</td>
<td>Not mentioned</td>
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</table>

### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<td>50 – 400 µg/ml</td>
<td>UV</td>
<td>70 %</td>
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</table>
**Cloxacillin**

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>AUC (ng.h/ml)</td>
<td>CL\text{tot} (ml/min/kg)</td>
<td>Vd\text{ss} (l/kg)</td>
<td>CL\text{ren} (ml/min/kg)</td>
</tr>
<tr>
<td>Nauta et al\textsuperscript{22}</td>
<td>Healthy n = 7 19-46 yrs</td>
<td>70.6</td>
<td>13.97</td>
<td>Infusion</td>
<td>0-8 hrs</td>
<td>Agar plate diffusion</td>
<td>2.5 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kunin et al\textsuperscript{10}</td>
<td>Healthy n = 6</td>
<td>In-vivo Equilibrium dialysis</td>
<td>Therapeutic dose</td>
<td>Cup Plate method</td>
<td>95.2 ± 0.5 %</td>
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</table>
Dicloxacillin

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Kampf et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Patients with normal renal function n = 4</td>
<td>67.6 ± 20</td>
<td>30</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-36 hrs Agar well technique</td>
<td>-</td>
<td>-</td>
<td>Compart-mental</td>
<td>Cumulative</td>
</tr>
<tr>
<td>Lofgren et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Healthy n = 6</td>
<td>75</td>
<td>24.6</td>
<td>Infusion for 30 mins</td>
<td>0-12 hrs</td>
<td>0-10 hrs Agar well technique</td>
<td>sensitivity = 0.1 mg/l</td>
<td>-</td>
<td>Compart-mental</td>
<td>Cumulative</td>
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</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Kunin et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Healthy n = 6</td>
<td>In-vivo Equilibrium dialysis</td>
<td>Therapeutic dose</td>
<td>Cup Plate method</td>
<td>97.9 ± 0.6 %</td>
</tr>
<tr>
<td>Pacifici et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Healthy n = 8</td>
<td>In-vitro Equilibrium dialysis</td>
<td>15 µg/ml</td>
<td>Liquid scintillation</td>
<td>f&lt;sub&gt;a&lt;/sub&gt; = 7.3 ± 0.8%</td>
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<tr>
<td>Roder et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Healthy n = 12</td>
<td>In-virol Ultrafiltration</td>
<td>10 mg/l, 20 mg/l, 40 mg/l</td>
<td>Cup Plate method</td>
<td>Median = 95.7% 94.7-96.2 %</td>
</tr>
</tbody>
</table>
Urine excretion study:

Kampf et al:\(^{23}\)

Urine collection: 0-4, 4-8, 8-12, 12-24, 24-36 hr
Renal clearance \(CL_{\text{ren}} = Ae(36)AUC_{[0,36]}\) where \(Ae^{36}\) is cumulative amount of drug excreted unchanged in urine upto 36 hrs

Flucloxacillin

PK studies:

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<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>Assay</th>
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<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
<td>CL_{tot} (ml/min/kg)</td>
<td>Vd_{ss} (l/kg)</td>
<td>CL_{ren} (ml/min/kg)</td>
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<tr>
<td>Gath et al(^{27})</td>
<td>Elderly, Healthy n = 7 68-87 yrs</td>
<td>67.7 ± 12.5</td>
<td>7.02</td>
<td>Bolus 0-8 hrs 0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental Cumulative</td>
<td>-</td>
<td>1.38 (± 0.22)</td>
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<tr>
<td>Landersdorfer et al(^{28})</td>
<td>Healthy n = 10 70 (assumed)</td>
<td>7.14</td>
<td>14.3</td>
<td>Infusion for 5 mins 0-24 hrs 0-24 hrs</td>
<td>HPLC</td>
<td>0.5 mg/l</td>
<td>5 mg/l</td>
<td>Noncompartmental Cumulative</td>
<td>-</td>
<td>GM - 1.94</td>
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<tr>
<td>Nauta et al(^{22})</td>
<td>Healthy n = 7 19-46 yrs</td>
<td>70.6</td>
<td>13.97</td>
<td>Infusion - 0-8 hrs</td>
<td>Agar plate diffusion</td>
<td>2.5 μg/ml</td>
<td>-</td>
<td>Compartmental Cumulative</td>
<td>-</td>
<td>1.74 (± 0.18)</td>
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### Plasma protein binding studies:

<table>
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<th>Protein binding</th>
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<tbody>
<tr>
<td>Thijssen et al (1982)</td>
<td>Healthy n = 3</td>
<td>In-vivo Equilibrium</td>
<td>Dose = 1 gm</td>
<td>HPLC</td>
<td>f_u = 6.1 % (± 0.3)</td>
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<tr>
<td></td>
<td></td>
<td>dialysis</td>
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<td></td>
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<tr>
<td>Roder et al</td>
<td>Healthy n = 12</td>
<td>In-viro Ultrafiltration</td>
<td>10 mg/l, 20 mg/l, 40 mg/l</td>
<td>Cup Plate method</td>
<td>Median – 95.7% 94.7-96.2 %</td>
</tr>
</tbody>
</table>

**Bioavailability study:** Gath et al
Healthy (n = 7)
Formulation: Capsule (500 mg sodium flucloxacillin)
Sampling: 0-8 hrs
Analysis: HPLC
F<sub>oral</sub> = 54.4 ± 18.8 %
Oxacillin

PK studies:

<table>
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<tr>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kampf et al\textsuperscript{23}</td>
<td>Patients with normal renal function 43.0 ± 23.2</td>
<td>67.6 ± 20.0</td>
<td>30</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-36 hrs</td>
<td>Agar well technique</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
</tr>
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Plasma protein binding studies:

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<tbody>
<tr>
<td>Kunin et al\textsuperscript{10}</td>
<td>Healthy n = 6</td>
<td>In-vivo Equilibrium dialysis</td>
<td>Therapeutic dose</td>
<td>Cup Plate method</td>
<td>94.2 ± 2.1 %</td>
</tr>
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</table>

Urine excretion study:

Kampf et al\textsuperscript{23}.
Urine collection: 0-4, 4-8, 8-12, 12-24, 24-36 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(36)\text{AUC}_{36}$ where $\text{Ae}^{36}$ is cumulative amount of drug excreted unchanged in urine upto 36 hrs
**Mezlocillin**

**PK studies:**

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<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>**Bergan et al (1978)**18</td>
<td>Healthy n = 10 22-29 yrs</td>
<td>73.5 27.2 68.0</td>
<td>13.6 27.2 13.97</td>
<td>Bolus 0-8 hrs 0-8 hrs</td>
<td>Plasma Urine 0-8 hrs Agar well method</td>
<td>Plasma Urine Cumulative</td>
<td>AUC (ng.h/ml) 32030 (calculated) CL_{tot} (ml/min kg) 7.1 (± 1.72) Vd_{ss} (l/kg) 0.31 (calculated)</td>
<td>CL_{ren} (ml/min kg) 4.31 (± 1.39) fe = 60.8% (± 13.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aronoff et al</strong>30</td>
<td>Healthy n = 6 32.8 ± 8 yrs</td>
<td>71.6 ± 4.8 13.97</td>
<td>13.97 13.97 13.97</td>
<td>Bolus 0-24 hrs 0-24 hrs</td>
<td>Plasma-Agar well diffusi</td>
<td>Plasma Urine Non-compartmental Cumulative</td>
<td>AUC (ng.h/ml) 59500 (± 11500) CL_{tot} (ml/min kg) 4.50 (± 0.65) Vd_{ss} (l/kg) 0.24 (calculated)</td>
<td>CL_{ren} (ml/min kg) 2.98 (± 0.29) fe = 69.0% (± 12.1)</td>
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### Plasma protein binding studies:

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<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenkranz et al⁷</td>
<td>Healthy</td>
<td>Equilibrium dialysis</td>
<td>20 µg/ml</td>
<td>Circular dichroism</td>
<td>35 %</td>
</tr>
</tbody>
</table>

### Urine excretion study:

Bergan et al¹⁸  
Urine collection: 0-2, 2-4, 4-6, 6-8 hr

Aronoff et al³⁰:  
Urine collection: 0-2, 2-4, 4-6, 6-12, 12-24 hrs

Pancoast et al²⁰:  
Urine collection: 0-3, 3-6, 6-12 hrs  
Renal clearance $CL_{ren} = f_e \times CL_{tot}$
Nafcillin

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waller et al³¹</td>
<td>Healthy n = 6</td>
<td>63-75</td>
<td>7.25</td>
<td>Bolus</td>
<td>0-10 hrs</td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>AUC (ng.h/ml)</td>
<td>CLₜₒₜ (ml/min/kg)</td>
<td>Vdₜₚ (l/kg)</td>
</tr>
<tr>
<td></td>
<td>22-28 yrs</td>
<td></td>
<td></td>
<td></td>
<td>0-10 hrs</td>
<td>Cup plate method</td>
<td>-</td>
<td>Cumulative</td>
<td>36590 (± 2950)</td>
<td>3.33 (± 0.44)</td>
</tr>
</tbody>
</table>

Urine excretion study:

Urine collection: 0-2, 2-4, 4-6, 6-8, 8-10 hr
Renal clearance \( \text{CL}_{\text{ren}} = \text{Ae}(\infty)\text{AUC}_{\text{0}}^{\infty} \) where \( \text{Ae}^{\infty} \) is cumulative amount of drug excreted unchanged in urine

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al³²</td>
<td>Pooled serum</td>
<td>Ultrafiltration</td>
<td>2.85-3.45 µg/ml</td>
<td>Cup plate method</td>
<td>89.40%</td>
</tr>
</tbody>
</table>
Mecillinam

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW  (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td>Plasma</td>
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<tr>
<td>Gambertoglio et al (1980) (^{33})</td>
<td>Healthy n = 12 27.5 yrs</td>
<td>70.5</td>
<td>11.5</td>
<td>Infusion for 15 mins</td>
<td>0-480 mins</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
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</table>

Plasma protein binding studies:

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<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tybring et al (^{34})</td>
<td>Healthy</td>
<td>In-vitro Ultrafiltration</td>
<td>-</td>
<td>-</td>
<td>5-10%</td>
</tr>
</tbody>
</table>

Urine excretion study: Gambertoglio et al (1980) \(^{33}\)

Urine collection: Half hourly for first 3 hrs and then hourly every 6 hrs and then pooled from 6 -24 hrs

Renal clearance CL\(_{\text{ren}}\) = Ae\(_{24}\)AUC\(_{0-24}\) here Ae\(_{24}\) is cumulative amount of drug excreted unchanged in urine upto 24 hrs
### Temocillin

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg) ± SD</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
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<tr>
<td>Staniforth et al³⁵</td>
<td>Healthy n = 12 25.58 ± 5.71 yrs</td>
<td>73.51 ± 15.4</td>
<td>13.60</td>
<td>Bolus</td>
<td>0-32 hrs</td>
<td>Plasma, Urine</td>
<td>Plasma, Urine</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml) = 77.1%</td>
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<tr>
<td>Boelaert et al³⁶</td>
<td>Patients with normal renal function n = 6 46 yrs</td>
<td>70.2 ± 15</td>
<td>15</td>
<td>Bolus</td>
<td>0-72 hrs</td>
<td>Plate assay</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
<td>AUC (± 115000) = 62% (± 15.2)</td>
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<tr>
<td>Hampel et al³⁷</td>
<td>Healthy n = 10 26.7 yrs</td>
<td>69.8 ± 7.16</td>
<td>7.16</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>Agar well diffusion</td>
<td>Sensitivity- 5 mg/l</td>
<td>Compartmental</td>
<td>Cumulative</td>
<td>AUC (± 18700) = 0.26 (± 0.05)</td>
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</tbody>
</table>

**Abbreviations:**
- **PK:** Pharmacokinetic
- **BW:** Body weight
- **Dose:** Drug dose
- **Rate:** Administration rate
- **Sampling schedule:** Time points for sampling
- **Assay:** Method used for determination
- **LOQ:** Limit of quantification
- **PK Analysis:** Type of analysis
- **Urine Collection method:** Method used for urine collection
- **PK endpoints:** Pharmacokinetic endpoints
- **AUC:** Area under the curve
- **CL<sub>tot</sub>** (ml/min/kg): Total clearance
- **Vd<sub>ss</sub>** (l/kg): Volume of distribution
- **CL<sub>ren</sub>** (ml/min/kg): Renal clearance
- **fe:** Fraction of dose excreted in urine
<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range</th>
<th>Dose Details</th>
<th>0-24 hrs</th>
<th>0-24 hrs</th>
<th>0-24 hrs</th>
<th>0-24 hrs</th>
<th>0-24 hrs</th>
<th>0-24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overbosch et al</td>
<td>18-30 yrs</td>
<td>21.4 mg/kg for 20 min infusion, followed by 250 mg/h for 3 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>1 mg/l</td>
<td>1 mg/l</td>
<td>Noncompartmental</td>
<td>Cumulative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21.4</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
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</tr>
</tbody>
</table>

fe = 74.0% (± 12.9)
fe = 66.1% (± 16.8)
fe = 68.1% (± 6.0)
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staniforth et al(^3)</td>
<td>Healthy n = 12</td>
<td>In-vivo</td>
<td>0-500 µg/ml</td>
<td>Cup plate method</td>
<td>55-94 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrafiltration</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hampel et al(^3)</td>
<td>Healthy</td>
<td>In-vitro</td>
<td>200 mg/l</td>
<td>Agar well diffusion</td>
<td>63 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrafiltration</td>
<td>100 mg/l</td>
<td></td>
<td>86 %</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>50 mg/l</td>
<td></td>
<td>88 %</td>
</tr>
<tr>
<td>Overbosch et al(^3)</td>
<td>Healthy n = 4</td>
<td>In-vivo</td>
<td>131.4 mg/l</td>
<td>HPLC</td>
<td>83 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Equilibrium</td>
<td>220.7 mg/l</td>
<td></td>
<td>74 %</td>
</tr>
</tbody>
</table>

Urine excretion study:
Boelaert et al\(^3\):
Urine collection: 0-4, 4-8, 8-24, 24-32 hr
Azidocillin

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td></td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Bergan et al&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Healthy n = 9, 23 yrs</td>
<td>68.2</td>
<td>10.4</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>0-12 hrs</td>
<td>Agar well diffusion method</td>
<td>0.02 µg/ml</td>
<td>-</td>
<td>Compart mental</td>
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<td>7.48 (± 1.49)</td>
</tr>
</tbody>
</table>

**Bioavailability study:** Bergan et al<sup>39</sup>
Healthy (n = 9)
Formulation: Tablets (375, 750, 1500 mg azidocillin sodium)
              Suspension (750 mg azidocillin sodium)
Sampling: 0-8 hrs
Analysis: HPLC
F_{ora} (tablet) = 59.5 %
F_{ora} (suspension) = 64.1 %
Furazlocillin

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Hinderling et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Healthy n = 5 23-30 yrs</td>
<td>78.2</td>
<td>25.6</td>
<td>Bolus</td>
<td>0-6 hr 0-12 hr</td>
<td>Agar well diffusion</td>
<td>1.0 µg/ml</td>
<td>1.0 µg/ml</td>
<td>Compartmental</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>

Urine excretion study:

Hinderling et al<sup>40</sup>

Urine collection: 0-12 hr
Renal clearance CL<sub>ren</sub> = Ae(∞)AUC<sub>0</sub> where Ae<sup>∞</sup> is cumulative amount of drug excreted unchanged in urine

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hinderling et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Healthy n = 2</td>
<td>In-vitro</td>
<td>50, 100, 200, 400 µg/ml</td>
<td>HPLC</td>
<td>66 %</td>
</tr>
</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hinderling et al&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Healthy n = 5</td>
<td>In-vitro</td>
<td>HPLC</td>
<td>fraction in RBC – 0.055 (± 0.031)</td>
</tr>
</tbody>
</table>
Carbapenams

Biapenem

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Kozawa et al⁴¹</td>
<td>Healthy n = 5</td>
<td>59.4 ± 7.2</td>
<td>5.05</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>LOD – 0.1 µg/ml</td>
<td>Compartmental</td>
<td>Cumulative</td>
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<tr>
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<td>Healthy n = 5</td>
<td>23.0 ± 3.5 yrs</td>
<td>10.10</td>
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<td>LOD – 1.0 µg/ml</td>
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</table>

**Urine excretion study:** Kozawa et al⁴¹

Urine collection: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 hr

Renal clearance $CL_{\text{ren}} = Ae(12)AUC_{0}^{24}$ where $Ae^{24}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs

$AUC_{0}^{24}$ here $Ae^{24}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs

$CL_{\text{tot}}$ (ml/min/kg)

$\text{Vd}_{\alpha}$ (l/kg)

$CL_{\text{ren}}$ (ml/min/kg)

$fe = 52.6\% ± 3.0\%$
Ertapenem

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majumdar et al (2002)</td>
<td>Healthy n = 16 (18-49 yrs)</td>
<td>70</td>
<td>7.14</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>total drug – 0.125 µg/ml, unbonded drug = 0.25 µg/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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<td>14.3</td>
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<td>305600 (± 36800)</td>
<td>0.39 (± 0.046)</td>
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<td>28.6</td>
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<td>572100 (± 68600)</td>
<td>0.42 (± 0.049)</td>
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<td>42.9</td>
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<td>1011400 (± 118000)</td>
<td>0.48 (± 0.058)</td>
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<td>1407200 (± 230100)</td>
<td>0.52 (± 0.074)</td>
</tr>
</tbody>
</table>
**Urine excretion study:** Majumdar et al (2002) \(^{42}\)

Urine collection: 0-24 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(12)\text{AUC}_{24}$ here Ae\(^{24}\) is cumulative amount of drug excreted unchanged in urine upto 24 hrs

### Doripenem

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Cirillo et al (2008)(^{43})</td>
<td>Healthy n = 5 20.5 yrs</td>
<td>87.5</td>
<td>5.71</td>
<td>Infusion</td>
<td>0-48 hrs</td>
<td>0-48 hrs</td>
<td>LC-MS/MS</td>
<td>0.10 μg/ml</td>
<td>0.20 μg/ml</td>
<td>Noncompartmental</td>
</tr>
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</table>

**Plasma protein binding studies:** 8.1 % (Greer et al\(^{44}\))
### Meropenem

#### PK studies:

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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml) CL&lt;sub&gt;tot&lt;/sub&gt; (ml/min/ kg) Vd&lt;sub&gt;α&lt;/sub&gt; (l/kg) CL&lt;sub&gt;ren&lt;/sub&gt; (ml/min/ kg)</td>
</tr>
<tr>
<td>Dreetz et al (1996)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Healthy n = 12 29.4 ± 6 yrs</td>
<td>80.3 ± 7.2</td>
<td>12.45</td>
<td>Infusion for 30 mins</td>
<td>0-8 hrs</td>
<td>0-12 hrs</td>
<td>HPLC</td>
<td>LOD – 0.3 mg/l</td>
<td>LOD – 3.5 mg/l</td>
<td>Noncompartmental</td>
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#### Plasma protein binding studies:

<table>
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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
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<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Dreetz et al (1996)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Healthy</td>
<td>In-vitro Ultrafiltration</td>
<td>4, 2 and 1 mg/l</td>
<td>Agar plate diffusion</td>
<td>8 %</td>
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Faropenem

Plasma protein binding studies:

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<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td></td>
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<td>25 mg/l</td>
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<td>95 %</td>
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Imipenem

PK studies:

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<th>Sampling schedule</th>
<th>Assay</th>
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<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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n = 10
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range(µg/ml)</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standiford et al\textsuperscript{48}</td>
<td>Pooled serum</td>
<td>In-vitro Ultrafiltration</td>
<td>10.3 \hspace{1cm} 25.8 \hspace{1cm} 51.3</td>
<td>HPLC</td>
<td>fu = 96 %</td>
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<td>87 %</td>
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</table>
**Monobactams**

**Azeftomam**

**PK studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
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<th>Sampling schedule</th>
<th>Assay</th>
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<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
<tbody>
<tr>
<td>Burgess et al(^9)</td>
<td>Healthy n = 8</td>
<td>74.6 ± 14.0</td>
<td>80.42</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>1-100 µg/ml</td>
<td>-</td>
<td>Noncompartmental</td>
</tr>
<tr>
<td>Swabb et al(^50)</td>
<td>Healthy n = 4</td>
<td>73.3 (69.2-80.1)</td>
<td>13.6</td>
<td>2 infusions of 500 mg for 2 mins</td>
<td>0-16 hrs</td>
<td>0-144 hrs</td>
<td>Agar diffusion method</td>
<td>0.04 µg/ml</td>
<td>0.08 µg/ml</td>
<td>Compartimental</td>
</tr>
</tbody>
</table>

526
First Generation Cephalosporin

Cefatrizine

PK studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
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<tr>
<td>Pfeffer et al\textsuperscript{51}</td>
<td>Healthy n = 18</td>
<td>69 ± 10</td>
<td>3.77</td>
<td>0-6.5 hr</td>
<td>0-24 hrs</td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>Noncompartmental</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>28 ± 11</td>
<td></td>
<td></td>
<td>Infusion for 30 mins</td>
<td>LOD 0.12 µg/ml</td>
<td>LOD 0.30 µg/ml</td>
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<td>19100</td>
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<tr>
<td></td>
<td>n = 6</td>
<td>28 ± 11</td>
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<td>37600</td>
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<td></td>
<td>n = 6</td>
<td>32 ± 11</td>
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<td>82900</td>
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Urine excretion study: Pfeffer et al\textsuperscript{51}

Urine collection: 0-1, 1-2, 2-3, 3-4, 4-6, 6-9, 9-12, 12-24 hr
Renal clearance $CL_{\text{ren}} = Ae(12)AUC_{e24}$ where $Ae^{24}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pfeffer et al(^{51})</td>
<td>Healthy</td>
<td>\textit{In-vitro} Ultrafiltration</td>
<td>5, 10, 25, 50 (\mu g/ml)</td>
<td>Cylinder plate bioassay method</td>
<td>62.7 %, 60.9 %, 62.4 %, 63.9 %</td>
</tr>
</tbody>
</table>

Bioavailability study: Pfeffer et al\(^{51}\)
Healthy \((n = 6/\text{group})\)
Formulation: Capsule \((252.5, 505, 1010 \text{ mg Cefatrizine})\)
Sampling: 0-6.5 hrs
Analysis: Cylinder plate bioassay method
\(F_{\text{oral}} = 76.8 \pm 6.8 \% \text{ (252.5 mg)}\)
\(75.0 \pm 10.2 \% \text{ (505 mg)}\)
\(46.8 \pm 10.2 \% \text{ (1010 mg)}\)
Cephalexin

**PK Studies:**

<table>
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<tr>
<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
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<tbody>
<tr>
<td>Tally et al 54</td>
<td>Pooled human serum</td>
<td>In-vitro</td>
<td>10 µg/ml 50 µg/ml</td>
<td>Agar diffusion assay</td>
<td>17 %  20 %</td>
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<tr>
<td>Greene et al 53</td>
<td>Healthy n = 3</td>
<td>Ultrafiltration In-vitro</td>
<td>2.10-35.3 µg/ml</td>
<td>Agar diffusion assay</td>
<td>12.4 % (± 0.4)</td>
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**Plasma protein binding studies:**

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<td>Greene et al 55</td>
<td>Healthy n = 3</td>
<td>Ultrafiltration In-vitro</td>
<td>2.10-35.3 µg/ml</td>
<td>Agar diffusion assay</td>
<td>12.4 % (± 0.4)</td>
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Cephradine

PK Studies:

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<th>Dose (mg/kg)</th>
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<tr>
<td>Schwinghammer et al&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Healthy n = 10 21.9 ± 1.7 yrs</td>
<td>66.4 ± 11.3</td>
<td>15.1</td>
<td>Infusion for 5 mins</td>
<td>0-12 hrs</td>
<td>0-12 hrs</td>
<td>Microbiologic assay</td>
<td>0.0625 µg/ml</td>
<td>-</td>
<td>Noncompartmental</td>
</tr>
<tr>
<td>Rattie et al&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Healthy n = 8 22-39 yrs</td>
<td>75.6</td>
<td>13.2</td>
<td>Bolus</td>
<td>0-360 mins</td>
<td>-</td>
<td>Agar disk plate method</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
</tr>
<tr>
<td>Roberts et al&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Healthy n = 8 19-23 yrs</td>
<td>71</td>
<td>7.04</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>-</td>
<td>Plate diffusion method</td>
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<td>Compartmental</td>
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Plasma protein binding studies:

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<th>Protein binding</th>
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<tbody>
<tr>
<td>Singhvi et al&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Healthy n = 3</td>
<td>Ultrafiltration In-vitro</td>
<td>2.12-38.2 µg/ml</td>
<td>Agar diffusion assay</td>
<td>13.8% (± 0.8)</td>
</tr>
</tbody>
</table>
**Bioavailability study**: Schwinghammer et al\textsuperscript{56}
Healthy (n = 19)
Formulation: Two 500 mg Capsule  (Dose = 1 gm)
Sampling: 0-12 hrs
Analysis: Microbiological assay
\( F_{oral} = 94.0 \pm 11.9 \% \)

### Cephalothin

**PK Studies:**

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<tr>
<td>Barza et al\textsuperscript{59}</td>
<td>Healthy n = 12</td>
<td>70</td>
<td>28.6</td>
<td>Infusion</td>
<td>0-6 hrs</td>
<td>Plasma</td>
<td>Plasma</td>
<td>Urine</td>
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<td>Healthy n = 12</td>
<td>70</td>
<td>28.6</td>
<td>Infusion</td>
<td>0-6 hrs</td>
<td>Agar diffusion assay</td>
<td>0.3 µg/ml</td>
<td>-</td>
<td>Non-compartmental</td>
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<tr>
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<td>Healthy n = 12</td>
<td>70</td>
<td>28.6</td>
<td>Infusion</td>
<td>0-6 hrs</td>
<td>Agar diffusion assay</td>
<td>0.3 µg/ml</td>
<td>-</td>
<td>Non-compartmental</td>
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<tr>
<td>Rattie et al\textsuperscript{57}</td>
<td>Healthy n = 20</td>
<td>56.6</td>
<td>17.67</td>
<td>Bolus</td>
<td>0-240 mins</td>
<td>Agar disk plate method</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
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<tr>
<td></td>
<td>21-42 yrs</td>
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### Plasma protein binding studies:

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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Singhvi et al\textsuperscript{55}</td>
<td>Healthy n = 3</td>
<td>Ultrafiltration</td>
<td>5.67-64.8 µg/ml</td>
<td>Agar diffusion assay</td>
<td>71.2 % (± 0.7)</td>
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531
Cefazedone

PK Studies:

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<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Plasma, Urine</td>
<td>Plasma, Urine</td>
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<td></td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Pabst et al (^60)</td>
<td>Healthy n = 10</td>
<td>72.71 (± 7.04)</td>
<td>13.20</td>
<td>Bolus 0-480 mins</td>
<td>0-24 hr</td>
<td>Agar diffusion test</td>
<td>1.0 µg/ml</td>
<td>2.0 µg/ml</td>
<td>Cumulative</td>
<td>182000 (± 30,000)</td>
</tr>
<tr>
<td></td>
<td>Healthy n = 6</td>
<td>70.1 (± 8.2)</td>
<td>14.3</td>
<td>Bolus 0-24 hrs</td>
<td>0-24 hr</td>
<td>Agar diffusion test</td>
<td>1.0 µg/ml</td>
<td>2.0 µg/ml</td>
<td>Cumulative</td>
<td>215300 (± 15400)</td>
</tr>
</tbody>
</table>

**Urine excretion study:**
Pabst et al \(^60\):  
Urine collection: 0-2, 2-4, 4-6, 6-8, 8-24 hr  
Renal clearance CL_{ren} = \text{Ae}(12)\text{AUC}_{24} here Ae^{24} is cumulative amount of drug excreted unchanged in urine up to 24 hrs

Ungethum et al \(^61\):  
Urine collection: 0-2, 2-4, 4-6, 6-8, 8-24 hr
Cefazolin

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
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<tr>
<td>Pabst et al(^{90})</td>
<td>Healthy n = 10 29.3 yrs (± 8.8)</td>
<td>72.71 (± 7.04)</td>
<td>13.75</td>
<td>Bolus</td>
<td>0-480 mins</td>
<td>0-24 hr</td>
<td>Agar diffusion test</td>
<td>1.0 µg/ml</td>
<td>2.0 µg/ml</td>
<td>Compart-mental</td>
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<tr>
<td>Singhvi et al(^{55})</td>
<td>Healthy n = 3</td>
<td>Ultrafiltration</td>
<td>In-vitro</td>
<td>5.21-56.0 µg/ml</td>
<td>Agar diffusion assay</td>
<td>89.2 % (± 0.9)</td>
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Plasma protein binding studies:

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<thead>
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<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeffer et al(^{62})</td>
<td>Healthy</td>
<td>In-vitro</td>
<td>25-205 µg/ml</td>
<td>Cylinder plate bioassay method</td>
<td>89.7 %</td>
</tr>
<tr>
<td>Singhvi et al(^{55})</td>
<td>Healthy n = 3</td>
<td>Ultrafiltration</td>
<td>In-vitro</td>
<td>5.21-56.0 µg/ml</td>
<td>Agar diffusion assay</td>
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</table>
Ceftezole

PK Studies:

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<th>Study</th>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay Method</th>
<th>LOQ Assay</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
<th>AUC (ng.h/ml)</th>
<th>CL\textsubscript{tot} (ml/min/kg)</th>
<th>V\textsubscript{nc} (l/kg)</th>
<th>CL\textsubscript{ren} (ml/min/kg)</th>
<th>fe (%)</th>
</tr>
</thead>
</table>
| Ohkawa et al\textsuperscript{63} | Healthy 
\textit{n} = 4
19-80 yrs | 53      | 37.7         | Infusion for 120 mins | 0-6 hrs | 0-6 hrs | Agar plate method | - | - | Noncomartmental | Cumulative | 0.17 (calculated) | 3.41 (calculated) | 2.76 (calculated) | fe = 81.0 ± 4.3 |

Plasma protein binding studies:

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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay Method</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Noto et al\textsuperscript{64}</td>
<td>Human serum</td>
<td>Equilibrium dialysis</td>
<td>50 µg/ml</td>
<td>Paper disc method</td>
<td>69 %</td>
</tr>
</tbody>
</table>

Urine excretion study: Ohkawa et al\textsuperscript{63}
Urine collection: 0-2, 2-4, 4-6 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae(6)AUC}_0^6$ where $\text{Ae}^6$ is cumulative amount of drug excreted unchanged in urine upto 6 hrs
## Cephapirin

### PK Studies:

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<th>Dose (mg/kg)</th>
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<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arvidsson et al(^6)</td>
<td>Healthy n = 5</td>
<td>70 (assumed)</td>
<td>14.3</td>
<td>Infusion for 10 mins</td>
<td>0-8 hr</td>
<td>0-12 hr</td>
<td>HPLC</td>
<td>0.5 µg/ml</td>
<td>1.0 µg/ml</td>
<td>Cumulative</td>
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<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
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</tr>
<tr>
<td>Cabana et al(^6)</td>
<td>Healthy n = 10</td>
<td>66</td>
<td>15.2</td>
<td>Bolus</td>
<td>0-4 hrs</td>
<td>0-6 hrs</td>
<td>Cup plate assay</td>
<td>LOD-0.3 µg/ml</td>
<td>-</td>
<td>Noncompartamental</td>
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<td>Plasma</td>
<td>Urine</td>
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### Plasma protein binding studies:

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<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Arvidsson et al(^6)</td>
<td>Healthy n = 5</td>
<td>In-vitro Ultrafiltration</td>
<td>2-250 µg/ml</td>
<td>HPLC</td>
<td>62 % (± 4 %)</td>
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</table>
**Cefacetrile**

**PK Studies:**

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<th>Dose (mg/kg)</th>
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<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
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<tr>
<td>Westenfelder et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Urinary tract infection patient n = 7</td>
<td>70 (assumed)</td>
<td>14.29</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-8 hrs</td>
<td>Cup-plate method</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
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</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding (%)</th>
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</thead>
<tbody>
<tr>
<td>Nakai et al&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Human pooled plasma</td>
<td>In-vitro Ultracentrifugation</td>
<td>13 µg/ml</td>
<td>Liquid scintillation</td>
<td>15.2</td>
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<td>50 µg/ml</td>
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<td>130 µg/ml</td>
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<td>340 µg/ml</td>
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**Urine excretion study:** Westenfelder et al<sup>67</sup>

Urine collection: 0-1, 14, 4-8, 8-24 hrs
Cefaloridine

PK Studies:

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<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Mathews et al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Surgical patients n = 10 28 yrs</td>
<td>60</td>
<td>16.7</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>Plasma</td>
<td>Plasma</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
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<td>Urine</td>
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<td>93648 (calculated)</td>
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<tr>
<td>Arvidsson et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Healthy n = 5</td>
<td>70</td>
<td>14.3</td>
<td>Infusion for 10 mins</td>
<td>0-8 hr</td>
<td>0-12 hr</td>
<td>HPLC</td>
<td>0.5 µg/ml</td>
<td>1.0 µg/ml</td>
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Plasma protein binding studies:

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<tr>
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<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Nishida et al&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Human serum</td>
<td>Invitro Ultrafiltration</td>
<td>300 µg/ml</td>
<td>Disk diffusion method</td>
<td>55 %</td>
</tr>
<tr>
<td>Arvidsson et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Healthy n = 5</td>
<td>In-vitro Ultrafiltration</td>
<td>2-250 µg/ml</td>
<td>HPLC</td>
<td>37 % (± 7 %)</td>
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</table>
## Cefroxadine

**PK Studies:**

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<th>Study</th>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
<tbody>
<tr>
<td>Cadorniga et al(^7)</td>
<td>Healthy n = 9 21-28 yrs</td>
<td>62.44</td>
<td>16.02</td>
<td>Infusion for 30 min</td>
<td>0-6 hrs 0-8 hrs</td>
<td>bioassay</td>
<td>0.30 µg/ml</td>
<td>-</td>
<td>Compart-mental</td>
<td>AUC: 70860 (SE ± 6560)</td>
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</table>
Second Generation Cephalosporin

Cefmetazole

PK Studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ (µg/ml)</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borin et al'72</td>
<td>Healthy 21-40 yrs</td>
<td>68 ± 15.2</td>
<td>6.84 Bolus</td>
<td>0-16 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>2</td>
<td>Noncompartmental</td>
<td>Cumulative</td>
<td>83100 (± 19300)</td>
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<td>15</td>
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<td>151000 (± 29800)</td>
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<td>301000 (± 60400)</td>
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<td>Group</td>
<td>n</td>
<td>Age Range</td>
<td>Route</td>
<td>Time Period</td>
<td>Analytical Method</td>
<td>Compartment</td>
<td>Cumulative Amount (SE ±)</td>
<td>Elimination Fraction (SE ±)</td>
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<tr>
<td>Ko et al&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Healthy</td>
<td>16</td>
<td>20-49 yrs</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>HPLC</td>
<td>Noncompartmental</td>
<td>295000 (SE ± 3700)</td>
<td>1.46 (SE ± 0.06)</td>
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<tr>
<td>Rodriguez-Barbero et al&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Healthy</td>
<td>7</td>
<td>24-27 yrs</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>HPLC</td>
<td>Compartmental</td>
<td>335700 (± 70600)</td>
<td>1.44 (± 0.26)</td>
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</tbody>
</table>

**Urine excretion study:** Ko et al<sup>73</sup>
Urine collection: 0-1, 1-2, 2-4, 4-8, 8-12, 12-24 hr
Renal clearance \( CL_{\text{ren}} = A_{\text{e}(24)}A_{\text{UC}}^{24} \) where \( A_{\text{e}}^{24} \) is cumulative amount of drug excreted unchanged in urine up to 24 hrs
### Cefotiam

#### PK Studies

<table>
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<tr>
<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
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<th>LOQ</th>
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<tr>
<td>Brisson et al (1984)</td>
<td>Healthy n = 8 yrs</td>
<td>62</td>
<td>8.1</td>
<td>Bolus</td>
<td>0-6 hrs, 0-24 hrs</td>
<td>HPLC</td>
<td>0.3-250 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
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<tr>
<td>Rouan et al (1986)</td>
<td>Healthy n = 3 yrs</td>
<td>72.5</td>
<td>6.9</td>
<td>Bolus</td>
<td>0-8 hrs, 0-24 hrs</td>
<td>HPLC</td>
<td>0.2-120 µg/ml</td>
<td>20-2500 µg/ml</td>
<td>Noncompartmental</td>
<td>Cumulative</td>
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</table>

- **Brisson et al**: Study population was healthy adults, n = 8, age 23 years, with BW of 62 kg, dose of 8.1 mg/kg, and a bolus injection. Sampling schedule was 0-6 hours and 0-24 hours, with plasma and urine analysis using HPLC. LOQ was 0.3-250 µg/ml. PK analysis was compartmental, with cumulative AUC of 26600 ng·h/ml, CL\text{tot} of 5.27 ml/min/kg, and V\text{dss} of 2.77 ml/min/kg.

- **Rouan et al**: Study population was healthy adults, n = 3, age 19-31 years, with BW of 72.5 kg, dose of 6.9 mg/kg, and a bolus injection. Sampling schedule was 0-8 hours and 0-24 hours, with plasma and urine analysis using HPLC. LOQ was 0.2-120 µg/ml, with cumulative AUC of 18800 ng·h/ml, CL\text{tot} of 6.2 ml/min/kg, and V\text{dss} of 3.7 ml/min/kg.
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Querol-Ferrer et al77</td>
<td>Pooled healthy serum</td>
<td>Equilibrium dialysis</td>
<td>1-10 µM</td>
<td>Liquid scintillation</td>
<td>44.5 % (-2.1%)</td>
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Cefotetan

PK Studies:

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<th>Dose (mg/kg)</th>
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<tr>
<td>Ohkawa et al (1983)78</td>
<td>Healthy n = 8 59.4 yrs</td>
<td>52.8</td>
<td>8.41</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>Compart mental</td>
<td>Not mentioned</td>
<td>AUC (ng.h/ml) 0.73 (± 0.07) CL_{tot} (ml/min/kg) 0.15 (± 0.07) Vd_{ss} (l/kg) 0.611 (± 0.07) fe = 83.3% (± 3.8)</td>
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<tr>
<td>Nagakawa et al79</td>
<td>Healthy n = 24 35.3 ± 1.0 yrs</td>
<td>60.4</td>
<td>8.3</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>LOD-0.7 µg/ml</td>
<td>LOD-1.0 µg/ml</td>
<td>Compart mental</td>
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</table>
### Urine excretion study: Ohkawa et al (1983)\(^7\)
Urine collection: 0-2, 2-4, 4-6, 6-8, 8-24 hr

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Carver et al(^8)</td>
<td>Healthy n = 6</td>
<td>In-vivo Ultrafiltration</td>
<td>IV infusion- 2 gm</td>
<td>Disc diffusion assay</td>
<td>85 % (± 4.2%)</td>
</tr>
<tr>
<td>Yates et al(^8)</td>
<td>Caucasian n = 10</td>
<td>In-vivo Equilibrium</td>
<td>IV Bolus – 2 gm</td>
<td>HPLC</td>
<td>88 % (78-91%)</td>
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</tbody>
</table>

### Plasma protein binding studies:

<table>
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<tr>
<th>Study</th>
<th>Subjects</th>
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<th>Concentration range</th>
<th>Assay</th>
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<td>HPLC</td>
<td>88 % (78-91%)</td>
</tr>
</tbody>
</table>
Cefamandole

PK Studies:

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<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
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<tr>
<td>Barza et al (1976)(^{59})</td>
<td>Healthy n = 12</td>
<td>70 (assumed)</td>
<td>28.6</td>
<td>Infusion for 30 mins</td>
<td>0-6 hrs</td>
<td>0-6 hrs</td>
<td>Agar diffusion bioassay</td>
<td>sensitivity - 0.3 µg/ml</td>
<td>-</td>
<td>Noncompartmental</td>
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Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barza et al (1976)(^{59})</td>
<td><em>In-vitro</em></td>
<td>20 µg/ml</td>
<td>Agar diffusion bioassay</td>
<td>67 % (± 2 %)</td>
</tr>
<tr>
<td>Mellin et al (^{82})</td>
<td><em>In-vivo</em></td>
<td>5-40 µg/ml</td>
<td>Cup plate method</td>
<td>32% (17-58%) (SE ± 11 %)</td>
</tr>
</tbody>
</table>

Urine excretion study:
Barza et al (1976)\(^{59}\)
Urine collection: 0-2, 2-6 hr
Renal clearance CL\(_{\text{ren}}\) = (dXu/dt)/Cp
### Ceforanide

#### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
<td>CL$_{tot}$ (ml/min/kg)</td>
</tr>
<tr>
<td>Pfeffer et al$^{62}$</td>
<td>Healthy n = 24 22-40 yrs</td>
<td>72.5±1.3 (SE)</td>
<td>15.6</td>
<td>Infusion for 30 mins</td>
<td>0-12 hr</td>
<td>0-12 hrs</td>
<td>Cup-plate bioassay</td>
<td>2.0 µg/ml</td>
<td>-</td>
<td>Compart mental</td>
</tr>
</tbody>
</table>

#### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeffer et al$^{62}$</td>
<td>Pooled plasma</td>
<td>Ultrafiltration</td>
<td>27, 53, 99, 200 µg/ml</td>
<td>Cup-plate assay</td>
<td>80.6%</td>
</tr>
</tbody>
</table>
### Cefuroxime

#### PK Studies:

<table>
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<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Gower et al</td>
<td>Healthy n = 6</td>
<td>72.3</td>
<td>7.1</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>Plate assay</td>
<td>0.01 µg/ml</td>
<td>1.0 µg/ml</td>
<td>Compartmental</td>
<td>Cumulative</td>
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<tr>
<td></td>
<td>33.7 yrs</td>
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<td>0-24 hrs</td>
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</table>

#### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeffer et al</td>
<td>Pooled plasma</td>
<td>Ultrafiltration</td>
<td>9 and 75 µg/ml</td>
<td>Cup-plate assay</td>
<td>44.7 %</td>
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</table>
Cefprozil

**PK Studies:**

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<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
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<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
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<tr>
<td>Shyu et al84</td>
<td>Healthy n = 24</td>
<td>77.1 ± 7.7</td>
<td>3.24</td>
<td>Infusion for 30 mins</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>0.1-20 µg/ml</td>
<td>5-500 µg/ml</td>
<td>Noncomartmental</td>
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<tr>
<td></td>
<td>26 ± 6 yrs</td>
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<td>12.9</td>
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**Plasma protein binding studies:**

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<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lode et al85</td>
<td>Healthy</td>
<td>Invitro equilibrium dialysis</td>
<td>10 and 25 µg/ml</td>
<td>HPLC</td>
<td>42 % (± 4.8%)</td>
</tr>
</tbody>
</table>

**Urine excretion study:**

Shyu et al84

Urine collection: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 hr
Renal clearance $\text{CL}_{\text{ren}} = (\text{d}Xu/\text{dt})/Cp$

**Bioavailability study:** Shyu et al84
Healthy (n = 7)
Formulation: capsule (500 mg cefprozil)
Sampling: 0-8 hrs
Analysis: HPLC
$F_{oral} = 89 \% \ (± 7)$

**Ceforanide**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</tr>
<tr>
<td>Pfeffer et al$^{62}$</td>
<td>Healthy n = 24 22-40 yrs</td>
<td>72.5±2.3</td>
<td>15.6</td>
<td>Bolus</td>
<td>0-12 hr</td>
<td>Cup plate method</td>
<td>limit of sensitivity 2.0 µg/ml</td>
<td>1-10 µg/ml</td>
<td>Compart mental</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>

**Urine excretion study:**
Pfeffer et al$^{62}$
Urine collection: 0-2, 2-4, 4-6, 6-9, 9-12, 12-24 hr
Renal clearance $CL_{ren} = (dXu/dt)/Cp$

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Pfeffer et al$^{62}$</td>
<td>Fresh pooled plasma</td>
<td>Ultrafiltration</td>
<td>27, 53, 99, 200 µg/ml</td>
<td>Cup plate method</td>
<td>80.6%</td>
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Cefaclor

Plasma protein binding studies:

<table>
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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
</table>
| Tally et al\textsuperscript{54} | Pooled human serum    | In-vitro | 10 µg/ml
50 µg/ml | Agar diffusion assay | 47 %
57 %   |
Cefoxitin

PK Studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling Schedule</th>
<th>Assay</th>
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<tr>
<td>Carver et al³¹</td>
<td>Healthy</td>
<td>27.3 yrs</td>
<td>68.4</td>
<td>29.2</td>
<td>Infusion</td>
<td>Diffusion</td>
<td>limit of sensitivity – µg/ml</td>
<td>-</td>
<td>Compart mental</td>
<td>128800 (± 25200)</td>
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</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Carver et al³¹</td>
<td>Healthy</td>
<td>In-vivo Ultrafiltration</td>
<td>IV infusion- 2 gm</td>
<td>Disc diffusion assay</td>
<td>52 % (± 2.8 %)</td>
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</table>
### Third Generation Cephalosporin

#### Ceftriaxone

**PK Studies:**

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyers et al (1983)&lt;sup&gt;86&lt;/sup&gt;</td>
<td>Healthy n = 6</td>
<td>72.3 ± 10</td>
<td>40.3 ± 14.6 yrs</td>
<td>13.8</td>
<td>Infusion</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>Agar well diffusion</td>
<td>-</td>
<td>Compart mental</td>
</tr>
<tr>
<td>Paradis et al&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Healthy 23.9 yrs</td>
<td>72.0</td>
<td>13.9</td>
<td>Infusion for 30 mins</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>sensitivity = 0.6 µg/ml</td>
<td>-</td>
<td>Compart mental</td>
</tr>
<tr>
<td>Patel et al&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Healthy n = 12</td>
<td>74.1</td>
<td>6.75</td>
<td>Infusion for 30 mins</td>
<td>0-24 hrs</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative</td>
</tr>
</tbody>
</table>

fe = 37%
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
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<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popick et al&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Healthy</td>
<td>In vitro Equilibrium dialysis</td>
<td>&lt; 100 µg/ml &gt; 400 µg/ml</td>
<td>HPLC</td>
<td>90-95%</td>
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<tr>
<td></td>
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<td>In-vivo</td>
<td>2 gm infusion 166-209 µg/ml</td>
<td>HPLC</td>
<td>60%</td>
</tr>
<tr>
<td>Stoeckel et al&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Healthy pooled plasma n = 6</td>
<td>In-vivo Equilibrium dialysis</td>
<td>Dose -150 mg Dose -500 mg Dose -1500 mg</td>
<td>HPLC</td>
<td>fu =0.59 (± 0.07)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>fu = 0.64 (± 0.07)</td>
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<td></td>
<td>fu = 0.65 (± 0.04)</td>
</tr>
</tbody>
</table>
Cefotaxime

**PK Studies:**

Plasma protein binding studies:  30% ± 10% (just mentioned)

Urine excretion study:
Rodondi et al \(^92\)
Urine collection: 0-6, 6-8, 8-12, 12-24 hr
Renal clearance \( \text{CL}_{\text{ren}} = \text{Ae}(24)\text{AUC}_{0}^{24} \) where \( \text{Ae}^{24} \) is cumulative amount of drug excreted unchanged in urine upto 24 hrs

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu et al (1979)(^91)</td>
<td>Healthy n = 10 26.4 yrs</td>
<td>70 (assumed)</td>
<td>14.3</td>
<td>Infusion for 30 mins</td>
<td>0-240 mins</td>
<td>0-24 hrs</td>
<td>Plasma Urine Plasma Urine</td>
<td>LOD &gt;0.16 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
</tr>
<tr>
<td>Rodondi et al (^92)</td>
<td>Healthy n = 8 27 ± 4 yrs</td>
<td>69 ± 15</td>
<td>30</td>
<td>Infusion for 25 mins</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>Plasma HPLC LOD-0.5 µg/ml LOD-1.0 µg/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>145200 (± 37200)</td>
</tr>
<tr>
<td>Kemmeric h et al (^93)</td>
<td>Healthy n = 10 32 yrs</td>
<td>66.7</td>
<td>14.9</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>Plasma Agar diffusion cup plate method LOD-0.3 µg/ml</td>
<td>-</td>
<td>compartmental</td>
<td>Cumulative</td>
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</tbody>
</table>
## Ceftazidime

### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>LeBel et al (1985)(^94)</td>
<td>Healthy n = 12 22.9 ± 3.3 yrs</td>
<td>65.4 ± 11.0</td>
<td>15.3</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC sensitivity – 0.75 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
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<td>133700 (± 13200)</td>
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<td>1.48 (± 0.24)</td>
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<td>Mouton et al (^95)</td>
<td>Healthy n = 8 20-29 yrs</td>
<td>78.3 ± 12.0</td>
<td>total-75 mg/kg every 8 hrs over 24 hrs for 25 mins</td>
<td>intermittent infusion</td>
<td>0-8 hrs</td>
<td>0-8 hrs</td>
<td>HPLC sensitivity – 0.5 µg/ml</td>
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<td>285400 (± 22700)</td>
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<td>0.178 (± 0.023)</td>
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<tr>
<td>Paradis et al (^87)</td>
<td>Healthy 23.9 yrs</td>
<td>72.0</td>
<td>13.9</td>
<td>Infusion for 30 mins</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>HPLC sensitivity – 0.15 µg/ml</td>
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<td>Cumulative</td>
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<td>153000 (± 19840)</td>
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<td>0.21 (± 0.03)</td>
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<td>1.40 (± 0.23)</td>
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Plasma protein binding studies:

<table>
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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Mouton et al 95</td>
<td>Healthy</td>
<td>In-vitro Ultrafiltration</td>
<td>Dose – 25 mg/kg every 8 hrs over 24 hrs for 25 mins</td>
<td>HPLC</td>
<td>18.7% (± 2.9)</td>
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</table>

Urine excretion study: LeBel et al (1985)94

Urine collection: 0-2, 2-4, 4-8, 8-12, 12-24 hr

Renal clearance $CL_{ren} = Ae(24)AUC_{24}$ where $Ae$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs

Cefetamet

PK Studies:

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<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
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<tr>
<td>Blouin et al 96</td>
<td>Healthy n = 12 20-39 yrs</td>
<td>70.3 ± 7.0</td>
<td>7.32</td>
<td>Infusion for 20 mins</td>
<td>0-36 hrs</td>
<td>0-36 hrs</td>
<td>HPLC</td>
<td>LOD – 0.2 µg/ml</td>
<td>LOD – 20 µg/ml</td>
<td>Non-compartmental</td>
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<tr>
<td>Koup et al 97</td>
<td>Healthy 27 yrs n = 4</td>
<td>73.1</td>
<td>133</td>
<td>Infusion for 20 mins</td>
<td>0-12 hrs</td>
<td>0-48 hr</td>
<td>HPLC</td>
<td>0.2 µg/ml</td>
<td>20 µg/ml</td>
<td>Non-compartmental</td>
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</table>
### Urine excretion study: Blouin et al°6

Urine collection: 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24 and 24-36 hr

Renal clearance \( \text{CL}_{\text{ren}} = \frac{\text{Ae}(24)}{\text{AUC}_{0}^{24}} \) where \( \text{Ae}^{24} \) is cumulative amount of drug excreted unchanged in urine upto 24 hrs

Koup et al°7:

Urine collection: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36 hr

Renal clearance \( \text{CL}_{\text{ren}} = \frac{\text{Ae}(36)}{\text{AUC}_{0}^{36}} \) where \( \text{Ae}^{36} \) is cumulative amount of drug excreted unchanged in urine upto 36 hrs

### Plasma protein binding studies:

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<tr>
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<th>Subjects</th>
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<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td>Koup et al°7</td>
<td>Healthy pooled plasma</td>
<td>Equilibrium</td>
<td>1-110 µg/ml</td>
<td>HPLC</td>
<td>22%</td>
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</table>
Cefonicid

PK Studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
<tbody>
<tr>
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<td>Plasma, Urine</td>
<td>Plasma, Urine</td>
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<tr>
<td>Fourtillan et al&lt;sup&gt;98&lt;/sup&gt;</td>
<td>Healthy n = 8 25 ± 6 yrs</td>
<td>68 ± 6</td>
<td>14.7</td>
<td>Bolus</td>
<td>0-36 hrs</td>
<td>HPLC</td>
<td>5-100 µg/ml</td>
<td>-</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml)</td>
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<td>0-48 hrs</td>
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<td>621410 (± 129570)</td>
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<td>fe = 52.8% (± 11.4)</td>
</tr>
<tr>
<td>Barriere et al&lt;sup&gt;99&lt;/sup&gt;</td>
<td>Healthy n = 5 26-34 yrs</td>
<td>83.5 (79-88)</td>
<td>7.5</td>
<td>Infusion for 5 min</td>
<td>Agar diffusion method</td>
<td>0.4-100 µg/ml</td>
<td>-</td>
<td></td>
<td>Cumulative</td>
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<td>fe = 88% (± 6%)</td>
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Plasma protein binding studies:

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<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Dudley et al&lt;sup&gt;100&lt;/sup&gt;</td>
<td>Healthy n = 6</td>
<td>Invitro Ultrafiltration</td>
<td>Saturable binding declines to 2% below 100 µg/ml</td>
<td>Disk diffusion method</td>
<td>17.6 % (± 6.1%)</td>
</tr>
</tbody>
</table>
Cefoperazone

PK Studies:

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<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemmerich et al\textsuperscript{101}</td>
<td>Healthy n = 10 31.3 yrs</td>
<td>65.9 ± 6.0</td>
<td>30.3</td>
<td>Infusion for 30 mins</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>Cup plate method</td>
<td>LOD-0.15-0.6 mg/l</td>
<td>-</td>
<td>Compart-mental</td>
</tr>
<tr>
<td>Kemmerich et al\textsuperscript{93}</td>
<td>Healthy n = 10 32 yrs</td>
<td>66.7</td>
<td>14.9</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>Agar diffusion cup plate method</td>
<td>LOD – 0.3 µg/ml</td>
<td>-</td>
<td>Compart-mental</td>
</tr>
<tr>
<td>Boscia et al\textsuperscript{102}</td>
<td>Healthy n = 6 70 (assumed)</td>
<td>28.6</td>
<td>28.6</td>
<td>Infusion for 15 mins</td>
<td>0-24 hrs</td>
<td>0-8 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compart-mental</td>
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<tr>
<td>Hoffler et al\textsuperscript{103}</td>
<td>Healthy n = 12</td>
<td>65.4</td>
<td>30.6</td>
<td>Bolus</td>
<td>0-240 mins</td>
<td>-</td>
<td>Cup plate method</td>
<td>-</td>
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<td>Compart-mental</td>
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Urine excretion study:

Kemmerich et al\textsuperscript{101}  
Urine collection: 0-3, 3-6, 6-24 hr  
Renal clearance CL$_{ren}$ = Ae(24)AUC$_e$\textsuperscript{24} where Ae\textsuperscript{24} is cumulative amount of drug excreted unchanged in urine upto 24 hrs

Kemmerich et al\textsuperscript{93}.  
Urine collection: 0-3, 3-6, 6-12, 12-24 hr
Renal clearance $\text{CL}_{\text{ren}} = f_e \times \text{CL}_{\text{tot}}$

Boscia et al$^{102}$:
Urine collection: 0-8 hr
Renal clearance $\text{CL}_{\text{ren}} = Ae(8) \text{AUC}_{\text{0}}^8$ where $Ae^8$ is cumulative amount of drug excreted unchanged in urine upto 8 hrs

**Latamoxef (Moxalactam)**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>PK Analysis</th>
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<td>Plasma</td>
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<td>Plasma</td>
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<tr>
<td>Kemmeric h et al$^{93}$</td>
<td>Healthy n = 10 32 yrs</td>
<td>66.7</td>
<td>14.9</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>Plasma</td>
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<td>0-24 hrs</td>
<td>Agar diffusion cup plate method</td>
<td>LOD = 0.15 µg/ml</td>
<td>-</td>
<td>compartmenental</td>
<td>Cumulative</td>
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<td>CL$_{\text{ren}}$</td>
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<td>192500 (± 29100)</td>
<td>1.23 (± 0.19)</td>
<td>0.28 (± 0.08)</td>
<td>0.75 (± 0.14)</td>
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**Plasma protein binding studies:**

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<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td>Standiford et al$^{48}$</td>
<td>Pooled serum</td>
<td>In-vitro Ultrafiltration</td>
<td>22.2</td>
<td>HPLC</td>
<td>fu = 41.9%</td>
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<td>55.5</td>
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<td>111</td>
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<td>36.3</td>
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**Cefmenoxime**

**PK Studies:**

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<th>Dose (mg/kg)</th>
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<tr>
<td>Granneman et al(^{104})</td>
<td>Healthy adults n = 5 20-35 yrs</td>
<td>71.2 (60.8-81.6)</td>
<td>7.0</td>
<td>IV infusion</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>0.05 µg/ml</td>
<td>5 µg/ml</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml)</td>
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<td>HPLC plasma</td>
<td>Plasma</td>
<td>Urine</td>
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<td>30800 (±3600)</td>
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**Plasma protein binding studies:**

Granneman et al\(^{104}\): Plasma protein binding: 77% (just mentioned)
**Cefodizime**

**PK Studies:**

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<th>Study</th>
<th>Population</th>
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<th>Dose (mg/kg)</th>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
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<tr>
<td>Lenfant et al&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Healthy n = 12</td>
<td>71± 2 (60-81)</td>
<td>7.0</td>
<td>Infusion for 5 mins</td>
<td>0-34 hrs</td>
<td>0-34 hrs</td>
<td>HPLC</td>
<td>0.02 µg/ml</td>
<td>1.0 µg/ml</td>
<td>Cumulative</td>
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<td>n = 18-40 yrs</td>
<td>14.1</td>
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<td>1.0</td>
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<td>42.3</td>
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<td>1.0</td>
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<tr>
<td>Conte et al&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Healthy n = 20</td>
<td>70 (assumed)</td>
<td>14.3 or 28.6</td>
<td>Infusion for 30 mins</td>
<td>0-48 hrs</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>LOD - 0.4 µg/ml</td>
<td>LOD - 13 µg/ml</td>
<td>Cumulative</td>
</tr>
<tr>
<td>Bryskier et al&lt;sup&gt;107&lt;/sup&gt;</td>
<td>Healthy n = 8</td>
<td>76.5</td>
<td>13.1</td>
<td>Bolus</td>
<td>0-36 hrs</td>
<td>0-36 hrs</td>
<td>HPLC</td>
<td>0.05 µg/ml</td>
<td>0.05 µg/ml</td>
<td>Cumulative</td>
</tr>
<tr>
<td></td>
<td>24-34 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>1.0</td>
</tr>
</tbody>
</table>

fe = 67.1% (± 12.1)

fe = 61.6%
<table>
<thead>
<tr>
<th>yrs</th>
<th>Healthy n = 12</th>
<th>Bolus</th>
<th>0-24 hrs</th>
<th>0-48 hrs</th>
<th>HPLC</th>
<th>-</th>
<th>-</th>
<th>Noncompartmental</th>
<th>Cumulative</th>
<th>(SE ± 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dagrosa et al(^{108})</td>
<td>78 ± 11 yrs</td>
<td>12.8</td>
<td>0-24 hrs</td>
<td>0-48 hrs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
<td>426000 (± 65000)</td>
<td>0.51 (± 0.08)</td>
</tr>
<tr>
<td>Conte et al(^{106})</td>
<td>19.2</td>
<td></td>
<td>0-24 hrs</td>
<td>0-48 hrs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
<td>621000 (± 103000)</td>
<td>0.53 (± 0.08)</td>
</tr>
<tr>
<td>Bryskier et al(^{107})</td>
<td>25.6</td>
<td></td>
<td>0-24 hrs</td>
<td>0-48 hrs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
<td>790000 (± 142000)</td>
<td>0.56 (± 0.09)</td>
</tr>
</tbody>
</table>

**Urinary excretion data:**

Lenfant et al\(^{105}\):
Urine collection: 0-2, 2-4, 4-6, 6-10, 10-15, 15-24 and 24-34 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(34)\text{AUC}_{0}^{34}$ where $\text{Ae}^{34}$ is cumulative amount of drug excreted unchanged in urine upto 34 hrs

Conte et al\(^{106}\):
Urine collection: 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(48)\text{AUC}_{0}^{48}$ where $\text{Ae}^{48}$ is cumulative amount of drug excreted unchanged in urine upto 48 hrs

Bryskier et al\(^{107}\):
Urine collection: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(36)\text{AUC}_{0}^{36}$ where $\text{Ae}^{36}$ is cumulative amount of drug excreted unchanged in urine upto 36 hrs

**Plasma protein binding studies:**

Lenfant et al\(^{105}\): Conc < 180 mg/l – 89%
180 mg/l – 83%
260 mg/l – 78%
350 mg/l – 73%
470 mg/l – 69%
Average – 78.4%
Cefpiramide

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Nakagawa et al(^{109})</td>
<td>Healthy n = 21 38 yrs</td>
<td>61</td>
<td>8.20</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Plasma, Urine</td>
<td>Plasma, Urine</td>
<td>AUC (ng.h/ml)</td>
<td>CL(_{tot}) (ml/min/kg)</td>
<td>Vd(_{ss}) (l/kg)</td>
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<td></td>
<td>539600 (± 93800)</td>
<td>0.26 (± 0.02)</td>
<td>0.085 (± 0.005)</td>
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<td></td>
<td>966000 (± 24200)</td>
<td>0.28 (± 0.01)</td>
<td>0.111 (± 0.007)</td>
</tr>
<tr>
<td>Conte et al(^{110})</td>
<td>Healthy n = 10 18-62 yrs</td>
<td>70</td>
<td>28.6</td>
<td>Infusion for 30 mins</td>
<td>0-48 hrs</td>
<td>Plasma, Urine</td>
<td>Plasma, Urine</td>
<td>AUC (ng.h/ml)</td>
<td>CL(_{tot}) (ml/min/kg)</td>
<td>Vd(_{ss}) (l/kg)</td>
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<td></td>
<td>1148000 (± 93800)</td>
<td>0.82 (± 0.20)</td>
<td>0.15 (± 0.03)</td>
</tr>
</tbody>
</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conte et al(^{110})</td>
<td>Healthy n = 10</td>
<td>Ultrafiltration In-vivo</td>
<td>205.3 µg/ml</td>
<td>HPLC</td>
<td>95.2 ± 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>140.6 µg/ml</td>
<td></td>
<td>96.8 ± 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82 µg/ml</td>
<td></td>
<td>98.1 ± 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41.1 µg/ml</td>
<td></td>
<td>99.3 ± 0.8</td>
</tr>
</tbody>
</table>
**Cefsoludin**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matzke et al(^{111})</td>
<td>Healthy n = 6 27.7 yrs</td>
<td>73.5</td>
<td>7.02</td>
<td>infusion for 30 mins</td>
<td>0-36 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>0.2 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
</tr>
<tr>
<td>Gibson et al(^{112})</td>
<td>Healthy n = 5 33.2 yrs</td>
<td>57.4 ± 9.2</td>
<td>8.7</td>
<td>infusion for 30 min</td>
<td>0-36 hrs</td>
<td>0-24 hr</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
</tr>
</tbody>
</table>

**Plasma protein binding:** 15 % (Gibson et al\(^{112}\))
Cefpimizole

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Lakings et al\textsuperscript{113}</td>
<td>Healthy n = 6 18-37 yrs</td>
<td>70 (assumed)</td>
<td>14.28 28.57</td>
<td>Infusion</td>
<td>0-24 hrs 0-48 hrs</td>
<td>HPLC</td>
<td>1-400 µg/ml 10-800 µg/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>-</td>
</tr>
</tbody>
</table>

Urinary excretion data:

Lakings et al\textsuperscript{113}.

Urine collection: 0-0.5, 0.5-0.75, 0.75-1.0, 1-2, 2-6, 6-12, 12-24 and 24-48 hr

Renal clearance $\text{CL}_{\text{ren}} = Ae(48)\text{AUC}_{\text{J0}}$ where $Ae(48)$ is cumulative amount of drug excreted unchanged in urine up to 48 hrs
### Cefixime

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faulkner et al\textsuperscript{114}</td>
<td>Healthy n = 16</td>
<td>71 ± 8.9</td>
<td>2.82</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
</tr>
<tr>
<td>Duverne et al\textsuperscript{115}</td>
<td>Healthy n = 8</td>
<td>74</td>
<td>2.70</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>sensitivity- 0.05 μg/ml</td>
<td>-</td>
<td>Noncompartmental</td>
</tr>
</tbody>
</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al\textsuperscript{116}</td>
<td>pooled plasma</td>
<td>Ultrafiltration</td>
<td>400 mg oral dose</td>
<td>HPLC</td>
<td>65 % (± 4 %)</td>
</tr>
<tr>
<td>Bialer et al\textsuperscript{117}</td>
<td>pooled plasma</td>
<td>Ultrafiltration</td>
<td>0.5-500 μg/ml</td>
<td>HPLC</td>
<td>fu = 31.3 ± 3.3 %</td>
</tr>
</tbody>
</table>

**Urinary excretion data:**

Faulkner et al\textsuperscript{114};
Urine collection: 0-2, 2-4, 4-8, 8-12, 12-24 hr
Renal clearance $\text{CL}_{\text{ren}} = \text{Ae}(24)\text{AUC}_{0}^{24}$ where $\text{Ae}^{24}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs
### Ceftizoxime

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
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</tr>
<tr>
<td>Quintiliani et al&lt;sup&gt;118&lt;/sup&gt;</td>
<td>Myelography patients n = 10 18-65 yrs</td>
<td>70 (assumed)</td>
<td>30</td>
<td>Bolus 0-240 mins</td>
<td>-</td>
<td>HPLC</td>
<td>1.0 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
</tr>
</tbody>
</table>

**Plasma protein binding:** Quintiliani et al<sup>118</sup>. 31% (just mentioned)

### Cefpodoxime

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
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</tr>
<tr>
<td>Tremblay et al&lt;sup&gt;119&lt;/sup&gt;</td>
<td>Healthy n = 12 18-48 yrs</td>
<td>70</td>
<td>1.43</td>
<td>Infusion for 2 hrs 0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>0.02 µg/ml</td>
<td>2.0 µg/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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</table>
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al</td>
<td>pooled plasma</td>
<td>Ultrafiltration</td>
<td>0.5-8 µg/ml</td>
<td>HPLC</td>
<td>21% (±4%)</td>
</tr>
</tbody>
</table>
### Fourth Generation Cephalosporin

#### Cefepime

#### PK Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</tr>
<tr>
<td>Barbhaiya et al\textsuperscript{120}</td>
<td>Healthy n = 16</td>
<td>74.9±9.7</td>
<td>26.7</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>0-12 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
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<tr>
<td>Barbhaiya et al\textsuperscript{121}</td>
<td>Healthy n = 12</td>
<td>70 (assumed)</td>
<td>28.6</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
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<tr>
<td>Barbhaiya et al\textsuperscript{122}</td>
<td>Healthy n = 31</td>
<td>71.7</td>
<td>3.49</td>
<td>Infusion</td>
<td>0-16 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>0.5 µg/ml</td>
<td>2.0 µg/ml</td>
<td>Noncompartmental</td>
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</tbody>
</table>

- **BW (kg):** Body weight (kg)
- **Dose (mg/kg):** Dose per kg
- **Rate:** Administration rate
- **Sampling schedule:** Timing of blood and urine collections
- **Assay:** Method of analysis
- **LOQ:** Limit of quantitation
- **PK Analysis:** Type of PK analysis
- **Urine Collection method:** Method of urine collection
- **PK endpoints:** Key PK endpoints

---

*Barbhaiya et al\textsuperscript{120} n = 16, 29 ± 8 yrs*

*Barbhaiya et al\textsuperscript{121} n = 12*

*Barbhaiya et al\textsuperscript{122} n = 31*
Urine excretion study: Barbhaiya et al\textsuperscript{120}
Urine collection: 0-4, 4-8, 8-12, 12-24 hr
Renal clearance \(\text{CL}_{\text{ren}} = \frac{\text{Ae}^{24}}{\text{AUC}^{24}}\) where \(\text{Ae}^{24}\) is cumulative amount of drug excreted unchanged in urine upto 24 hrs

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbhaiya et al\textsuperscript{124}</td>
<td>Human serum</td>
<td>Ultrafiltration</td>
<td>40-400 µg/ml</td>
<td>HPLC</td>
<td>16.4 %</td>
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</tbody>
</table>
### Cefpirome

#### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis method</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paradis et al[^87]</td>
<td>Healthy 23.9 yrs</td>
<td>72.0</td>
<td>13.9</td>
<td>Infusion for 30 mins</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>HPLC LOD – 0.1 µg/ml</td>
<td>-</td>
<td>Compartmen tal</td>
</tr>
<tr>
<td>Nakayama et al[^123]</td>
<td>Healthy n = 42</td>
<td>Healthy 29.7 yrs</td>
<td>65.2</td>
<td>7.7</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>HPLC LOD – 0.1 µg/ml LOD – 5.0 µg/ml</td>
<td>Compartmen tal</td>
<td>Cumulative</td>
</tr>
<tr>
<td>Nakayama et al[^123]</td>
<td>Healthy n = 42</td>
<td>Healthy 29.7 yrs</td>
<td>65.2</td>
<td>7.7</td>
<td>Infusion for 1 hr</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC LOD – 0.1 µg/ml LOD – 5.0 µg/ml</td>
<td>Compartmen tal</td>
</tr>
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</tr>
</tbody>
</table>

\[^87\] Paradis et al, 1987
\[^123\] Nakayama et al, 1987
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer et al126</td>
<td>Pooled plasma</td>
<td>Ultracentrifugation</td>
<td>5.0-150 µg/ml</td>
<td>MEKC</td>
<td>12 ± 2%</td>
</tr>
</tbody>
</table>
**Beta Lactamase Inhibitors**

Clavulanic acid

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW  (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td>Hoffken et al\textsuperscript{16}</td>
<td>Healthy n = 10 32.5 yrs</td>
<td>69.8 (59.9-79.2)</td>
<td>2.40</td>
<td>Infusion for 15 mins</td>
<td>0-10 hrs</td>
<td>0-24 hrs</td>
<td>Agar diffusion</td>
<td>LOD 0.06 mg/l</td>
<td>-</td>
<td>Compart-mental</td>
</tr>
</tbody>
</table>
Tazobactam

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Sorgel et al(^{127})</td>
<td>Not mentioned, n = 4</td>
<td>70 (assumed)</td>
<td>1.43</td>
<td>Infusion for 30 mins</td>
<td>0-8 hrs</td>
<td>Not mentioned</td>
<td>HPLC</td>
<td>0.05 mg/l</td>
<td>0.05 mg/l</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>n = 3</td>
<td>14.3</td>
<td></td>
<td></td>
<td></td>
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</table>

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorgel et al(^{127})</td>
<td>-</td>
<td>In-vitro Ultrafiltration</td>
<td>1-100 mg/l</td>
<td>HPLC</td>
<td>20-23%</td>
</tr>
</tbody>
</table>
**Sulbactam**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foulds et al.128</td>
<td>Healthy n =3</td>
<td>70</td>
<td>1.79</td>
<td>Infusion</td>
<td>0-6 hrs</td>
<td>GC-MS</td>
<td>LOD-0.5 µg/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>AUC (ng.h/ml)</td>
</tr>
<tr>
<td></td>
<td>(assumed)</td>
<td></td>
<td>3.57</td>
<td></td>
<td></td>
<td></td>
<td>LOD-7 µg/ml</td>
<td></td>
<td></td>
<td>Mean = 5900</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean = 19800</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean = 28900</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean = 66400</td>
</tr>
</tbody>
</table>

|                   |                 |         |              |             |                   |             |              |              |                          | Mean = 2.91 |
|                   |                 |         |              |             |                   |             |              |              |                          | ± 0.63 |
|                   |                 |         |              |             |                   |             |              |              |                          | fe = 75.5% |
### Fifth Generation Cephalosporin

**Ceftobiprole medocaril**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scmitt-Hoffmann et al(^{1,2})</td>
<td>Healthy n = 6/dose</td>
<td>70 (assumed)</td>
<td>125</td>
<td>Infusion</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>20 ng/ml</td>
<td>100 ng/ml</td>
<td>Noncompartmental Cumulative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infusion</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infusion</td>
<td>43700 (+ 5990)</td>
<td>1.38 (+ 0.20)</td>
<td>0.25 (+ 0.04)</td>
<td>1.04 (+ 0.14)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infusion</td>
<td>76600 (+ 3880)</td>
<td>1.56 (+ 0.08)</td>
<td>0.28 (+ 0.03)</td>
<td>1.21 (+ 0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Infusion</td>
<td>135000 (+ 27600)</td>
<td>1.37 (+ 0.27)</td>
<td>0.26 (+ 0.04)</td>
<td>0.97 (+ 0.18)</td>
<td></td>
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<td></td>
<td>Infusion</td>
<td>151000 (+ 9040)</td>
<td>1.59 (+ 0.09)</td>
<td>0.27 (+ 0.03)</td>
<td>0.99 (+ 0.14)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Infusion</td>
<td>166500 (+ 9540)</td>
<td>1.36 (+ 0.26)</td>
<td>0.26 (+ 0.04)</td>
<td>1.04 (+ 0.14)</td>
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<tr>
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<td></td>
<td></td>
<td>Infusion</td>
<td>224000 (+ 13300)</td>
<td>1.59 (+ 0.09)</td>
<td>0.27 (+ 0.03)</td>
<td>0.99 (+ 0.14)</td>
<td></td>
</tr>
</tbody>
</table>
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murthy et al(^{136})</td>
<td>Healthy</td>
<td>Ultracentrifugation</td>
<td>0.5, 5, 24, 100 µg/ml</td>
<td>HPLC</td>
<td>17.3% (\pm 4.58%)</td>
</tr>
</tbody>
</table>
References:

Appendix II (a)

Animal PK Study Summaries for Opioids

Agonists

**Morphine**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Langguth et al¹</td>
<td>Mongrel Dogs n = 3</td>
<td>23.1</td>
<td>3.85</td>
<td>Bolus</td>
<td>0-500 mins</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>PLasma Urine  Plasma Urine</td>
</tr>
<tr>
<td>Barnhart et al²</td>
<td>Beagle dogs n = 6</td>
<td>9.8 (± 1.5)</td>
<td>0.19</td>
<td>Bolus</td>
<td>0-480 mins</td>
<td>-</td>
<td>GC-MS</td>
<td>-</td>
<td>-</td>
<td>PLasma Urine  Plasma Urine</td>
</tr>
<tr>
<td>Dohoo et al³</td>
<td>Marshall Beagles n = 6 1 yr</td>
<td>11.0 (9.8-12.6)</td>
<td>0.187</td>
<td>Bolus</td>
<td>0-720 mins</td>
<td>-</td>
<td>RIA</td>
<td>2.5-250 ng/ml</td>
<td>-</td>
<td>PLasma Urine  Plasma Urine</td>
</tr>
<tr>
<td>Study</td>
<td>Species</td>
<td>Dose</td>
<td>Time</td>
<td>Method</td>
<td>Units</td>
<td>Concentration</td>
<td>% in LysoPC</td>
<td></td>
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</tr>
<tr>
<td>Garrett et al.</td>
<td>Dogs n=2/dose grp</td>
<td>0.3</td>
<td>0-50 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu et al.</td>
<td>Male Sprague Dawley rats n = 3</td>
<td>0.25-0.35</td>
<td>0-60 mins</td>
<td>HPLC</td>
<td>-</td>
<td>Compartmental</td>
<td>29.5 (± 1.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groenen-daal et al</td>
<td>Wistar rats n = 14</td>
<td>0.25-0.35</td>
<td>Bolus</td>
<td>HPLC</td>
<td>25 ng/ml</td>
<td>-</td>
<td>80.3 (SE± 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor et al.</td>
<td>Domestic cats n = 6</td>
<td>2.9-4.4</td>
<td>Bolus</td>
<td>HPLC</td>
<td>LOD 5 ng/ml</td>
<td>Non-compartmental</td>
<td>24.1 (± 10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milne et al.</td>
<td>Sheep n = 4</td>
<td>48 (± 8)</td>
<td>Infusion</td>
<td>HPLC</td>
<td>-</td>
<td>Non-compartmental</td>
<td>32.9 (± 5.62)</td>
<td></td>
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</tr>
</tbody>
</table>

Note: The table values are approximate and may vary.
<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>n</th>
<th>Method</th>
<th>Treatment</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sloan et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Adult merino ewes n = 4</td>
<td>48 (± 8)</td>
<td>Infusion 0-360 mins to HPLC</td>
<td>0-48 hrs</td>
<td>Sensitivity = 0.5 ng/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>34.16 (± 3.75)</td>
</tr>
<tr>
<td>Uhrig et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Llamas n = 6</td>
<td>144 (± 3.4)</td>
<td>Bolus 0-24 hrs</td>
<td>HPLC 5 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>300 (± 120)</td>
<td>149.34 (± 66.80)</td>
</tr>
<tr>
<td>Combie et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Horses n = 4</td>
<td>415-577</td>
<td>Bolus 0-48 hrs</td>
<td>GC</td>
<td>Compart mental</td>
<td>-</td>
<td>11572 (calculated)</td>
<td>8.6 (calculated)</td>
</tr>
<tr>
<td>Anders et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Goat n = 5</td>
<td>14.8-45</td>
<td>Bolus 0-24 hrs</td>
<td>RIA 0.25 ng/ml</td>
<td>Compart mental</td>
<td>-</td>
<td>3493.4 (calculated)</td>
<td>33.9 (calculated)</td>
</tr>
<tr>
<td>Guedes et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Dogs n = 5</td>
<td>14.8 ± 0.3 follo-follo</td>
<td>Bolus 0-240 min</td>
<td>HPLC 7 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>66.52 (± 20.25)</td>
<td>1.34 (± 0.78)</td>
</tr>
</tbody>
</table>
Urinary excretion studies:

1. **Dogs**: Langguth et al.\(^1\) estimated renal clearances by regression of the cumulative amount excreted in the urine and plotting against AUC (\(\Sigma U = CL_{\text{ren}} \cdot AUC + \text{ Intercept}\)).

   Garrett et al.\(^4\): Urine was collected every 10 min up to 1 hr, then hourly up to 12 hr and then every 12 hr up to 100 hr. Renal clearance is estimated from the slope of \(dU/dt\) versus plasma concentration plots.

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Age</th>
<th>Infusion Rate</th>
<th>Bolus</th>
<th>0-180 mins</th>
<th>180-100 mins</th>
<th>100-144 mins</th>
<th>144-168 mins</th>
<th>168-240 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handal et al(^1)</td>
<td>C57BL/6 J-Bom</td>
<td>7-8 weeks, n = 8</td>
<td>0.17 mg/kg/h, 0.34 mg/kg/h</td>
<td>80 umol/kg</td>
<td>0.014 - 0.024</td>
<td>HPLC</td>
<td>Non-compartmental</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
2. Rats: Sloan et al\textsuperscript{9} estimated renal clearance.

Urine was collected from 0-6 h, 6-24 h, 24-48 h.
Analysis: HPLC (sensitivity- 0.5 ng/ml)
Direct $CL_{\text{ren}} =$ product of renal extraction ratio and renal blood flow – 11.88 ml/min/kg (± 1.46)
Indirect $CL_{\text{ren}} =$ product of CL and urinary recovery of unmetabolized morphine –
4.38 ml/min/kg (± 1.46) % dose excreted unchanged in urine in 48 hrs = 12.3% (± 2.7)

3. Sheep: Milne et al\textsuperscript{8} estimated renal clearance:
Urine was collected 0-6 h, 6-24 h, 24-48 h, urine volume and pH were measured.
Analysis: HPLC
Urinary recovery was calculated as the percentage of the morphine dose given over 6h as the unchanged drug.

### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crugten et al\textsuperscript{13}</td>
<td>Rat n = 6</td>
<td>Ultrafiltration</td>
<td>100 ng/ml 1000 ng/ml</td>
<td>HPLC</td>
<td>Average $fu = 0.68$</td>
</tr>
<tr>
<td>Baggot et al\textsuperscript{16}</td>
<td>Different species</td>
<td>Equilibrium dialysis</td>
<td>0.177 x 10^{-6} M - 7.080 x 10^{-6} M</td>
<td>Liquid scintillation</td>
<td></td>
</tr>
<tr>
<td>Goat (n = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.0 ± 0.87</td>
</tr>
<tr>
<td>Sheep (n = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.4 ± 1.53</td>
</tr>
<tr>
<td>Ox (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23.6 ± 1.83</td>
</tr>
<tr>
<td>Horse (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.5 ± 0.98</td>
</tr>
<tr>
<td>Pony (n = 8)</td>
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<td></td>
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<td>20.1 ± 1.13</td>
</tr>
<tr>
<td>Swine (n = 7)</td>
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<td></td>
<td>10.6 ± 0.89</td>
</tr>
<tr>
<td>Dog (n = 15)</td>
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<td></td>
<td></td>
<td>12.1 ± 0.94</td>
</tr>
<tr>
<td>Cat (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.8 ± 2.01</td>
</tr>
<tr>
<td>Monkey (n =)</td>
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<td></td>
<td></td>
<td>19.0 ± 0.71</td>
</tr>
<tr>
<td>Study</td>
<td>Animal</td>
<td>Method</td>
<td>Concentration range</td>
<td>Assay</td>
<td>B:P ratio</td>
</tr>
<tr>
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<td>---------------------</td>
<td>---------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Garrett et al.¹⁴</td>
<td>Dog</td>
<td>In-vitro</td>
<td>1, 10, 100 and 1000 ng/ml</td>
<td>Liquid scintillation</td>
<td>1.11 (± 0.35)</td>
</tr>
<tr>
<td>Combie et al.¹¹</td>
<td>Horses n = 4 8-21 yrs</td>
<td>In-vitro</td>
<td>3.88 x 10⁻³ M – 3.50 x 10⁻⁸ M</td>
<td>Liquid scintillation</td>
<td>0.63 (calculated)</td>
</tr>
<tr>
<td>Mistry et al.¹⁵</td>
<td>Sprague Dawley rats</td>
<td>In-vitro</td>
<td>0.5-500 ng/ml</td>
<td>Liquid scintillation</td>
<td>1.34 (± 0.05)</td>
</tr>
</tbody>
</table>
Morphine metabolites:

PK Studies:

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<td>M6G</td>
<td>Wu et al5</td>
<td>Male Sprague Dawley rats n =3</td>
<td>0.25-0.35</td>
<td>0.023 nmol</td>
<td>Bolus</td>
<td>0.25-60 mins</td>
<td>HPLC</td>
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<td>Handal et al14</td>
<td>C57BL/6 J-Bom Mice 7-8 weeks n =8</td>
<td>0.014 - 0.024</td>
<td>80 µmol/kg</td>
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<td>HPLC</td>
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<td>Ekblom et al18</td>
<td>Male Sprague Dawley rats n =7</td>
<td>0.304 (± 0.025)</td>
<td>86.7 µmol/kg</td>
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<td>Garrett et al4</td>
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<td>0-50 hrs</td>
<td>0-800 mins</td>
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<td>Milne et al10</td>
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<td>48 ± 5</td>
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## Plasma protein binding studies:

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<td>Van Crugten$^{15}$</td>
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<td>Wu et al$^{7}$</td>
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<td>10 nM</td>
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<td>Mean ± SE 73.4 ± 7.1% (4%HSA) 76.4 ± 1.3% (4%RSA) 69.9 ± 5.5% (100% serum)</td>
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<tr>
<td>Milne et al$^{19}$</td>
<td>Sheep</td>
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<td>81.5 nM</td>
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## Blood –to–plasma ratio studies:

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<td>Garrett et al$^{4}$</td>
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<td>50-500 ng/ml</td>
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<td>Hoke et al²⁰</td>
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<td>Chism et al²¹</td>
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<td>Haidar et al²²</td>
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<td>Johnso n et al²³</td>
<td>Swine n = 8</td>
<td>21-31</td>
<td>0.010</td>
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**Remifentanil**

**PK Studies:**
## Alfentanil

### PK Studies:

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<td>Bjorkman et al.26</td>
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<td>2.60 (2.55-2.75)</td>
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<td>GLC</td>
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<td>Pascoe et al.27</td>
<td>Horses n = 6 3-10 yrs</td>
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<td>Bjorkman et al(^26)</td>
<td>New Zealand white rabbits Control n = 9</td>
<td>Ultracentrifugation</td>
<td>IV infusion-0.22 mg/kg for 10 min</td>
<td>GLC</td>
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Plasma protein binding studies:

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<td>Ilkiw et al(^29)</td>
<td>Rabbits n = 5</td>
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<td>Sheep n = 5</td>
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<td>Dogs n = 5</td>
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Blood –to –plasma ratio studies:

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<td>Dog</td>
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<td>0.623 ± 0.011</td>
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Fentanyl

PK Studies:

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<th>Rate</th>
<th>Sampling schedule</th>
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<th>LOQ</th>
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<th>Urine Collection method</th>
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<td>Lee et al32</td>
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<td>LOD</td>
<td>Compartmental</td>
<td>Median 320400</td>
<td>19.8 (± 2.7)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.56 (± 0.32)</td>
</tr>
<tr>
<td>Study</td>
<td>Species</td>
<td>n</td>
<td>Median or range</td>
<td>Procedure</td>
<td>0.1 ng/ml</td>
<td>Compartmental</td>
<td>LOD</td>
<td>Compart. LOD</td>
<td>LOD</td>
<td>LOD</td>
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<tr>
<td>Kyles et al.33</td>
<td>Beagle Dogs</td>
<td>6</td>
<td>13.5 (± 1.90)</td>
<td>Bolus</td>
<td>0.032</td>
<td>-</td>
<td>RIA</td>
<td>-</td>
<td>LOD</td>
<td>-</td>
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<tr>
<td>Hughes et al.34</td>
<td>Greyhound dogs</td>
<td>7</td>
<td>25.58 (± 3.38)</td>
<td>Infusion</td>
<td>0.007</td>
<td>-</td>
<td>RIA</td>
<td>-</td>
<td>LOD</td>
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<tr>
<td>Carroll et al.35</td>
<td>Goats</td>
<td>8</td>
<td>40.4 (± 7.5)</td>
<td>Bolus</td>
<td>0.002</td>
<td>-</td>
<td>RIA</td>
<td>0.1 ng/ml</td>
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<tr>
<td>Murphy et al.36</td>
<td>Mongrel dogs</td>
<td>5</td>
<td>13.9</td>
<td>Bolus</td>
<td>0.006</td>
<td>0-6 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Maxwell et al.37</td>
<td>Horses</td>
<td>6</td>
<td>464-585</td>
<td>Bolus</td>
<td>0.003</td>
<td>0-8 hrs</td>
<td>RIA</td>
<td>0.25 ng/ml</td>
<td>-</td>
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<tr>
<td>Thomas et al.38</td>
<td>Horses</td>
<td>8</td>
<td>545 ± 31</td>
<td>Bolus</td>
<td>0.002</td>
<td>0-10hrs</td>
<td>LC-MS</td>
<td>0.1 ng/ml</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Egan et al.39</td>
<td>Pig</td>
<td>18</td>
<td>-</td>
<td>Bolus</td>
<td>0.005</td>
<td>0-370 mins</td>
<td>RIA</td>
<td>0.1 ng/ml</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Valverde et al.40</td>
<td>Rhesus monkeys</td>
<td>6</td>
<td>11.75 ± 1.88</td>
<td>Bolus</td>
<td>0.008</td>
<td>0-480 mins</td>
<td>RIA</td>
<td>0.1 ng/ml</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy et al (^36)</td>
<td>Dog</td>
<td>-</td>
<td>0.1-100 ng/ml</td>
<td>-</td>
<td>62 %</td>
</tr>
<tr>
<td>Meuldermans et al (^30)</td>
<td>Male Wistar rats</td>
<td>Equilibrium dialysis (20 rpm, 37(^o)C/ 4hrs, pH 7.35)</td>
<td>0.01µg/ml</td>
<td>Liquid scintillation</td>
<td>(f_b) 0.834 ± 0.006</td>
</tr>
<tr>
<td>Meuldermans et al (^30)</td>
<td>Male Beagle dogs</td>
<td>Equilibrium dialysis (20 rpm, 37(^o)C/ 4hrs, pH 7.35)</td>
<td>0.01µg/ml</td>
<td>Liquid scintillation</td>
<td>(f_b) 0.782± 0.031</td>
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</tbody>
</table>

### Blood–to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
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</thead>
<tbody>
<tr>
<td>Meuldermans et al (^30)</td>
<td>Male Wistar rats</td>
<td>\textit{In-vitro}</td>
<td>0.01 µg/ml</td>
<td>Liquid scintillation</td>
<td>0.891 ± 0.042</td>
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<tr>
<td></td>
<td>Male Beagle dogs</td>
<td>\textit{In-vitro}</td>
<td></td>
<td></td>
<td>0.939 ± 0.083</td>
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<tr>
<td>Bjorkman et al (^41)</td>
<td>Pig</td>
<td>\textit{In-vitro}</td>
<td>15 ng/ml</td>
<td>GLC</td>
<td>(f_u = 24.0 ± 5.6%)</td>
</tr>
</tbody>
</table>
Sufentanil

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Meuldermans et al(^{30})</td>
<td>Male Wistar rats (n = 7)</td>
<td>0.25-0.30</td>
<td>0.0.30 mg/k g in 40 min</td>
<td>Infusion</td>
<td>-</td>
<td>-</td>
<td>1 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
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Plasma protein binding studies:

<table>
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<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meuldermans et al(^{30})</td>
<td>Male Wistar rats</td>
<td>Equilibrium dialysis (20 rpm, 37°C/ 4hrs, pH 7.35)</td>
<td>1.0 ng/ml</td>
<td>Liquid scintillation</td>
<td>(f_b = 0.931 \pm 0.003)</td>
</tr>
<tr>
<td>Meuldermans et al(^{30})</td>
<td>Male Beagle dogs</td>
<td>Equilibrium dialysis (20 rpm, 37°C/ 4hrs, pH 7.35)</td>
<td>-</td>
<td>-</td>
<td>(f_b = 0.928 \pm 0.015)</td>
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</table>
### Blood–to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
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</thead>
<tbody>
<tr>
<td>Meuldermans et al.[30]</td>
<td>Male Wistar rats</td>
<td><em>In-vitro</em></td>
<td>1.0 µg/ml</td>
<td>Liquid scintillation</td>
<td>0.744 ± 0.016</td>
</tr>
<tr>
<td></td>
<td>Male Beagle dogs</td>
<td><em>In-vitro</em></td>
<td></td>
<td></td>
<td>0.658 ± 0.013</td>
</tr>
</tbody>
</table>
## Hydromorphone

### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wegner et al&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Cats n = 6</td>
<td>5.9</td>
<td>0.089</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>LC-MS</td>
<td>1.0 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>Median=4078.9 SEM=284.51</td>
</tr>
<tr>
<td>Chang et al&lt;sup&gt;43&lt;/sup&gt;</td>
<td>New Zealand white rabbits n = 3</td>
<td>2.95</td>
<td>5</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>240000 (calculated)</td>
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</tbody>
</table>
**Oxycodone**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostrom et al(^44)</td>
<td>Sprague Dawley rats n = 8</td>
<td>0.25-0.32</td>
<td>0.3</td>
<td>Infusion</td>
<td>0-180 mins</td>
<td>-</td>
<td>LC/MS-MS</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
</tr>
<tr>
<td>Chan et al(^45)</td>
<td>Sprague Dawley rats n = 5</td>
<td>250-300</td>
<td>5</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>-</td>
<td>HPLC-MS</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
</tr>
</tbody>
</table>

Excretion studies: Ishida et al\(^46\) carried excretion studies in 4 species:

Male rabbits (2.8-3.5 kg), n = 4, % dose- urine-0.4(SE ± 0.4), feces – 0.8 (SE ± 0.3)
Guinea pigs (450-500 kg), n = 4, % dose- urine-2.7(SE ± 0.3), feces – 2.2 (SE ± 0.6)
Male rats (150-200 kg), n = 4, % dose- urine-1.3(SE ± 0.3), feces – 2.0 (SE ± 0.3)
Male mice (18-23 kg), n = 20, % dose- urine-1.7(SE ± 0.7), feces – 0.6 (SE ± 0.2)
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostrom et al(^4)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male Sprague Dawley rats</td>
<td></td>
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<tr>
<td>Centrifugation</td>
<td>50 ng/ml 500 ng/ml</td>
<td>LC-MS</td>
<td>74.3%</td>
<td></td>
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### Blood–to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostrom et al(^4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Sprague Dawley rats</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>In-vitro</em></td>
<td>50 and 500 ng/ml</td>
<td>LC-MS</td>
<td>1.3 (± 0.3)</td>
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</table>
## Meperidine

### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahlstrom et al</td>
<td>Male Wistar rats</td>
<td>0.2 (± 0.010)</td>
<td>8.71</td>
<td>Bolus</td>
<td>0-180 mins</td>
<td>-</td>
<td>MS</td>
<td>2 ng/ml</td>
<td>Compart-mental</td>
<td>AUC (ng.min/ml)</td>
</tr>
<tr>
<td>Ritschel et al</td>
<td>Beagle dogs</td>
<td>10.53 (± 0.95)</td>
<td>5</td>
<td>Bolus</td>
<td>0-360 mins</td>
<td>-</td>
<td>GC</td>
<td>-</td>
<td>Noncompartmental</td>
<td></td>
</tr>
<tr>
<td>Waterman et al</td>
<td>Dogs</td>
<td>28.0 (± 2.5)</td>
<td>1.74</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>-</td>
<td>GLC</td>
<td>-</td>
<td>Compart-mental</td>
<td></td>
</tr>
<tr>
<td>Kalthum et al</td>
<td>Dogs control</td>
<td>21-30</td>
<td>2.0</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>-</td>
<td>GLC</td>
<td>Limit of sensitivity = 21 ng/ml</td>
<td>Compart-mental</td>
<td></td>
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<tr>
<td>Ranheim et al</td>
<td>Pigs</td>
<td>18.2-26.5</td>
<td>4.35</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>GC</td>
<td>-</td>
<td>Noncompartmental</td>
<td>Median-139000 (103000-165000)</td>
</tr>
<tr>
<td>Szeto et</td>
<td>Pregnant</td>
<td>-</td>
<td>2.5</td>
<td>Bolus</td>
<td>0-120</td>
<td>-</td>
<td>GLC</td>
<td>20</td>
<td>Compartm</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Animal</td>
<td>Method</td>
<td>Concentration range</td>
<td>Assay</td>
<td>Protein binding</td>
<td></td>
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</tr>
<tr>
<td>Szeto et al^{53}</td>
<td>Pregnant sheep</td>
<td>Equilibrium dialysis</td>
<td>0.5 µg/ml</td>
<td>GLC</td>
<td>54 ± 2.39%</td>
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<tr>
<td>Knodell et al^{54}</td>
<td>Rat</td>
<td>Equilibrium dialysis</td>
<td>5 µg/ml</td>
<td>GC</td>
<td>43 ± 1.0%</td>
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</table>

**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knodell et al^{54}</td>
<td>Sprague Dawley rats n = 4</td>
<td>Equilibrium dialysis</td>
<td>0.288 (± 0.038) mins</td>
<td>GC</td>
<td>113.2 (calculated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.5 Bolus 0-120 mins</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>GLC - - Compartmental</td>
<td>-</td>
<td>2043 x 10^3 ml/min</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(SE ± 0.306)</td>
<td></td>
<td>(SE ± 1116) ml/min</td>
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</tbody>
</table>

606
## Methadone

### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>PK Collection method</th>
<th>AUC (ng.min/ml)</th>
<th>CL(_{\text{tot}}) (ml/min/kg)</th>
<th>Vd(_{\beta}) (l/kg)</th>
<th>CL(_{\text{ren}}) (ml/min/kg)</th>
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</thead>
<tbody>
<tr>
<td>Garrett et al(^55)</td>
<td>Mongrel male dogs n = 4</td>
<td>19-25</td>
<td>0.72-1.99</td>
<td>Bolus</td>
<td>0-600 mins</td>
<td>HPLC</td>
<td>Sensitivity -5 ng/ml</td>
<td>-</td>
<td>Compart-mental And Cumulative</td>
<td>-</td>
<td>40.8 (± 4.7)</td>
<td>6.81 (calculated)</td>
<td>1.59 (± 0.41) (3.6% excreted unchanged in urine)</td>
</tr>
<tr>
<td>Ling et al(^56)</td>
<td>Male Sprague Dawley rats n = 6 /group</td>
<td>0.25-0.30</td>
<td>1.5 Bolus</td>
<td>0-480 mins</td>
<td>- RIA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>62.4 (SE± 9.2)</td>
<td>7.81 (SE± 1.65)</td>
<td>-</td>
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<tr>
<td>Schmidt et al(^57)</td>
<td>Beagle dogs n = 4</td>
<td>18.5</td>
<td>0.5 Bolus</td>
<td>0-15 hrs</td>
<td>- HPLC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>16260 (± 3900)</td>
<td>17.2 (± 4.97)</td>
<td>6.08 (calculated)</td>
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<tr>
<td>Kukani et al(^58)</td>
<td>Beagle dogs n = 6</td>
<td>7.3-13.0</td>
<td>1 Bolus</td>
<td>0-8 hrs</td>
<td>- HPLC Or fluoresc</td>
<td>HPLC-20 ng/ml</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>44558 ± 14989</td>
<td>25.14 (± 9.79)</td>
<td>3.46 (± 1.09)</td>
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</table>
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ling et al56</td>
<td>Rat</td>
<td>Equilibrium dialysis</td>
<td>20 ng/ml</td>
<td>RIA</td>
<td>83 ± 0.51%</td>
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<tr>
<td></td>
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<td></td>
<td>200 ng/ml</td>
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<td>74.0 ± 0.70 %</td>
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### Codeine

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Shah et al^59</td>
<td>Sprague Dawley rats</td>
<td>0.25-0.30</td>
<td>0.73</td>
<td>0.25-0.30</td>
<td>0.73</td>
<td>Bolus</td>
<td>HPLC</td>
<td>Sensitivity- 2 ng/ml</td>
<td>Compartmental</td>
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<tr>
<td></td>
<td>n = 3/grp</td>
<td>1.1</td>
<td>2.21</td>
<td>2.94</td>
<td>1.1</td>
<td>2.21</td>
<td>2.94</td>
<td>-</td>
<td></td>
<td>AUC (ng.min/ml)</td>
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<td>9500 (± 2400)</td>
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<td>30279 (± 6238)</td>
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<tr>
<td>Shah et al^60</td>
<td>Sprague Dawley rats</td>
<td>0.25-0.30</td>
<td>2.21</td>
<td>0.25-0.30</td>
<td>2.21</td>
<td>Bolus</td>
<td>HPLC</td>
<td>2 ng/ml</td>
<td>Noncompartmental</td>
<td>101.6(±13.3)</td>
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<tr>
<td></td>
<td>n = 6</td>
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<td>-</td>
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<td>39700 (± 5600)</td>
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<td>27800 (± 4700)</td>
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<td>12500 (±1300)</td>
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<td>30279 (± 6238)</td>
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<td>101.6(±13.3)</td>
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Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baggot et al\textsuperscript{16}</td>
<td>Goat (n=12)</td>
<td>Equilibrium dialysis</td>
<td>$0.167 \times 10^{-6}$ M - $6.680 \times 10^{-6}$ M</td>
<td>Liquid scintillation</td>
<td>$9.2 \pm 1.21$</td>
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<tr>
<td></td>
<td>Sheep (n=12)</td>
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<td>$7.2 \pm 0.76$</td>
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<td></td>
<td>Ox (n=6)</td>
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<td>$14.2 \pm 1.50$</td>
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<td></td>
<td>Horse (n=7)</td>
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<td></td>
<td>$12.8 \pm 1.84$</td>
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<td>Pony (n=8)</td>
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<td>$13.1 \pm 1.57$</td>
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<tr>
<td></td>
<td>Swine (n=9)</td>
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<td></td>
<td>$7.9 \pm 0.90$</td>
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<tr>
<td></td>
<td>Dog (n=12)</td>
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<td>$9.6 \pm 1.06$</td>
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<tr>
<td></td>
<td>Cat (n=10)</td>
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<td>$7.6 \pm 0.81$</td>
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<td></td>
<td>Monkey (n=12)</td>
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<td>$8.2 \pm 1.19$</td>
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<tr>
<td></td>
<td>Rat (n=12)</td>
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<td>$7.5 \pm 1.00$</td>
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<tr>
<td></td>
<td>Rabbit (n=7)</td>
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<td>$15.6 \pm 1.69$</td>
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<td>Opossum (n=4)</td>
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<td>$23.1 \pm 1.91$</td>
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<tr>
<td></td>
<td>Man (n=7)</td>
<td></td>
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<td>$7.0 \pm 0.81$</td>
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Tramadol

PK Studies:

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<tr>
<th>Study</th>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Assay Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Kukanich et al61</td>
<td>Beagle dogs n = 6</td>
<td>7-12</td>
<td>3.9</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>AUC (ng.min/ml) 72194 (± 10891) CL_{tot} (ml/min/kg) 54.63 (± 8.19) Vd_{ss} (l/kg) 3.01 (± 0.45)</td>
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<tr>
<td>Kucuk et al62</td>
<td>New Zealand white rabbits n = 2</td>
<td>3.2-3.75</td>
<td>10</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>HPLC</td>
<td>0.4 µg/ml</td>
<td>-</td>
<td>Non-compart mental</td>
<td>AUC (ng.min/ml) 145.2 (calculated) CL_{tot} (ml/min/kg) 4.13 (calculated) Vd_{ss} (l/kg) 1.41 (calculated)</td>
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<tr>
<td>Parasram-puria et al63</td>
<td>Sprague Dawley rats n = 4</td>
<td>0.250 ± 30</td>
<td>20</td>
<td>Bolus</td>
<td>0-300 mins</td>
<td>HPLC</td>
<td>25 ng/ml</td>
<td>-</td>
<td>Non-compart mental</td>
<td>AUC (ng.min/ml) 193000 (± 105000) CL_{tot} (ml/min/kg) 62.5 (± 27.2) Vd_{ss} (l/kg) 4.2 (± 2.06)</td>
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<tr>
<td>Cagnardi et al64</td>
<td>Cats n = 12 6-8 mth old</td>
<td>2.5-4</td>
<td>2</td>
<td>Bolus</td>
<td>0-10 hrs</td>
<td>HPLC</td>
<td>0.05 µg/ml</td>
<td>-</td>
<td>Non-compart mental</td>
<td>AUC (ng.min/ml) 13.72 (± 5.7) CL_{tot} (ml/min/kg) 1.88 (± 0.37) Vd_{ss} (l/kg) -</td>
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<tr>
<td>Zonca et al64</td>
<td>Horse n = 5 3-8 yr</td>
<td>402-488</td>
<td>2.5</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>HPLC</td>
<td>0.02 µg/ml</td>
<td>-</td>
<td>Non-compart mental</td>
<td>AUC (ng.min/ml) 10.89 (± 0.85) CL_{tot} (ml/min/kg) 0.63 (± 0.133) Vd_{ss} (l/kg) -</td>
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</table>
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
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<tbody>
<tr>
<td>Cagnardi et al(^64)</td>
<td>Cat</td>
<td>Ultrafiltration</td>
<td>-</td>
<td>HPLC</td>
<td>15.59 ± 0.59</td>
</tr>
<tr>
<td>Zonca et al(^64)</td>
<td>Horse</td>
<td>Ultrafiltration</td>
<td>-</td>
<td>HPLC</td>
<td>19.50 ± 1.62</td>
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</table>
### Dextropropoxyphene

**PK Studies:**

<table>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.min/ml)</td>
</tr>
<tr>
<td>Roberts et al&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Male Sprague Dawley rats n = 6</td>
<td>0.26-0.35</td>
<td>0.008 ± 0.03</td>
<td>Bolus</td>
<td>0-8 hr</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>124.6 ± 11.7</td>
</tr>
<tr>
<td>Giacomini et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Male mongrel dogs n = 4</td>
<td>14-27</td>
<td>1.8</td>
<td>Bolus</td>
<td>0-8 hr</td>
<td>-</td>
<td>GLC</td>
<td>-</td>
<td>-</td>
<td>19.9 (calculated)</td>
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</table>

**Plasma protein binding studies:**

<table>
<thead>
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<th>Method</th>
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<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Giacomini et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Dog</td>
<td>Equilibrium dialysis</td>
<td>1.2 µg/ml</td>
<td>GLC</td>
<td>0.129 (± 0.037)</td>
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Heroin

PK Studies:

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<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td></td>
<td>Dogs n = 9</td>
<td>13.8</td>
<td>0.1-0.5</td>
<td>Bolus</td>
<td>0-840 mins 0-24 hrs</td>
<td>Liquid scintillation 1-3 ng/ml</td>
<td>-</td>
<td>Comparative Fractionated</td>
<td>1213 (calculated)</td>
<td>214.5</td>
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Plasma protein binding studies:

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<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td>Garrett et al'87</td>
<td>Dog</td>
<td>Ultrafiltration</td>
<td>9-5500 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.40 ± 0.06</td>
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Blood–to–plasma ratio studies:

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<th>Assay</th>
<th>B:P ratio</th>
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<tbody>
<tr>
<td>Garrett et al</td>
<td>Dog</td>
<td>In-vitro</td>
<td>-</td>
<td>Liquid scintillation</td>
<td>0.8 ± 0.1</td>
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# Partial Agonist

## Nalbuphine

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<th>Study</th>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al(^1)</td>
<td>New Zealand white rabbits n = 9 18 mths old</td>
<td>3.1 (±0.4)</td>
<td>9.07</td>
<td>Bolus</td>
<td>0-240 mins</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
</tr>
<tr>
<td>Aungst et al(^2)</td>
<td>Sprague Dawley rats n = 6</td>
<td>-</td>
<td>0.5</td>
<td>Bolus</td>
<td>0-5 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
</tr>
<tr>
<td>Beagle dogs N = 6</td>
<td>-</td>
<td>1</td>
<td>Bolus</td>
<td>0-7 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
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<tr>
<td>Groene n-daal et al(^3)</td>
<td>Wistar rats n = 8</td>
<td>0.25-0.35</td>
<td>10</td>
<td>Bolus</td>
<td>0-4 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>25 ng/ml</td>
<td>-</td>
<td>Compartmental</td>
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**Butorphanol**

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621
<table>
<thead>
<tr>
<th>Study</th>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>Groenen -daal et al³</td>
<td>Wistar rats n = 6</td>
<td>0.25-0.35</td>
<td>10</td>
<td>Bolus</td>
<td>0-4 hrs</td>
<td>Plasma, Urine</td>
<td>Plasma</td>
<td>50 ng/ml</td>
<td>Compartmental</td>
<td>- 76 (SE± 11)</td>
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<tr>
<td>Vaughan et al⁴</td>
<td>Hound dogs n = 3</td>
<td>23 (± 1.73)</td>
<td>0.05</td>
<td>Bolus</td>
<td>0-720 mins</td>
<td>Plasma, Urine</td>
<td>Plasma</td>
<td>0.23-8.8 ng/ml</td>
<td>Non-compartmental</td>
<td>- 340.04 (± 82.92)</td>
</tr>
<tr>
<td>Carroll et al⁵</td>
<td>Llamas n = 6</td>
<td>103 (± 16)</td>
<td>0.1</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Plasma, Urine</td>
<td>Plasma</td>
<td>6.7 ng/ml LOD-0.4 ng/ml</td>
<td>Compartmental</td>
<td>- 2181 (± 714)</td>
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<tr>
<td>Sellon et al⁶</td>
<td>Horses n = 7</td>
<td>-</td>
<td>0.1-0.13</td>
<td>Bolus</td>
<td>0-36 hrs</td>
<td>Plasma, Urine</td>
<td>Plasma</td>
<td>7.8 ng/ml</td>
<td>Non-compartmental</td>
<td>- 6300 (± 9.48)</td>
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<tr>
<td>Court et al⁷</td>
<td>Healthy Jersey cows n = 6</td>
<td>314 ± 39</td>
<td>0.25</td>
<td>Bolus</td>
<td>0-240 mins</td>
<td>Plasma, Urine</td>
<td>Plasma</td>
<td>0.0125 ng/ml</td>
<td>Compartmental</td>
<td>- 7567 (± 1554)</td>
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### Buprenorphine

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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>PK Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>Garrett et al⁸</td>
<td>Mongrel dogs n = 6</td>
<td>22.1</td>
<td>0.7</td>
<td>Bolus</td>
<td>0-800 mins</td>
<td>HPLC</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
<td>AUC (ng.min/ml)</td>
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<td>16.8 (SE± 0.99)</td>
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<td>CL_{tot} (ml/min/kg)</td>
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<td>26.5 (SE± 0.003)</td>
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<td>V_{dss} (l/kg)</td>
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<td>0.0018-0.045</td>
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<td>0.35% dose excreted</td>
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<td>(SE ± 0.08)</td>
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<td>16.8 (SE± 0.99)</td>
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<tr>
<td>Gopal et al⁹</td>
<td>Male Sprague Dawley rats n = 6</td>
<td>0.18-0.2</td>
<td>1</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>GC-MS</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>23520 (± 7140)</td>
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<td>45 (±10.2)</td>
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<td>8.37 (±3.38)</td>
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<td>69060 (± 14700)</td>
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<td>45 (±9.8)</td>
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<td>8.72 (±3.92)</td>
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<td>133200 (± 7860)</td>
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<td>75.3 (± 4.5)</td>
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<td>14.5 (± 1.28)</td>
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<td>310380 (± 74700)</td>
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<td>101.6 (± 24.6)</td>
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<td>18.2 (±4.49)</td>
</tr>
<tr>
<td>Taylor et al¹⁰</td>
<td>Domestic cats n = 6 2-11 yrs</td>
<td>2.9-4.4</td>
<td>0.01</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>RIA LOD</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>16.7 (± 6.2)</td>
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<td>5 ng/ml</td>
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<td>7.1 (± 3.2)</td>
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<td>Median = 9.30</td>
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<td>(3.63-10.32)</td>
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<tr>
<td>Roberts et al¹¹</td>
<td>Cats n = 6 1-3 yrs</td>
<td>4.1-6.6</td>
<td>0.018</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>RIA LOD</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>Median = 4.81</td>
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<td></td>
<td>0.1 ng/ml</td>
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<td>(2.54-4.81)</td>
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</table>
Urinary excretion study (Garett et al\(^8\)):
Mongrel dogs, n = 6
Urine was collected at intervals 15-60 min to 24 hrs

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garrett et al(^{13})</td>
<td>Dog</td>
<td>Ultracentrifugation</td>
<td>10 µg/ml</td>
<td>HPLC</td>
<td>0.95 (± 0.03)</td>
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<tr>
<td>Mistry et al(^{14})</td>
<td>Sprague Dawley rats</td>
<td>Equilibrium dialysis</td>
<td>0.5-500 ng/ml</td>
<td>Liquid scintillation</td>
<td>(f_u = 0.07 \pm 0.001)</td>
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</tbody>
</table>

Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garrett et al(^{13})</td>
<td>Dog</td>
<td>(In-vitro)</td>
<td>0.2-1.4 µg</td>
<td>HPLC</td>
<td>0.80</td>
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<tr>
<td>Mistry et al(^{14})</td>
<td>Sprague Dawley rats</td>
<td>(In-vitro)</td>
<td>0.5-500 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.60 (± 0.05)</td>
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</table>
### Pentazocine

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
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<tr>
<td>Suzuki et al(^{15})</td>
<td>Female Wistar rats n = 3/grp</td>
<td>0.18-0.2</td>
<td>2.5</td>
<td>0.5</td>
<td>5.0</td>
<td>10.0</td>
<td>Bolus</td>
<td>0-300 mins</td>
<td>HPLC LOD 5 ng/ml</td>
<td>-</td>
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<td>Compartmental</td>
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<tr>
<td>Pittman et al(^{16})</td>
<td>Adult female rhesus monkeys n = 1/grp</td>
<td>3.8-4.8</td>
<td>0.544</td>
<td>0.054</td>
<td>0.05</td>
<td>0.05</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
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<td>Compartmental</td>
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<tr>
<td>Ichimura et al(^{17})</td>
<td>Rabbits n = 6</td>
<td>2.8-3.5</td>
<td>0.5-5</td>
<td>0.5-5</td>
<td>0.5-5</td>
<td>0.5-5</td>
<td>Bolus followed by</td>
<td>0-6 hrs</td>
<td>GLC LOD 5 ng/ml</td>
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</tbody>
</table>

**PK endpoints:**
- **AUC (ng.min/ml):**
  - Suzuki et al\(^{15}\): 35160, 53640, 91620
  - Pittman et al\(^{16}\): 48.2 (calculated)
  - Ichimura et al\(^{17}\): 40.64 (calculated)

- **CL\(_{tot}\) (ml/min/kg):**
  - Suzuki et al\(^{15}\): 71.1(± 10), 93.2(± 12.3), 109.2(± 9.1)
  - Pittman et al\(^{16}\): 48.2 (calculated)
  - Ichimura et al\(^{17}\): 40.64 (calculated)

- **V\(_{dss}\) (l/kg):**
  - Suzuki et al\(^{15}\): 71.1(± 10), 93.2(± 12.3), 109.2(± 9.1)
  - Pittman et al\(^{16}\): 48.2 (calculated)
  - Ichimura et al\(^{17}\): 40.64 (calculated)

- **CL\(_{ren}\) (ml/min/kg):**
  - Suzuki et al\(^{15}\): 71.1(± 10), 93.2(± 12.3), 109.2(± 9.1)
  - Pittman et al\(^{16}\): 48.2 (calculated)
  - Ichimura et al\(^{17}\): 40.64 (calculated)
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ichimura et al(^{17})</td>
<td>Rabbit</td>
<td>Equilibrium dialysis (37°C / 15 hr)</td>
<td>20 µg/ml</td>
<td>GLC</td>
<td>60% (± 2)</td>
</tr>
<tr>
<td>Tobin et al(^{18})</td>
<td>Horse</td>
<td>Equilibrium dialysis (37°C / 15 hr)</td>
<td>10-1000 ng/ml</td>
<td>GC</td>
<td>80%</td>
</tr>
</tbody>
</table>

### Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
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<tbody>
<tr>
<td>Ichimura et al(^{17})</td>
<td>Rabbit</td>
<td>Estimated</td>
<td>20 µg/ml</td>
<td>-</td>
<td>1.55 (± 0.06)</td>
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</table>
Dezocine

<table>
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<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Sisenwine et al(^{19})</td>
<td>Rhesus Monkeys n = 3</td>
<td>7.7 ± 0.2</td>
<td>1 Bolus</td>
<td>0-12 hrs</td>
<td>0-48 hrs</td>
<td>GLC</td>
<td>LOD 4 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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<tr>
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<td>Beagle dogs n = 3</td>
<td>12.1 ± 2.2</td>
<td>1 Bolus</td>
<td>0-12 hrs</td>
<td>0-48 hrs</td>
<td>GLC</td>
<td>LOD 4 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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</table>

Urinary excretion study: (Sisenwine et al.)

Urine was collected for 0-6, 6-12, 12-24, 24-48 hrs.
Monkeys: % dose excreted as dezocine: 2.1 ± 0.5
Dogs: % dose excreted as dezocine: 0.6 ± 0.2
## Antagonist

### Naltrexone

<table>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Reuning et al(^{20})</td>
<td>Female rhesus monkeys n = 6</td>
<td>4.5-6.2</td>
<td>10</td>
<td>Bolus</td>
<td>0-2880 mins</td>
<td>GC</td>
<td>Sensitivity 0.3ng/ml</td>
<td>-</td>
<td>Compart mental</td>
<td>Cummulative</td>
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<tr>
<td>Pace et al(^{21})</td>
<td>Mongrel dogs n = 5</td>
<td>10</td>
<td>5</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>RIA</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>-</td>
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<tr>
<td>Reuning et al(^{22})</td>
<td>Foxhound dogs n = 2</td>
<td>20</td>
<td>0.72</td>
<td>Bolus</td>
<td>0-400 mins</td>
<td>MS</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative</td>
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<tr>
<td>Monkeys n = 6</td>
<td></td>
<td>5.15</td>
<td>10</td>
<td>Bolus</td>
<td>0-400 mins</td>
<td>MS</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>Cumulative</td>
</tr>
<tr>
<td>Garrett et al(^{23})</td>
<td>Mongrel Dogs n = 5</td>
<td>14-26</td>
<td>0.45 4.52</td>
<td>Bolus</td>
<td>0-720 mins</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
<td>Fractionated</td>
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</table>
Urinary excretion studies:

Monkeys (Reuning et al\textsuperscript{20}): Urine was collected at time points 0-30, 30-60, 60-90, 90-120, 120-210, 210-330, 330-450, 450-510, 510-1440 and 1440-2280 min after IV dose.

Analysis: GC
% dose excreted unchanged = 2.26% (±1.37)

Dogs: Garrett et al\textsuperscript{23} studied urinary excretion studies in dogs. Urine was collected 15, 30, 45, 60, 90, 120, 180 min and then every 60 min upto 720 min, then every 12 h for upto 6-15 days. Renal clearance is estimated from the slope of du/dt vs t\textsubscript{mid} plot.

% dose excreted in urine = 7 ± 1%

Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range (ng/ml)</th>
<th>Assay</th>
<th>Protein binding (%)</th>
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<tbody>
<tr>
<td>Ludden et al\textsuperscript{25}</td>
<td>Monkey</td>
<td>Equilibrium dialysis</td>
<td>0.108</td>
<td>Liquid scintillation</td>
<td>18.9 ± 2.49</td>
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<td>7.73</td>
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<td>21.3 ± 2.86</td>
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<td>527</td>
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<td>20.7 ± 0.23</td>
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<td>Guinea pig</td>
<td>Equilibrium dialysis</td>
<td>0.104</td>
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<td>20.4 ± 2.78</td>
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<td>7.50</td>
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<td>20.9 ± 2.43</td>
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<td>512</td>
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<td>21.9 ± 4.46</td>
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<td>Rat</td>
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<td></td>
<td>0.0995</td>
<td>Liquid scintillation</td>
<td>19.8 ± 2.3</td>
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<td>7.80</td>
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<td>19.9 ± 1.35</td>
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<td>514</td>
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<td>19.4 ± 1.82</td>
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<tr>
<td>Mouse</td>
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<td></td>
<td>0.104</td>
<td>Liquid scintillation</td>
<td>23.1 ± 1.56</td>
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**Binding in different species:**

<table>
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<th>n</th>
<th>Mean conc. In plasma ng/ml</th>
<th>% Bound</th>
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<tbody>
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<td>Humans</td>
<td>3</td>
<td>13.5</td>
<td>20.7 ± 0.47</td>
</tr>
<tr>
<td>Monkey</td>
<td>3</td>
<td>7.73</td>
<td>21.3 ± 2.86</td>
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<tr>
<td>Dogs</td>
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<tr>
<td>Mongrel</td>
<td>2</td>
<td>13.8</td>
<td>26.2</td>
</tr>
<tr>
<td>Beagles</td>
<td>14</td>
<td>13.3</td>
<td>26.8 ± 2.12</td>
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<tr>
<td>Foxhounds</td>
<td>2</td>
<td>12.7</td>
<td>20.2</td>
</tr>
<tr>
<td>Guinea pigs</td>
<td>6</td>
<td>7.50</td>
<td>20.9 ± 2.43</td>
</tr>
<tr>
<td>Rat</td>
<td>6</td>
<td>7.80</td>
<td>19.9 ± 1.35</td>
</tr>
<tr>
<td>Mouse</td>
<td>3</td>
<td>7.80</td>
<td>20.9 ± 2.25</td>
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</tbody>
</table>

**Blood –to –plasma ratio studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derendorf et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Dog</td>
<td>In-vitro</td>
<td>10-3500 ng/ml</td>
<td>HPLC</td>
<td>1.21 ± 0.08</td>
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</table>
### Naloxone

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Ngai et al</td>
<td>Male Sprague Dawley rats</td>
<td>0.25-0.30</td>
<td>4.52</td>
<td>Bolus</td>
<td>1-4 hrs</td>
<td>-</td>
<td>RIA</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Pace et al</td>
<td>Mongrel dogs n = 5</td>
<td>10</td>
<td>5</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>-</td>
<td>RIA</td>
<td>-</td>
<td>Compart mental</td>
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<tr>
<td>Veng-Pedersen</td>
<td>Beagle dogs n = 8</td>
<td>11.7-13.4</td>
<td>0.048 /kg</td>
<td>Infusion</td>
<td>0-420 mins</td>
<td>-</td>
<td>RIA</td>
<td>LOQ in linear range</td>
<td>Non-compartmental</td>
<td></td>
</tr>
<tr>
<td>Garrett et al</td>
<td>Mongrel dogs n = 6</td>
<td>21.3</td>
<td>0.47-4.7</td>
<td>Bolus</td>
<td>0-2160 mins</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>Non-compartmental</td>
<td></td>
</tr>
</tbody>
</table>

**Urinary excretion study:** (Garrett et al)

Urine was collected at 15, 30, 45, 60, 75, 90, 120, 180 min, then every 60 min upto 720 min and then every 12h for upto 4 days.
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range (ng/ml)</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derendorf et al(^{26})</td>
<td>Dog</td>
<td>Ultracentrifugation</td>
<td>10-3500 ng/ml</td>
<td>HPLC</td>
<td>30.1% ± 5.1</td>
</tr>
<tr>
<td>Mistry et al(^{14})</td>
<td>Sprague Dawley rats</td>
<td>Equilibrium dialysis</td>
<td>0.5-500 ng/ml</td>
<td>Liquid scintillation</td>
<td>(f_u = 0.62 (± 0.07))</td>
</tr>
</tbody>
</table>

### Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>B:P ratio</th>
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</thead>
<tbody>
<tr>
<td>Derendorf et al(^{26})</td>
<td>Dog</td>
<td>In-vitro</td>
<td>10-3500 ng/ml</td>
<td>HPLC</td>
<td>1.49 (± 0.25)</td>
</tr>
<tr>
<td>Mistry et al(^{14})</td>
<td>Sprague Dawley rats</td>
<td>In-vitro</td>
<td>0.5-500 ng/ml</td>
<td>Liquid scintillation</td>
<td>0.60 (± 0.05)</td>
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</table>

### Nalmefene

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate (mg/hr)</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ (ng/ml)</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venge-Pedersen et al(^{28})</td>
<td>Beagle Dogs (n = 8)</td>
<td>11.7-13.4</td>
<td>0.012</td>
<td>Infusion</td>
<td>0-420 mins</td>
<td>-</td>
<td>RIA</td>
<td>0.0625-2.0</td>
<td>Non-compartmental</td>
<td>-</td>
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<tr>
<td>Study</td>
<td>Animal</td>
<td>BW (kg)</td>
<td>Dose (mg/kg)</td>
<td>Rate</td>
<td>Sampling schedule</td>
<td>Assay</td>
<td>LOQ</td>
<td>PK Analysis</td>
<td>Urine Collection method</td>
<td>PK endpoints</td>
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<tr>
<td>Murthy et al\textsuperscript{30}</td>
<td>Sprague Dawley rats (n = 4)</td>
<td>0.175 - 0.200</td>
<td>4.55</td>
<td>Bolus</td>
<td>0-300 mins</td>
<td>-</td>
<td>LC-MS</td>
<td>1 ng/ml</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Boscan et al\textsuperscript{31}</td>
<td>Horses (n = 4) 9 ± 4 yrs</td>
<td>-</td>
<td>1</td>
<td>Bolus</td>
<td>0-240 mins</td>
<td>-</td>
<td>LC-MS</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
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</table>

**Methylnaltrexone**
References

Appendix II (b)

Animal PK Study Summaries for β-ARLs

Xamoterol

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Plasma</td>
<td>Plasma</td>
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</tr>
<tr>
<td>Marten et al¹</td>
<td>Beagle dogs</td>
<td>14.9</td>
<td>1</td>
<td></td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Liquid</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>n = 3</td>
<td>(13.4-16.1)</td>
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<td></td>
<td></td>
<td>scintillation</td>
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</tbody>
</table>

Notes:
- LOQ: Limit of Quantification
- PK Analysis: Plasma and/or Urine
- PK endpoints: AUC (ng.min/ml), CL_{tot} (ml/min/kg), V_dss (l/kg), CL_{ren} (ml/min/kg)
### Propranolol

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Motheova et al²</td>
<td>Male Wistar rats n not mentioned</td>
<td>0.200 - 0.250</td>
<td>1 Bolus 0-96 hrs 0-96 hrs</td>
<td>Liquid scintillation</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Cumulative</td>
<td>-</td>
</tr>
<tr>
<td>Belpaire et al³</td>
<td>Male Wistar rats 12 mths n = 8</td>
<td>0.467</td>
<td>1 Bolus 0-120 mins</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>compartmental</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Iwamoto et al⁴</td>
<td>Male wistar rats n = 4 36 weeks</td>
<td>0.547 - 0.613</td>
<td>1 Bolus - 0-2 hrs</td>
<td>Spectrofluorimetry</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Fractionated</td>
<td>-</td>
</tr>
<tr>
<td>Vu et al⁵</td>
<td>Dog n = 4 (assumed)</td>
<td>10 0.6 Infusion 0-300 mins 0-72 hrs</td>
<td>Fluorimetry</td>
<td>3-5 ng/ml</td>
<td>-</td>
<td>Compartmenatal</td>
<td>Cumulative</td>
<td>-</td>
<td>-</td>
<td>50.3 (±2.5)</td>
</tr>
<tr>
<td>Aramaki et al⁶</td>
<td>Horse n = 8 9-13 yrs</td>
<td>533 0.2 Bolus 0-12 hrs 0-12 hrs</td>
<td>HPLC-plasma LOD - 0.1 ng/ml</td>
<td>-</td>
<td>Compartmenatal</td>
<td>Cumulative</td>
<td>7914 (±1517)</td>
<td>22.85 (±4.43)</td>
<td>3.049 (±0.3087)</td>
<td>0.69 (calculated)</td>
</tr>
<tr>
<td>Study</td>
<td>Animal</td>
<td>Method</td>
<td>Concentration range</td>
<td>Assay</td>
<td>Protein binding</td>
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<tr>
<td>Belpaire et al(^3)</td>
<td>Rat n = 7</td>
<td>Equilibrium dialysis</td>
<td>50 ng/ml</td>
<td>HPLC</td>
<td>(f_u = 11.0% \pm 0.4)</td>
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<tr>
<td>Laethem et al(^9)</td>
<td>Dog n = 5</td>
<td>Equilibrium dialysis</td>
<td>50 ng/ml</td>
<td>HPLC</td>
<td>(f_u = 0.27 \pm 0.03)</td>
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<tr>
<td>Murai-Kushiya et al(^7)</td>
<td>Rabbit n = 8</td>
<td>Equilibrium dialysis</td>
<td></td>
<td></td>
<td>(f_u = 0.75 \pm 0.01)</td>
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<tr>
<td></td>
<td>Rats</td>
<td>Equilibrium dialysis</td>
<td>10 µg/ml</td>
<td>HPLC</td>
<td>Binding = 67.7%</td>
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<tr>
<td>Bai et al(^11)</td>
<td>Mongrel Dogs n = 7</td>
<td>Equilibrium dialysis</td>
<td>(In-vivo)</td>
<td>Liquid scintillation</td>
<td>(f_u = 14.8 \pm 9.2)%</td>
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<tr>
<td>Evans et al(^12)</td>
<td>Monkey n = 4</td>
<td>Equilibrium dialysis</td>
<td>(In-vivo)</td>
<td>Fluorimetry</td>
<td>Binding = 99.2% (98.9-99.5)</td>
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<tr>
<td></td>
<td>Dog</td>
<td></td>
<td></td>
<td></td>
<td>Binding = 96.6% (95.2-98.5)</td>
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<tr>
<td></td>
<td>Rat</td>
<td></td>
<td></td>
<td></td>
<td>Binding = 92.2% (91.9-92.6)</td>
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</table>

Plasma protein binding studies:
Blood –to –plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vu et al5</td>
<td>Dogs</td>
<td>In-vitro</td>
<td>Liquid scintillation</td>
<td>0.87 (SE ± 0.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>fu = 0.152 (SE ± 0.012)</td>
</tr>
<tr>
<td>Bai et al11</td>
<td>Mongrel Dogs</td>
<td>In-vivo</td>
<td>Liquid scintillation</td>
<td>0.82 (± 0.10)</td>
</tr>
<tr>
<td>Evans et al12</td>
<td>Monkey</td>
<td>In-vivo</td>
<td>Fluorimetry</td>
<td>0.85</td>
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<tr>
<td></td>
<td>Dog</td>
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<td>0.85</td>
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<tr>
<td></td>
<td>Rat</td>
<td></td>
<td></td>
<td>0.80</td>
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</tbody>
</table>

Urinary excretion study:

Dog:
Vu et al5: Urine collection: 0-72 hr

Bioavailability study:

Dog:
Vu et al5: Formulation : Capsule (40 mg)
Sampling: 0-300 mins
Analysis: Fluorimetry
F_{oral} = 0.077 (SE ± 0.014)
Sotalol

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td>AUC (ng.min/ml)</td>
</tr>
<tr>
<td>Carr et al\textsuperscript{13}</td>
<td>Male Sprague Dawley rats n =18</td>
<td>0.2-0.5</td>
<td>5</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td>S -224940 (± 23400)</td>
</tr>
<tr>
<td>Carr et al\textsuperscript{14}</td>
<td>Male Sprague Dawley rats n =6</td>
<td>0.357 (± 0.032)</td>
<td>5</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>0-6 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
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<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td>S -128580 (± 24360)</td>
</tr>
<tr>
<td>Carr et al\textsuperscript{15}</td>
<td>Male Sprague Dawley rats n =8</td>
<td>0.3-0.4</td>
<td>10</td>
<td>Bolus</td>
<td>-</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>-</td>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td>R -21.4 (± 4.3)</td>
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### Plasma protein binding studies:

<table>
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<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
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<tr>
<td>Carr et al(^{18})</td>
<td>Male Sprague Dawley rats n = 4</td>
<td>Ultrafiltration</td>
<td>250 ng/ml</td>
<td>HPLC</td>
<td>&lt; 5 %</td>
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<td>500 ng/ml</td>
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<tr>
<td>Schnelle et al(^{19})</td>
<td>Mongrel dogs</td>
<td>Ultrafiltration</td>
<td>0.3-1000 µg/ml</td>
<td>Spectrofluorimetry</td>
<td>0 %</td>
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</tbody>
</table>

### Blood–to–plasma ratio studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnelle et al(^{19})</td>
<td>Mongrel dogs</td>
<td>\textit{In-vitro} ((0.5\text{-}1000\ \mu g/ml))</td>
<td>Spectrofluorimetry</td>
<td>1.16 ± 0.21</td>
</tr>
</tbody>
</table>

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642
Urinary excretion study:

**Rat:**
Carr et al\(^{13}\): Urine collection: 0-24 hrs
Renal clearance $CL_{\text{ren}} = \frac{Ae(24)}{[\text{AUC}]_0}$ where $Ae^{24}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs

**Dog:**
Ishizaki et al\(^{17}\): Urine collection: 0-8 hr
Renal clearance $CL_{\text{ren}} = \frac{Ae(8)}{[\text{AUC}]_0}$ where $Ae^8$ is cumulative amount of drug excreted unchanged in urine upto 8 hrs

Atenolol

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
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<tr>
<td>McAins h et al(^{20})</td>
<td>Beagle Dog n= 6</td>
<td>15.5 (12-19)</td>
<td>12.9 Bolus 0-48 hrs 0-72 hrs Fluorescence spectroscopy LOD- 0.5 - 1.0 µg/ml</td>
<td>-</td>
<td>Compartmen tal</td>
<td>Cumulative</td>
<td>3015600 (calculated)</td>
<td>4.28 (calculated)</td>
<td>1.355 (calculated)</td>
<td>3.57 (calculated)</td>
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<tr>
<td>Mehvar et al(^{21})</td>
<td>Sprague Dawley rats n = 6</td>
<td>0.250 (assumed)</td>
<td>10 Bolus 0-12 hr 0-24 hr HPLC sensitivity 10 ng/ml</td>
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<td>Non-compartmental</td>
<td>Cumulative</td>
<td>3895</td>
<td>21.9</td>
<td>3.48 (calculated)</td>
<td>14.1</td>
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<td>Mehvar et al(^{22})</td>
<td>Sprague-Dawley rats n =10</td>
<td>0.293 ± 0.026</td>
<td>10 Bolus 0-12 hrs 0-24 hrs HPLC sensitivity 10 ng/ml</td>
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<td>Non-compartmental</td>
<td>Cumulative</td>
<td>S(-)- 217800</td>
<td>S(+) - 24.9</td>
<td>R(+) - 22.3</td>
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<tr>
<td>Study</td>
<td>Species</td>
<td>Formulation</td>
<td>Dosage</td>
<td>Sampling Time</td>
<td>Method</td>
<td>Analysis</td>
<td>$F_{oral}$</td>
<td>$f_{e}$ (%)</td>
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<td><strong>Urinary excretion study:</strong></td>
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<tr>
<td><strong>Rat:</strong></td>
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<tr>
<td>Mehvar et al(^{21})</td>
<td>Male Wistar rats</td>
<td>12 mths n = 11</td>
<td>0.503</td>
<td>0-3 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>33.4 (SE ± 1.8)</td>
</tr>
<tr>
<td>McAinsh et al(^{20})</td>
<td>Cats n = 9</td>
<td></td>
<td>2.895</td>
<td>0-12 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>range 10 - 2000 ng/ml</td>
<td>-</td>
<td>Non-compartmental</td>
<td>244560 (± 54600)</td>
</tr>
<tr>
<td><strong>Cat:</strong></td>
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<tr>
<td>Quinones et al(^{23})</td>
<td>Cats n = 9</td>
<td>capsules</td>
<td>3 mg/kg</td>
<td>0-12 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>324720 (± 81180)</td>
</tr>
<tr>
<td>Shin et al(^{24})</td>
<td>Rabbit n = 8</td>
<td></td>
<td>2.5</td>
<td>0-24 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>324720 (± 81180)</td>
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</tbody>
</table>

**Urinary excretion study:**

**Rat:**
Mehvar et al\(^{21}\): Urine collection: 0-24 hrs
Renal clearance $\text{CL}_{\text{ren}} = \frac{\text{Ae}(24)}{[\text{AUC}]}$\(^{24}\) where $\text{Ae}$ is cumulative amount of drug excreted unchanged in urine upto 24 hrs

**Dog:**
McAinsh et al\(^{20}\): Urine collection: 0-24, 24-48, 48-72 hrs

**Bioavailability study:**

**Rat:**
Belpaire et al\(^{3}\): Formulation: Not mentioned (5mg/kg), n= 22
Sampling: 0-8 hrs
Analysis: HPLC
$F_{oral} = 33.5$ (SE ± 1.7)

**Cat:**
Quinones et al\(^{23}\): Formulation: capsules (3 mg/kg), n= 9
Sampling: 0-12 hrs
Analysis: HPLC
$F_{oral} = 0.90$ (± 0.09)
# Metoprolol

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>Belpaire et al(^3)</td>
<td>Male Wistar rats 12 mths n = 7</td>
<td>0.542</td>
<td>2</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>Compartmental</td>
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<tr>
<td>Tanabe et al(^25)</td>
<td>Male Wistar rats n = 5</td>
<td>0.24-0.3</td>
<td>5</td>
<td>Infusion for 15 mins</td>
<td>0-150 mins</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>Compartmental</td>
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<tr>
<td>Murthy et al(^26)</td>
<td>Greyhound dogs n = 4</td>
<td>31 ± 2</td>
<td>0.51</td>
<td>Bolus</td>
<td>0-420 min</td>
<td>0-24 hrs</td>
<td>GC-MS</td>
<td>-</td>
<td>Non-compart mental</td>
</tr>
<tr>
<td>Borg et al(^27)</td>
<td>Cats n not mentioned</td>
<td>3.25</td>
<td>2.6</td>
<td>Bolus</td>
<td>0-240 mins</td>
<td>-</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>Non-compart mental</td>
</tr>
<tr>
<td>Beagles n = 3</td>
<td>12</td>
<td>0.4</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>-</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>Non-compart mental</td>
<td>-</td>
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### Plasma protein binding studies:

<table>
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<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Komura et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Wistar rats n = 12-14 weeks</td>
<td>Equilibrium dialysis</td>
<td>1.0 µg/ml</td>
<td>HPLC</td>
<td>8.3 %</td>
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<tr>
<td>Bortolotti et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>New Zealand Rabbits n = 6</td>
<td>Ultrafiltration</td>
<td>3.9 mg/l</td>
<td>HPLC</td>
<td>32 %</td>
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### Blood –to –plasma ratio studies:

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<th>Animal</th>
<th>Method</th>
<th>Assay</th>
<th>B:P ratio</th>
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</thead>
<tbody>
<tr>
<td>Bortolotti et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>New Zealand Rabbits n = 6</td>
<td>In-vivo</td>
<td>HPC</td>
<td>1.14 (0.52-1.64)</td>
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</table>
### PK Studies:

<table>
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<tr>
<th>Study</th>
<th>Species</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamimura et al(^3)</td>
<td>Male Sprague Dawley rats</td>
<td>0.170 - 0.240</td>
<td>10</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
<td>56.7</td>
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<tr>
<td></td>
<td>Male Beagle Dogs</td>
<td>2.3 - 5.6</td>
<td>10</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
<td>10.7</td>
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<tr>
<td></td>
<td>Male cynomolgus monkeys</td>
<td>0.02</td>
<td>10</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>HPLC plasma</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
<td>19.79</td>
</tr>
<tr>
<td></td>
<td>Male ICR mice (4-7 weeks)</td>
<td>0.02</td>
<td>10</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>HPLC plasma</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
<td>19.79</td>
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<tr>
<td></td>
<td></td>
<td>0.02</td>
<td>10</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>HPLC plasma</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
<td>19.79</td>
</tr>
</tbody>
</table>

### Assay:
- HPLC
- GC

### Cumulative:
- 17400
- 30600
- 102600

### PK endpoints:
- 46189
- 21.7
- 3.83
Bioavailability study:

Rat:
Kamimura et al\textsuperscript{30}: Formulation : Solution (10 mg/kg, 30 mg/kg, 100 mg/kg) , n= 3/dose group
Sampling: 0-10 hrs
Analysis: HPLC
$F_{oral} = 22.1$ (10 mg/kg)
$F_{oral} = 31.4$ (10 mg/kg)
$F_{oral} = 26.8$ (10 mg/kg)

Monkeys:
Kamimura et al\textsuperscript{30}: Formulation : Solution (10 mg/kg, 30 mg/kg), n= 3/dose group
Sampling: 0-10 hrs
Analysis: HPLC
$F_{oral} = 65.9$ (10 mg/kg)
$F_{oral} = 57.4$ (30 mg/kg)

Dog:
Kamimura et al\textsuperscript{30}: Formulation : capsules (3 mg/kg, n= 4, 10 mg/kg, n=6, 30 mg/kg, n =3)
Sampling: 0-10 hrs
Analysis: HPLC
$F_{oral} = 65.9$ (10 mg/kg)
$F_{oral} = 57.4$ (30 mg/kg)

Mice:
Suzuki et al\textsuperscript{31}: Formulation : not mentioned (10 mg/kg)
Sampling: 0-8 hrs
Analysis: HPLC
$F_{oral} = 38.7\%$
**Timolol**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>Thalikonda et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Sprague Dawley rats n = 5</td>
<td>0.275</td>
<td>0.2</td>
<td>Bolus</td>
<td>0-15 hrs</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.min/ml)</td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt; (ml/min/kg)</td>
<td>Vdss (l/kg)</td>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
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Plasma protein binding studies:

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<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Lang et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Rat</td>
<td>In-vitro Equilibrium dialysis</td>
<td>3.3-66 µg/ml</td>
<td>Liquid scintillation</td>
<td>2-5%</td>
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Nafetolol (K 5407)

**PK Studies:**

<table>
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<th>Study</th>
<th>Animal</th>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.min/ml)</td>
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<tr>
<td>Goldani ga et al(^{35})</td>
<td>Beagle Dog n = 2</td>
<td>11</td>
<td>0.5</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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### Carteolol

**PK Studies:**

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<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Kudo et al\cite{36}</td>
<td>Rats</td>
<td>0.275</td>
<td>30</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>Non-compartmental</td>
<td>288161 (Calculated)</td>
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</table>

**PK Parameters:**
- **AUC:** Area Under the Curve (ng.min/ml)
- **Cl\text{tot}:** Total Clearance (ml/min/kg)
- **Vd\text{ss}:** Volume of Distribution at Steady State (l/kg)
- **Cl\text{ren}:** Renal Clearance (ml/min/kg)
Acebutolol

**PK Studies:**

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<tbody>
<tr>
<td>Piquette-Miller et al(^{37})</td>
<td>Sprague-Dawley rat n = 4</td>
<td>0.250 (assumed)</td>
<td>10</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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</tbody>
</table>

**PK endpoints**

- **AUC** (ng.min/ml): R - 80400 (± 4668), S - 85200 (± 3870)
- **CL\(_{tot}\)** (ml/min/kg): R - 61.9 (± 3.5), S - 58.5 (± 3.5)
- **Vd\(_{ss}\)** (l/kg): 5.82 (calculated)
- **CL\(_{ren}\)** (ml/min/kg): R - 14.6 (± 2.2), S - 15.7 (± 2.2)

**Fe**: 23.5% (± 3.1) for R, 26.9% (± 3.7) for S.
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piquette-Miller et al.</td>
<td>Sprague Dawley rats n = 4 pooled plasma</td>
<td>Equilibrium dialysis</td>
<td>100 ng/ml</td>
<td>HPLC</td>
<td>R-AC 8.0 ± 0.8 %</td>
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<td>S-AC 7.0 ± 1.2 %</td>
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<td>Avg – 7.5%</td>
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<td></td>
<td>500 ng/ml</td>
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<td>R-AC 10.0 ± 4.6 %</td>
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<td></td>
<td>S-AC 12.0 ± 5.0 %</td>
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<td>Avg – 11%</td>
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### PK Studies:

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<tr>
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<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lennernas et al</td>
<td>Sprague Dawley rats n = 5</td>
<td>0.22-0.27</td>
<td>0.3 µmol/kg</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
<td>Starved- fe = 47% ± 3.1</td>
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<td></td>
<td></td>
<td></td>
<td>0-72 hrs</td>
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<td></td>
<td>Unstarved- fe = 53% ± 3.4</td>
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<td>Starved- fe = 47% ± 3.9</td>
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<td></td>
<td>Unstarved- fe = 53% ± 10.1</td>
</tr>
<tr>
<td>Lennernas et al</td>
<td>Spargue Dawley rats n = 6/group</td>
<td>0.2-0.27</td>
<td>0.3 µmol/kg</td>
<td>0-600 mins</td>
<td></td>
<td>LC-Liquid scintillation</td>
<td>-</td>
<td>Non-compartmental</td>
<td></td>
<td>Starved-CL &lt; 51 (± 7.9)</td>
</tr>
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<td></td>
<td>Unstarved-CL &lt; 57 (± 6.3)</td>
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<td></td>
<td></td>
<td></td>
<td>Starved-CL &lt; 5.8 (± 1.5)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unstarved-CL &lt; 5.9 (± 0.6)</td>
</tr>
</tbody>
</table>

**Pafenolol**
<table>
<thead>
<tr>
<th></th>
<th>3.0 µmol/kg</th>
<th></th>
<th>Starved-56 (± 8.8) Unstarved 46 (± 3.9)</th>
<th>Starved-5.5 (± 1.8) Unstarved 5.9 (± 1.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstarved</td>
<td></td>
<td></td>
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</table>
### Bisoprolol

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>Urine Collection method</th>
<th>PK Analysis</th>
<th>PK endpoints</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buhring et al</td>
<td>Monkey</td>
<td>3-6</td>
<td>1</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>-</td>
<td>-</td>
<td>AUC (ng.min/ml)</td>
<td>NK</td>
<td>90749</td>
<td>11.05 (calculated)</td>
</tr>
<tr>
<td>Horikiri et al</td>
<td>Beagle dogs</td>
<td>13-18</td>
<td>0.16</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-48 hrs</td>
<td>HPL C</td>
<td>Plasma</td>
<td>-</td>
<td>R – 224 (± 23)</td>
<td></td>
</tr>
<tr>
<td>Tahara et al</td>
<td>Rats</td>
<td>n = 6 -9</td>
<td>1.8</td>
<td>Infusion</td>
<td>0-150 mins</td>
<td>-</td>
<td>HPL C</td>
<td>Plasma</td>
<td>Cumulative</td>
<td>S – 326 (± 5)</td>
<td></td>
</tr>
<tr>
<td>Beddies et al</td>
<td>Beagle dogs</td>
<td>10.4</td>
<td>1</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>HPL C-MS</td>
<td>Plasma</td>
<td>-</td>
<td>R – 6.05 (± 0.65)</td>
<td></td>
</tr>
</tbody>
</table>

**Urine Collection method:**

- Non-compart mental

**PK Analysis:**

- Non-compart mental

**PK endpoints:**

- Calculated

**Notes:**

- fe = 35.8% ± 6.7
- S –1.72 ± 0.21
- fe = 28.1% ± 7.0
- S –1.63 (± 0.12)
- fe = 35.8% ± 6.7
- S –1.72 (± 0.21)
- fe = 28.1% ± 7.0
**Plasma protein binding studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buhring et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Rat</td>
<td>Ultrafiltration</td>
<td>0.01-5 µg/ml</td>
<td>Liquid scintillation</td>
<td>13-16%</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td></td>
<td></td>
<td></td>
<td>23-26%</td>
</tr>
<tr>
<td></td>
<td>Monkey</td>
<td></td>
<td></td>
<td></td>
<td>25-26%</td>
</tr>
<tr>
<td>Carr et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Beagle dog #1</td>
<td>In-vitro</td>
<td>200 ng/ml</td>
<td>HPLC</td>
<td>S – 31.6%</td>
</tr>
<tr>
<td></td>
<td>Beagle dog #2</td>
<td>Ex-vivo</td>
<td></td>
<td></td>
<td>R – 29.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In-vitro</td>
<td></td>
<td></td>
<td>S – 40.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ex-vivo</td>
<td></td>
<td></td>
<td>R – 38.2%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>S – 29.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R – 29.9%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>S – 26.0%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>R – 23.9%</td>
</tr>
</tbody>
</table>

**Bioavailability study:**

Dog:
Beddies et al<sup>43</sup>: Formulation: Capsules (1 mg/kg)
Sampling: 0-24 hrs
Analysis: HPLC-MS
$F_{oral} = 91.4\%$
### Pindolol

#### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Komori et al(^{45})</td>
<td>Male Wistar rats (n = 8)</td>
<td>0.20-0.25</td>
<td>3</td>
<td>Bolus</td>
<td>0-60 min</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compart mental</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Komori et al(^{45})</td>
<td>Male Wistar rats (n = 8)</td>
<td>-</td>
<td>6 (\mu M)</td>
<td>HPLC</td>
<td>47.2 ± 4.3%</td>
</tr>
<tr>
<td>Murai-Kushiya et al(^{16})</td>
<td>Rats</td>
<td>Equilibrium dialysis</td>
<td>10 (\mu g/ml)</td>
<td>HPLC</td>
<td>Binding = 33.3%</td>
</tr>
</tbody>
</table>
Celiprolol

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipka et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Dog</td>
<td>10</td>
<td>5</td>
<td>Bolus</td>
<td>0-360 mins</td>
<td>-</td>
<td>-</td>
<td>Plasma</td>
<td>-</td>
<td>AUC (ng.min/ml)</td>
</tr>
<tr>
<td></td>
<td>n = 4</td>
<td>(assumed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(calculated)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt; (ml/min/kg)</td>
<td>46.2 (calculated)</td>
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<td></td>
<td></td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt; (l/kg)</td>
<td>7.01 (calculated)</td>
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<td></td>
<td></td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt; (ml/min/kg)</td>
<td>-</td>
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</table>

Labetalol

PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeleswaran et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Sheep</td>
<td>74.9 (± 4.9)</td>
<td>1.34</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Non-compart -mental</td>
</tr>
<tr>
<td></td>
<td>5-11 yrs</td>
<td>n = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(calculated)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>CL&lt;sub&gt;tot&lt;/sub&gt; (ml/min/kg)</td>
<td>29.00 (± 2.67)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt; (l/kg)</td>
<td>6.91 (± 1.13)</td>
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<td></td>
<td></td>
<td></td>
<td>CL&lt;sub&gt;ren&lt;/sub&gt; (ml/min/kg)</td>
<td>0.47 (calculated)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>fe = 1.61% (± 0.38)</td>
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</tr>
</tbody>
</table>
### Carvedilol

#### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenault et al(^{48})</td>
<td>Hound dogs (n = 8) 2-5 yrs</td>
<td>20-25</td>
<td>0.175</td>
<td>Bolus</td>
<td>0-1440 mins</td>
<td>HPLC</td>
<td>2.0-800 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>32141 (3994 - 70878) 5.6 (2.5-44) 2.0 (0.7-4.3) -</td>
</tr>
<tr>
<td>Sawangkoon et al(^{49})</td>
<td>Beagle Dog (n = 2) 10 (assumed)</td>
<td>10</td>
<td>0.16</td>
<td>Bolus</td>
<td>0-360 mins</td>
<td>HPLC</td>
<td>1.0 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>26.27 2.59 (calculated)</td>
</tr>
<tr>
<td>Bertera et al(^{50})</td>
<td>Male Wistar rats (n = 12) 0.22-0.25</td>
<td>1</td>
<td>0.22-0.25</td>
<td>Bolus</td>
<td>0-180 mins</td>
<td>HPLC</td>
<td>2.0 ng/ml</td>
<td>Compartmental</td>
<td>-</td>
<td>42180 (± 5220) 114.8 (± 19.6) 8.26 (± 1.30) -</td>
</tr>
</tbody>
</table>

#### Bioavailability study:

Dog:
Arsenault et al\(^{48}\), Formulation: Small meatball of canned dog food (1.5 mg/kg)
Sampling: 0-1440 mins
Analysis: HPLC
\(F_{oral} = 2.1\% (0.4-54)\)
### PK Studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>McAish et al51</td>
<td>Beagle dog</td>
<td>10 (assumed)</td>
<td>15</td>
<td>Bolus</td>
<td>0-48 hrs</td>
<td>0-48 hrs</td>
<td>HPLC</td>
<td>Plasma, Urine</td>
<td>Non-compartmental Cumulative</td>
<td>AUC (ng.min/ml) 293.67 (± 20) CL\text{\textsubscript{tot}} (ml/min/kg) 1.95 (± 3.24) Vd\textsubscript{ss} (l/kg) 4.7 (calculated) CL\text{\textsubscript{ren}} (ml/min/kg) 0.46 fe = 23.8 % ± 4.6</td>
</tr>
</tbody>
</table>

### Bioavailability study:

Dog:  
McAish et al51: Formulation : Solution (15 mg/kg)  
Sampling: 0-48 hrs  
Analysis: HPLC  
F\text{\textsubscript{oral}} = 0.41 (SE ± 0.05)
**Landiolol**

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsunekawa et al(^{52})</td>
<td>Male beagle dogs n = 3</td>
<td>10 (assumed)</td>
<td>0.3</td>
<td>Bolus Infusion 0-60 mins</td>
<td>-</td>
<td>HPLC -</td>
<td>-</td>
<td>0-24 hrs Cumulative</td>
<td>4400 (± 400)</td>
<td>69.1 (± 6.9)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
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<td></td>
</tr>
<tr>
<td>Tsunekawa et al(^{53})</td>
<td>Rat n = 4</td>
<td>0.250 (assumed)</td>
<td>1</td>
<td>Bolus Infusion 0-6 hrs</td>
<td>HPLC -</td>
<td>-</td>
<td>-</td>
<td>Cumulative</td>
<td>-</td>
<td>8.2</td>
</tr>
</tbody>
</table>

**Notes:**
- CL\(_{ren}\) = 1.98
- CL\(_{ren}\) = 0.48
- fe = 5.9%
- fe = 2.4%
- fe = 2.4%
- fe = 5.9%
### Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsunekawa et al54</td>
<td>Rats</td>
<td>Ultrafiltration</td>
<td>0.1, 1, 10, 50 µg/ml</td>
<td>HPLC</td>
<td>2.8± 2.4 % 5.3± 1.9 % 2.7± 2.6 % 4.1± 1.2 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean – 3.73%</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>Ultrafiltration</td>
<td>0.1, 1, 10, 50 µg/ml</td>
<td>HPLC</td>
<td>21.3± 3.7 % 19.7 ± 3.4 % 14.7 ± 4.3 % 16.3± 1.7 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean – 18 %</td>
</tr>
</tbody>
</table>
Esmolol

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quon et al&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Mongrel dogs n = 5</td>
<td>20 (assumed)</td>
<td>0.025 mg/kg/min</td>
<td>Infusion</td>
<td>0-60 mins</td>
<td>GLC</td>
<td>25 ng/ml</td>
<td>Non-compartmental</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.050 mg/kg/min</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.100 mg/kg/min</td>
<td></td>
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</table>
Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyamoto et al(^5)</td>
<td>Rats</td>
<td>Ultrafiltration</td>
<td>0.0, 0.05, 0.2, 1, 5, 20 µg/ml</td>
<td>HPLC</td>
<td>22.3 ± 2.8 % 22.4 ± 6.0 % 23.8 ± 1.1 % 23.2 ± 1.6 % 23.9 ± 0.5 % 22.0 ± 1.6 % mean= 22.9</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td></td>
<td>0.0, 0.05, 0.2, 1, 5, 20 µg/ml</td>
<td></td>
<td>20.0 ± 4.3 % 25.3 ± 0.5 % 28.5 ± 1.3 % 28.2 ± 0.8 % 28.9 ± 1.0 % 28.2 ± 0.3 % mean = 26.5</td>
</tr>
</tbody>
</table>
Betaxolol

**PK Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrandes et al(^57)</td>
<td>Rat n = 3</td>
<td>0.210</td>
<td>1</td>
<td>Bolus 0-8 hrs</td>
<td>Liquid scintillation</td>
<td>Plasma</td>
<td>Urine</td>
<td>Compartmental</td>
<td>Cumulative</td>
<td>AUC (ng.min/ml)</td>
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<tr>
<td></td>
<td>Dog n = 3</td>
<td>7</td>
<td>1</td>
<td>Bolus 0-24 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
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<td>Compartmental</td>
<td>Cumulative</td>
<td>4884</td>
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</tbody>
</table>

**Bioavailability study:**

Rat:
Ferrandes et al\(^57\): Formulation: Solution (5 mg/kg)
Sampling: 0-8 hrs
Analysis: Liquid scintillation
F\(_{oral}\) = 13%

Dog:
Ferrandes et al\(^57\): Formulation: Solution (5 mg/kg)
Sampling: 0-24 hrs
Analysis: Liquid scintillation
F\(_{oral}\) = 76%
Oxprenolol

PK Studies:

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<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
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<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Murai-Kushiya et al^7</td>
<td>Rats</td>
<td>0.205</td>
<td>5</td>
<td>Bolus</td>
<td>0-90 mins</td>
<td>HPLC</td>
<td>-</td>
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<td>S-14325</td>
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Plasma protein binding studies:

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<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td>Murai-Kushiya et al^10</td>
<td>Rats</td>
<td>Equilibrium dialysis</td>
<td>10 µg/ml</td>
<td>HPLC</td>
<td>Binding = 58.5 %</td>
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<td>Laethem et al^8</td>
<td>Dog</td>
<td>Equilibrium dialysis</td>
<td>50 mg/kg oral dose</td>
<td>HPLC</td>
<td>( f_u = 0.27 \pm 0.03 )</td>
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<tr>
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<td>Rabbit</td>
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<td>( f_u = 0.75 \pm 0.01 )</td>
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Terbutaline

PK Studies:

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<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
<th>Plasma</th>
<th>Urine</th>
<th>AUC (ng.min/ml)</th>
<th>CL_{tot} (ml/min/kg)</th>
<th>Vd_{ss} (l/kg)</th>
<th>CL_{ren} (ml/min/kg)</th>
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<tbody>
<tr>
<td>Torneke et al\textsuperscript{58}</td>
<td>Horse 2-12 yrs n = 6</td>
<td>452.5 (375-530)</td>
<td>0.01</td>
<td>Infusion for 30 mins</td>
<td>0-10 hrs</td>
<td>GC-MS</td>
<td>LOD – 0.15 ng/ml</td>
<td>Non-compartmental</td>
<td>Median-322.2</td>
<td>Median-31.7</td>
<td>Median-0.9</td>
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<tr>
<td>Tegner et al\textsuperscript{59}</td>
<td>Rat</td>
<td>-</td>
<td>-</td>
<td>Bolus</td>
<td>0-24 hr</td>
<td>Liquid scintillation</td>
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<td>-</td>
<td>f_{e} = 23.1%</td>
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<tr>
<td>Dog</td>
<td>Bolus</td>
<td>0-96 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
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<td>f_{e} = 79.7 ± 9.4 %</td>
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<tr>
<td>Nilsson et al\textsuperscript{60}</td>
<td>Dog</td>
<td>n = 8</td>
<td>10 (assumed)</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>72-96 hrs</td>
<td>Liquid scintillation</td>
<td>-</td>
<td>-</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
<td>47264 (calculated)</td>
<td>10.6 (calculated)</td>
<td>1.31 (calculated)</td>
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Plasma protein binding studies:

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<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Torneke et al\textsuperscript{58}</td>
<td>Horse n = 6</td>
<td>Equilibrium dialysis</td>
<td>1-100 ng/ml</td>
<td>GC-MS</td>
<td>Median-11.5%</td>
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Bioavailability study:
Horse:
Torneke et al\textsuperscript{58}; Formulation: Tablets (0.1 mg/kg)
Sampling: 0-10 hrs
Analysis: GC-MS
F_{oral} = Close to 0
## Fenoterol

**PK Studies:**

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<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ (ng/ml)</th>
<th>PK Analysis Method</th>
<th>Urine Collection Method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>Koster et al(^6)</td>
<td>Male Wistar rats n = 6</td>
<td>0.263</td>
<td>1</td>
<td>0-200 mins</td>
<td>Plasma Urine</td>
<td>Plasma Urine</td>
<td>385</td>
<td>Non-compartmental</td>
<td>-</td>
<td>AUC (ng.min/ml) = 53.8 (± 2.7)</td>
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<td></td>
<td>n = 5</td>
<td>0.274</td>
<td>2</td>
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<td>V(_d) (l/kg) = 0.95 (± 0.13)</td>
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669
Albuterol

PK Studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>Assay</th>
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<tr>
<td>Hernandez et al</td>
<td>Mongrel Dogs n = 5</td>
<td>24.5 ± 5.2</td>
<td>0.02</td>
<td>Bolus</td>
<td>0-6 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>0.5 ng/ml</td>
<td>Non-compartmental</td>
<td>1590000 (± 150000)</td>
</tr>
<tr>
<td>Perreault et al</td>
<td>New Zealand rabbits n = 4</td>
<td>2.5 ± 0.2</td>
<td>0.06</td>
<td>Bolus</td>
<td>0-90 mins</td>
<td>-</td>
<td>RIA</td>
<td>-</td>
<td>Non-compartmental</td>
<td>963 (calculated)</td>
</tr>
<tr>
<td>Perreault et al</td>
<td>New Zealand rabbits n = 6</td>
<td>2.5-2.8</td>
<td>0.06</td>
<td>Bolus</td>
<td>0-180 mins</td>
<td>-</td>
<td>RIA</td>
<td>-</td>
<td>Compartmental</td>
<td>729 (± 26)</td>
</tr>
<tr>
<td>Caccia et al</td>
<td>Male DC-COBS rats n = 4</td>
<td>0.2</td>
<td>1</td>
<td>Bolus</td>
<td>0-240 mins</td>
<td>-</td>
<td>HPLC</td>
<td>LOD – 5 ng/ml</td>
<td>-</td>
<td>284390</td>
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</tbody>
</table>
References:

57. Ferrandes B. Pharmacokinetics and metabolism of betaxalol in various animal species and man: Raven Press, NY; 1983.
Appendix II (c)

Animal PK Study Summaries for β-LAs

Penicillins

Amoxicillin

PK Studies:

<table>
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<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
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<th>Urine Collection method</th>
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<tr>
<td>Chesa-Jimenez et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Male Wistar rats n = 8</td>
<td>0.28-0.335</td>
<td>7.1 Bolus</td>
<td>0-130 mins</td>
<td>Diffusion LOD = 0.05 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td>443000 (± 31000)</td>
<td>16.1 (± 1.3)</td>
</tr>
<tr>
<td>Escudero et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Goats n = 10</td>
<td>38-43</td>
<td>20 Bolus</td>
<td>0-9 hrs</td>
<td>HPLC LOD = 0.45 µg/ml</td>
<td>-</td>
<td>Noncompartmental</td>
<td>-</td>
<td>163180 (± 22150)</td>
<td>2.0 (± 0.2)</td>
</tr>
<tr>
<td>Reynolds et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Healthy Female Pigs n = 8</td>
<td>24.7 (± 2.3)</td>
<td>20 Bolus</td>
<td>0-8 hrs</td>
<td>HPLC 0.025 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td>2100000 (± 338400)</td>
<td>9.7 (± 1.5)</td>
</tr>
</tbody>
</table>
Bioavailability studies:

Reyns et al\textsuperscript{3}:
Species: Pigs (n = 8)
Formulation: Tablets (20 mg/kg)
Sampling: 0-8 hrs
Assay: LC-MS/MS
F\textsubscript{oral} = 22.82\% ± 5.73

Ampicillin

PK Studies:

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<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td></td>
<td></td>
<td>Plasma, Urine</td>
<td>Plasma, Urine</td>
<td>AUC (ng.min/ml)</td>
<td>CL\textsubscript{tot} (ml/min/kg)</td>
<td>Vd\textsubscript{ss} (l/kg)</td>
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<tr>
<td>Pardue et al\textsuperscript{4}</td>
<td>Sprague Dawley rats n = 12</td>
<td>0.27-0.30</td>
<td>75</td>
<td>Bolus</td>
<td>0-2 hrs</td>
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<td>Agar diffusion assay</td>
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### Azlocillin

**PK Studies**

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<td>Urine</td>
<td>AUC (ng.min/ml)</td>
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<td>Millart et al&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Beagle dogs n = 12</td>
<td>8.6-17.5</td>
<td>100</td>
<td>Bolus</td>
<td>0-3hrs</td>
<td>HPLC</td>
<td>-</td>
<td>Compart mental</td>
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### Dicloxacillin

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<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.min/ml)</td>
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<tr>
<td>Dimitrova et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Mixed breed dogs n = 6</td>
<td>18-23</td>
<td>25</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>Agar plate diffusion</td>
<td>0.2 µg/ml</td>
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<td>Compart mental</td>
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Mezlocillin

PK Studies:

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<td>Jungbluth et al[7]</td>
<td>Sprague Dawley rats n = 4</td>
<td>0.350-0.50</td>
<td>20</td>
<td>Bolus</td>
<td>0-100 mins</td>
<td>HPLC</td>
<td>1.25 µg/ml</td>
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<td>Cumulative</td>
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Plasma protein binding studies:

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<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td>Jungbluth et al[7]</td>
<td>Sprague Dawley rats pooled plasma</td>
<td>Equilibrium dialysis</td>
<td>4 - 2000 µg/ml</td>
<td>HPLC</td>
<td>20-40%</td>
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Ticarcillin
PK Studies:

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<th>Rate</th>
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<tr>
<td>Woodnut et al 8</td>
<td>Albino rats n = 4</td>
<td>0.25-0.35</td>
<td>300 bolus</td>
<td>0-2 hrs</td>
<td>-</td>
<td>Agar diffusion</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td>23005800</td>
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<td></td>
<td>Rabbits n = 3</td>
<td>2-2.5</td>
<td>150 bolus</td>
<td>0-2 hrs</td>
<td>-</td>
<td>Agar diffusion</td>
<td>-</td>
<td>Compartmental</td>
<td>-</td>
<td>21744000</td>
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Plasma protein binding studies:

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<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Woodnut et al 8</td>
<td>Albino rats n = 4</td>
<td>Ultrafiltration</td>
<td>9.3-133 µg/ml</td>
<td>Agar diffusion</td>
<td>41.7 ± 3.4 %</td>
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<tr>
<td>Rabbits n = 3</td>
<td>20.7-830 µg/ml</td>
<td>Agar diffusion</td>
<td>49.6 ± 1.4 %</td>
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</table>
First generation cephalosporins

Cephradine

PK Studies:

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<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td>Nakashima et al⁹</td>
<td>Sprague Dawley rats n = 4</td>
<td>0.654</td>
<td>40</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>Plasma</td>
<td>1-400 µg/ml</td>
<td>-</td>
<td>Noncompartmental</td>
<td>AUC (ng.min/ml)</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td>6.17 (± 1.65)</td>
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Plasma protein binding studies:

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<th>Method</th>
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<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td>Nakashima et al⁹</td>
<td>Sprague Dawley rats</td>
<td>Ultrafiltration</td>
<td>40 mg/kg IV bolus</td>
<td>HPLC</td>
<td>$f_p = 0.82$ (± 0.01)</td>
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Cephalexin

**PK Studies:**

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<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
<tr>
<td></td>
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<td></td>
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<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Carli et al(^{10})</td>
<td>Beagle dogs n = 5</td>
<td>10-14</td>
<td>20</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>-</td>
<td>Agar plate diffusion</td>
<td>0.12 µg/ml</td>
<td>-</td>
<td>Compart mental</td>
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### Cefazolin

**PK Studies:**

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<th>Dose (mg/kg)</th>
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<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td></td>
<td>PK</td>
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<tr>
<td>Bakker-Woudenberget al(^{11})</td>
<td>Female albino rats 14-18 weeks n = 10</td>
<td>0.185 -215</td>
<td>0.68 1.59 2.31 mg/kg/hr</td>
<td>Infusion for 65 hrs</td>
<td>0-65 hrs</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
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<tr>
<td>Nadai et al(^{12})</td>
<td>Male Wistar 8-10 week</td>
<td>0.280 - 0.300</td>
<td>20</td>
<td>Bolus</td>
<td>0-210 mins 0-24 hrs</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Terasaki et al(^{13})</td>
<td>Male Wistar rats</td>
<td>0.240 - 0.270</td>
<td>20</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>-</td>
<td>HPLC</td>
<td>--</td>
<td>-</td>
<td>Compartmental</td>
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Plasma protein binding studies:

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<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Bakker-Woudenberg et al11</td>
<td>Female albino rats 14-18 weeks n = 10</td>
<td>Ultrafiltration</td>
<td>0.68</td>
<td>HPLC</td>
<td>93 % (± 1.6)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>1.59</td>
<td></td>
<td>92 % (± 0.9)</td>
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<td></td>
<td></td>
<td></td>
<td>2.31 mg/kg/hr infusion</td>
<td></td>
<td>89 % (± 0.5)</td>
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<tr>
<td>Nadai et al12</td>
<td>Wistar rats</td>
<td>Equilibrium</td>
<td>20 mg/kg IV</td>
<td>HPLC</td>
<td>$f_u = 0.17$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dialysis</td>
<td>Bolus</td>
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Cephalothin

PK Studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al\textsuperscript{14}</td>
<td>Sprague Dawley rats n = 6</td>
<td>0.280 - 0.350</td>
<td>50</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>HPLC</td>
<td>0.05- 50 µg/ml</td>
<td>-</td>
<td>-</td>
<td>AUC (ng.min/ml) 0.7 (± 5.4)</td>
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<td></td>
<td></td>
<td>CL\textsubscript{tot} (ml/min/kg) 32.2 (± 5.4)</td>
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<td></td>
<td>V\textsubscript{dss} (l/kg) 0.148 (calculated)</td>
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<td></td>
<td>CL\textsubscript{ren} (ml/min/kg) -</td>
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Plasma protein binding studies:

<table>
<thead>
<tr>
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<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
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</thead>
<tbody>
<tr>
<td>Chang et al\textsuperscript{14}</td>
<td>Sprague Dawley rats n = 6</td>
<td>Microdialysis</td>
<td>50 mg/kg IV bolus</td>
<td>HPLC</td>
<td>f\textsubscript{p} = 50.7 %</td>
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</table>
Cephaloridine

PK Studies:

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<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td></td>
</tr>
<tr>
<td>Tsai et al\textsuperscript{15}</td>
<td>Sprague Dawley rats (n = 6)</td>
<td>0.280 - 0.350</td>
<td>20</td>
<td>Bolus</td>
<td>0-150 mins</td>
<td>-</td>
<td>HPLC</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
</tr>
<tr>
<td>Waterman et al\textsuperscript{16}</td>
<td>Mongrel dogs (n = 6)</td>
<td>15-30</td>
<td>20</td>
<td>Bolus</td>
<td>0-4 hrs</td>
<td>-</td>
<td>Cup plate method</td>
<td>-</td>
<td>Non-compartmental</td>
<td>-</td>
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Plasma protein binding studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsai et al\textsuperscript{15}</td>
<td>Sprague Dawley rats</td>
<td>Microdialysis</td>
<td>0.5-1 µg/ml</td>
<td>HPLC</td>
<td>(f_u = 46.1%)</td>
</tr>
<tr>
<td>Waterman et al\textsuperscript{16}</td>
<td>Dog</td>
<td>Ultrafiltration</td>
<td>20 µg/ml</td>
<td>Cup plate method</td>
<td>6-15 %(mean -10 %)</td>
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</table>
## Second generation cephalosporins

### Cefprozil

#### PK Studies:

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<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ Plasma</th>
<th>Urine</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC (ng/min/ml)</td>
<td></td>
<td>CL_{tot} (ml/min/kg)</td>
<td>Vd_{ss} (l/kg)</td>
<td>CL_{ren} (ml/min/kg)</td>
</tr>
<tr>
<td>Barbhaiya et al.(^1)</td>
<td>Beagle dogs n = 4</td>
<td>10</td>
<td>12.5</td>
<td>Bolus</td>
<td>0-8 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>0.5 μg/ml</td>
<td>2.0 μg/ml</td>
<td>Non-compartmental</td>
<td>Cumulative</td>
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</table>
Cefoxitin

PK Studies:

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<th>Study</th>
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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakker-Woudenberg et al(^{11})</td>
<td>Female albino rats 14-18 weeks n = 10</td>
<td>0.185 - 0.215</td>
<td>5.25 mg/kg/hr</td>
<td>Infusion for 65 hrs</td>
<td>0-65 hrs</td>
<td>HPLC</td>
<td></td>
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<td></td>
<td>31.6</td>
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Plasma protein binding studies:

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<th>Method</th>
<th>Concentration range</th>
<th>Assay</th>
<th>Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakker-Woudenberg et al(^{11})</td>
<td>Female albino rats 14-18 weeks n = 10</td>
<td>Ultrafiltration</td>
<td>5.25 mg/kg/hr for 65 hrs</td>
<td>HPLC</td>
<td>34 % (± 6.9)</td>
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</table>
Cefuroxime

PK Studies:

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<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.min/ml)</td>
<td>Cl&lt;sub&gt;tot&lt;/sub&gt; (ml/min/kg)</td>
</tr>
<tr>
<td>Ruiz-Carretero et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Male Wistar rats n = 7</td>
<td>0.250 - 0.300</td>
<td>6.15</td>
<td>Bolus</td>
<td>0-210 mins</td>
<td>-</td>
<td>HPLC</td>
<td>0.9 µg/ml</td>
<td>-</td>
<td>Compartmental</td>
</tr>
<tr>
<td>Abo El-Souud et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Goats n = 5</td>
<td>20-34</td>
<td>20</td>
<td>Bolus</td>
<td>0-24 hrs</td>
<td>-</td>
<td>Microbiological assay</td>
<td>-</td>
<td>-</td>
<td>Compartmental Cumulative</td>
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Plasma protein binding studies:

<table>
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<tr>
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<th>Assay</th>
<th>Protein binding</th>
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<tbody>
<tr>
<td>Abo El-Souud et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Goats n = 5</td>
<td>Inhibition zone method</td>
<td>50 – 1.53 mg/ml</td>
<td>Microbiological assay</td>
<td>16.95 % (± 1.184)</td>
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</table>

688
Ceforanide

**PK Studies:**

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<tr>
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<th>Dose (mg/kg)</th>
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<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tbody>
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<td></td>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.min/ml)</td>
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<tr>
<td>Lee et al(^{20})</td>
<td>Beagle dogs</td>
<td>10</td>
<td>25</td>
<td>Infusion for 30 mins</td>
<td>0-8 hrs</td>
<td>0-8 hrs</td>
<td>Cup plate method</td>
<td>-</td>
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<td>Cumulative</td>
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<tr>
<td></td>
<td>Rabbit</td>
<td>3-4</td>
<td>30</td>
<td>Bolus</td>
<td>0-12 hrs</td>
<td>0-24 hrs</td>
<td>Cup plate method</td>
<td>-</td>
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<td>Cumulative</td>
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Cefapirin

PK Studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Cabana et al(^{21})</td>
<td>Beagle dogs (n = 4)</td>
<td>8.2</td>
<td>30</td>
<td>Bolus</td>
<td>0-3 hrs</td>
<td>Cup plate assay</td>
<td>-</td>
<td>-</td>
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<td>AUC (ng.min/ml)</td>
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<td>Cl(_{tot}) (ml/min/kg)</td>
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<td>Vd(_{ss}) (l/kg)</td>
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<td>Cl(_{rem}) (ml/min/kg)</td>
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</table>

AUC = 11.32 (calculated)
Vd\(_{ss}\) = 0.32 (calculated)
fe = 32% (± 4%)
### Third generation cephalosporins

**Cefoperazone**

**PK Studies:**

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
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<tbody>
<tr>
<td>Nakashima et al⁹</td>
<td>Sprague Dawley rats n = 4</td>
<td>0.654</td>
<td>40</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>-</td>
<td>HPLC</td>
<td>1-400 µg/ml</td>
<td>Noncompartamental</td>
<td>AUC (ng.min/ml)</td>
</tr>
<tr>
<td></td>
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<td>CL_{tot} (ml/min/kg)</td>
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<td>CL_{ren} (ml/min/kg)</td>
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**Plasma protein binding studies:**

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<th>Assay</th>
<th>Protein binding</th>
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<td>Nakashima et al⁹</td>
<td>Sprague Dawley rats</td>
<td>Ultrafiltration</td>
<td>40 mg/kg IV bolus</td>
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<td>f_{a} = 0.44 (± 0.06)</td>
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Moxalactam

PK Studies:

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<td>Sprague Dawley rats n = 4</td>
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<td>0-24 hrs</td>
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<td>Cynomolgus monkey n = 2</td>
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<td>0-24 hrs</td>
<td>Liquid scintillation</td>
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<td>Ganzinger et al(^2))</td>
<td>Rabbits n = 4</td>
<td>3-3.5</td>
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<td>0-4 hrs</td>
<td>-</td>
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Plasma protein binding studies:

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<td>Ganzinger et al(^2))</td>
<td>Rabbits n = 4</td>
<td>Ultrafiltration</td>
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Cefotaxime

PK Studies:

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<td>AUC (ng.min/ml)</td>
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<td>Hakim et al\textsuperscript{24}</td>
<td>Male Wistar rats n = 12</td>
<td>0.261 (± 0.013)</td>
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<td>HPLC</td>
<td>-</td>
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<td>Bolus</td>
<td>0-4 hrs</td>
<td>-</td>
<td>Agar diffusion</td>
<td>-</td>
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<td>Datta et al\textsuperscript{25}</td>
<td>Goats n = 12</td>
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Plasma protein binding studies:

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<td>10, 20, 30 µg/ml</td>
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<td>f_{u} = 0.48 ± 0.06</td>
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Ceftizoxime

PK Studies:

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<td>Plasma</td>
<td>Urine</td>
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<tr>
<td>Murakawa et al(^{26})</td>
<td>Mice (6 week old)</td>
<td>20</td>
<td>Bolus</td>
<td>0-4 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>Compartamental</td>
<td>Cumulative</td>
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<td>Rat (6 week old)</td>
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<td>0-4 hrs</td>
<td>0-24 hrs</td>
<td>HPLC</td>
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<td>Cumulative</td>
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<td>Beagle dog</td>
<td>7.5-15</td>
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<td>Rhesus monkey</td>
<td>5.8-9.1</td>
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<td>0-24 hrs</td>
<td>HPLC</td>
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Plasma protein binding studies:

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<th>Assay</th>
<th>Protein binding</th>
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<tr>
<td>Murakawa et al(^{26})</td>
<td>Mice</td>
<td>Ultrafiltration</td>
<td>30 µg/ml</td>
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<td>Rat</td>
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<td>32 %</td>
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<td>17 %</td>
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<td>Rabbit</td>
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<td>25 %</td>
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Cefpodoxime

PK Studies:

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<th>Dose (mg/kg)</th>
<th>Rate</th>
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<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<td>AUC (ng.min/ml)</td>
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<td>Brown et al\textsuperscript{27}</td>
<td>Beagle dogs (n = 12)</td>
<td>8-16</td>
<td>10</td>
<td>Bolus</td>
<td>0-48 hrs</td>
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### Ceftazidime

**PK Studies:**

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<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
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<tbody>
<tr>
<td>Matsui et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Sprague Dawley rats</td>
<td>0.200 - 0.250</td>
<td>20</td>
<td>Bolus</td>
<td>0-120 mins</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>AUC (ng.min/ml)</td>
</tr>
<tr>
<td>Female Beagle Dogs n = 3</td>
<td>12.2-12.6</td>
<td>20</td>
<td>0-6 hrs</td>
<td>0-24 hrs</td>
<td>Agar well diffusion</td>
<td>-</td>
<td>-</td>
<td>Compartmental</td>
<td>Cumulative</td>
<td>5580000 (+ 60000)</td>
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fe = 97.1 (+ 1.1)

fe = 86.3 (+ 4.8)
# Ceftriaxone

## PK Studies:

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<tr>
<td>Matsui et al(^{28})</td>
<td>Sprague Dawley rats</td>
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<td>0-120 mins</td>
<td>0-24 hrs</td>
<td>Agar well diffusion</td>
<td>Plasma</td>
<td>Urine</td>
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<td>Female Beagle Dogs n = 3</td>
<td>12.2 - 12.6</td>
<td>20</td>
<td>0-6 hrs</td>
<td>0-24 hrs</td>
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<tr>
<td></td>
<td>Rhesus monkeys n = 2</td>
<td>5.3 and 5.9</td>
<td>20</td>
<td>0-6 hrs</td>
<td>0-24 hrs</td>
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Cefpiramide

PK Studies:

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<th>Rate</th>
<th>Sampling schedule</th>
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<td>Matsui et al29</td>
<td>Mice n = 0.030</td>
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<td>0-120 mins</td>
<td>0-24 hrs</td>
<td>Disk-plate diffusion method</td>
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<td>CL_{tot} (ml/min/kg)</td>
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<td>0.200 - 0.250</td>
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<td>0-120 mins</td>
<td>0-24 hrs</td>
<td>- -</td>
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<td>Cumulative</td>
<td>41.5</td>
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<td>Male Albino rabbits n = 5</td>
<td>2.5-3.5</td>
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<td>0-180 mins</td>
<td>0-24 hrs</td>
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<td>1.30</td>
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<td>Beagle dogs n = 9</td>
<td>9-13</td>
<td>20</td>
<td>0-180 mins</td>
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<td>-</td>
<td>-</td>
<td>5.13</td>
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<td>Rhesus monkeys n = 3</td>
<td>4.5-5.1</td>
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<td>0-6 hrs</td>
<td>0-24 hrs</td>
<td>- -</td>
<td>-</td>
<td>-</td>
<td>0.52</td>
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## Fourth generation cephalosporins

### Cefepime

#### PK Studies:

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<td>Patani et al.</td>
<td>Goats</td>
<td>25-34</td>
<td>33.9</td>
<td>Bolus</td>
<td>0-24 hr</td>
<td>HPLC</td>
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Forgue et al.²⁰

Sprague Dawley rats
n = 5-7/group

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
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<th>PK endpoints</th>
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<tr>
<td></td>
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<td>0.255</td>
<td>- 0.4</td>
<td>Bolus</td>
<td>0-5 hr</td>
<td>HPLC</td>
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<td>Compartmen tal</td>
<td>-</td>
<td>1580</td>
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<td>(± 11.7)</td>
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<td>(± 11.7)</td>
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Cynomologus monkeys
n = 4-5/group

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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
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<tr>
<td></td>
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<td>4.0-6.3</td>
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<td>Bolus</td>
<td>0-10 hrs</td>
<td>HPLC</td>
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<td>Compartmen tal</td>
<td>-</td>
<td>9300</td>
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699
**Beta lactamase inhibitors**

**Clavulanic acid**

**PK Studies:**

<table>
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<th>Study</th>
<th>Animal</th>
<th>BW (kg)</th>
<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
<th>PK endpoints</th>
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<tr>
<td>Woodnut et al</td>
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<td>0.25-0.35</td>
<td>10 Bolus 0- 2 hrs</td>
<td>-</td>
<td>Agar diffusion</td>
<td>-</td>
<td>-</td>
<td>Compart mental</td>
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<td>2-2.5</td>
<td>5 Bolus 0-2 hrs</td>
<td>-</td>
<td>Agar diffusion</td>
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<td>-</td>
<td>Compart mental</td>
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<td>660000 (± 45600)</td>
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**Plasma protein binding studies:**

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<td>Albino rats</td>
<td>Ultrafiltration</td>
<td>0.23-19.5µg/ml</td>
<td>Agar diffusion</td>
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<tr>
<td>Rabbits</td>
<td>n = 3</td>
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<td>1.8-19.2 µg/ml</td>
<td>Agar diffusion</td>
<td>21.1 ± 4.4 %</td>
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Carbapenem

Imipenem

PK Studies:

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<th>Animal</th>
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<th>Dose (mg/kg)</th>
<th>Rate</th>
<th>Sampling schedule</th>
<th>Assay</th>
<th>LOQ</th>
<th>PK Analysis</th>
<th>Urine Collection method</th>
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<td>Barker et al(^3)</td>
<td>Dog 3-9 yr old n = 6</td>
<td>19.6-38.0</td>
<td>5 Bolus</td>
<td>0-12 hrs</td>
<td>HPLC</td>
<td>0.1 µg/ml</td>
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<td>-</td>
<td>1212000 (± 204000)</td>
<td>4.33 (± 1.0) 0.32 (± 0.04) -</td>
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References

Appendix III (a)

ALLOMETRIC SCALING PLOTS OF OPIOIDS

Morphine

![Graph 1: CLtot (ml/min) vs. BW (kg) for Rat, Dog, and Human](image)

![Graph 2: Vdss (l) vs. BW (kg) for Rat, Dog, and Human](image)
Remifentanil
**Alfentanil**
Fentanyl

- **CL\text{tot} (ml/min)** vs. BW (kg)
  - Rat
  - Dog
  - Human

- **V\text{dss} (l)** vs. BW (kg)
  - Rat
  - Dog
  - Human

- **CL\text{tot} (ml/min)** vs. BW (kg)
  - Rat
  - Cat
  - Goat
  - Monkey
  - Dog
  - Human
  - Horse
Hydromorphone

![Graph showing CLtot (ml/min) vs BW (kg) for Cat, Rabbit, and Human.](image1)

![Graph showing Vdss (l) vs BW (kg) for Cat, Rabbit, and Human.](image2)
Meperidine

![Graph showing the relationship between body weight (BW) and CL$_{tot}$ (ml/min) for different species: Rat, Dog, Human, and Pig.](image)
Methadone

![Graph showing CL_tot (ml/min) vs BW (kg) for different species. Rat, Dog, and Human are plotted on a linear scale.](image-url)
Tramadol

- **CL\(_{\text{tot}}\) (ml/min)**
  - Rat
  - Dog
  - Human

- **V\(_{dss}\) (l)**
  - Rat
  - Dog
  - Human
Dextropropoxyphene
Nalbuphine

![Graph showing CL_{tot} (ml/min) vs. BW (kg)]

![Graph showing V_{dss} (l) vs. BW (kg)]
Butorphanol
Buprenorphine
Pentazocine

![Graph of CLtot (ml/min) vs BW (kg)]

- Rat
- Dog
- Human

![Graph of Vdss (l) vs BW (kg)]

- Rat
- Dog
- Human
Dezocine

![Graph of CL_{tot} (ml/min) vs. BW (kg) for Dog, Monkey, and Human.]

![Graph of V_{dss} (l) vs. BW (kg) for Dog, Monkey, and Human.]

- CL_{tot} (ml/min)
- BW (kg)
- V_{dss} (l)
Naltrexone

![Graphs showing the relationship between body weight (BW) and clearance (CL) or volume of distribution (Vdss) for different species: Dog, Monkey, and Human. The graphs depict an increase in CL and Vdss with an increase in BW.](image-url)
The graphs illustrate the relationship between body weight (BW, kg) and total clearance (CLtot, ml/min) for different species. The graphs show a linear increase in CLtot with BW, with different species represented by distinct markers.

- The upper graph represents CLtot (in ml/min) for dog, monkey, goat, and human.
- The lower graph represents CLtot (in ml/min) for dog, monkey, and human, with a clear linear trend.

From these graphs, it can be observed that as BW increases, CLtot also increases, indicating a proportional relationship between BW and CLtot for these species.
Naloxone

\[
\text{CL}_{\text{tot}} \text{ (ml/min)} = \frac{10^n}{\text{BW (kg)}}
\]

\[
\text{Vd}_{\text{ss}} \text{ (l)} = \frac{10^n}{\text{BW (kg)}}
\]
Morphine-3-glucuronide:
Morphine-6-glucuronide

**CL_{tot} (ml/min)**

<table>
<thead>
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<th>BW (kg)</th>
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<th>Rat</th>
<th>Human</th>
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</tr>
<tr>
<td>100</td>
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<td>1000</td>
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**V_{dss} (l)**

<table>
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<th>BW (kg)</th>
<th>Mice</th>
<th>Rat</th>
<th>Human</th>
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<tr>
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Appendix III (b)

ALLOMETRIC SCALING PLOTS OF β-ARLS

Propranolol

\[ y = 63.592x^{0.801} \]

\[ R^2 = 0.9475 \]
\[ y = 4.8146x^{0.9536} \quad R^2 = 0.9606 \]

\[ y = 400.45x^{0.8173} \quad R^2 = 0.9849 \]
Sotalol

\[ y = 14.045x^{0.5541} \]
\[ R^2 = 0.9997 \]

- Rat
- Dog
- Human

\[ y = 26.133x^{1.1084} \]
\[ R^2 = 0.9922 \]

- Rat
- Dog
- Rabbit
- Human
\[ y = 2.1974x^{0.8606} \]
\[ \text{R}^2 = 1.0000 \]

\[ y = 14.614x^{0.5457} \]
\[ \text{R}^2 = 0.9995 \]
\[ y = 2.2863x^{0.8522} \]
\[ R^2 = 1 \]

\[ y = 11.086x^{0.5687} \]
\[ R^2 = 0.9969 \]
Atenolol

- y = 11.535x^{0.5604}
  \[ R^2 = 0.9974 \]

- y = 13.492x^{0.5453}
  \[ R^2 = 0.8291 \]
\[ y = 2.3363x^{0.8006} \]
\[ R^2 = 0.945 \]

\[ y = 19.97x^{0.5002} \]
\[ R^2 = 0.9716 \]
$y = 3.3876x^{0.7678}$
$R^2 = 0.9441$

$y = 15.905x^{0.5194}$
$R^2 = 0.986$

<table>
<thead>
<tr>
<th>Species</th>
<th>BW (kg)</th>
<th>CL\text{ren} (ml/min)</th>
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<td>Rat</td>
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</table>

- Rat
- Rabbit
- Human
- Dog
Metoprolol

\[ y = 77.959x^{0.6461} \]

\[ R^2 = 0.8703 \]

BW (kg) vs. CLtot (ml/min) for various species:
- Rat
- Rabbit
- Cat
- Dog
- Human
Amosulalol

\[ y = 2.9487x^{1.064} \quad R^2 = 0.9943 \]

\[ y = 30.229x^{0.5328} \quad R^2 = 0.8415 \]
**Graph 1:**

- Equation: \( y = 4.4527x^{0.5699} \)
- \( R^2 = 0.8431 \)

**Graph 2:**

- Equation: \( y = 5.3227x^{0.5803} \)
- \( R^2 = 0.9205 \)
Bisoprolol

\[ y = 24.247x^{0.5278} \]
\[ R^2 = 0.9897 \]

\[ y = 2.5809x^{1.0213} \]
\[ R^2 = 0.9974 \]
Carvedilol

\[ y = 62.273x^{0.5366} \]
\[ R^2 = 0.9869 \]

\[ y = 5.4332x^{0.7569} \]
\[ R^2 = 0.9948 \]
Landiolol

For CLtot (ml/min):

- Rat: $y = 18.463x^{1.2975}$
- Dog: $y = 18.463x^{1.2975}$
- Human: $y = 18.463x^{1.2975}$

$R^2$ values:
- Rat: 0.9634
- Dog: 0.9634
- Human: 0.9634

For Vdss (L):

- Rat: $y = 0.401x^{0.8339}$
- Dog: $y = 0.401x^{0.8339}$
- Human: $y = 0.401x^{0.8339}$

$R^2$ values:
- Rat: 0.9874
- Dog: 0.9874
- Human: 0.9874
Betaxalol

\[ y = 81.282x^{0.2942} \]
\[ R^2 = 0.9761 \]

Rat  | Dog  | Human

\[ y = 13.611x^{0.7641} \]
\[ R^2 = 0.9893 \]

Rat  | Dog  | Human

Albuterol
\[ y = 37.161x^{0.6962} \]
\[ R^2 = 0.9179 \]

- Rat
- Rabbit
- Dog
- Human

\[ y = 1.3133x^{1.0387} \]
\[ R^2 = 0.9626 \]

- Rat
- Rabbit
- Dog
- Human
Appendix III (c)

Allometric Scaling Plots of β-LAs

Amoxicillin

$y = 13.608x^{0.6919}$  
$R^2 = 0.9023$

$y = 0.5242x^{0.7723}$  
$R^2 = 0.9828$
Ticarcillin

\[ y = 8.7425x^{0.6288} \]
\[ R^2 = 0.9985 \]

\[ y = 0.1389x^{0.9585} \]
\[ R^2 = 0.8656 \]
$y = 16.561x^{0.7303}$
$R^2 = 0.9997$

$y = 0.2632x^{1.0601}$
$R^2 = 0.8813$
Cefepime

\[ y = 5.6752x^{0.6469} \]
\[ R^2 = 0.9035 \]

\[ y = 0.3551x^{0.9016} \]
\[ R^2 = 0.9791 \]

**BW (kg)**

**CLtot (ml/min)**

**Vdss (L)**

Rat

Monkey

Goat

Human
Moxalactam

\[ y = 2.8012x^{0.6608} \]
\[ R^2 = 0.6372 \]

\[ y = 0.2269x^{1.0526} \]
\[ R^2 = 0.9995 \]

<table>
<thead>
<tr>
<th>Rat</th>
<th>Rat</th>
<th>Rabbit</th>
<th>Monkey</th>
<th>Human</th>
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\( CL_{tot} \quad (\text{ml/min}) \)

\( V_{dss} \quad (\text{L}) \)

\( BW \quad (\text{kg}) \)
Cefotaxime

\[ y = 5.3442x^{0.8821} \]
\[ R^2 = 0.6673 \]

\[ y = 0.2393x^{1.1243} \]
\[ R^2 = 0.9506 \]
\[ y = 15.419x^{0.7856} \]
\[ R^2 = 0.8105 \]

\[ y = 0.6903x^{1.0277} \]
\[ R^2 = 0.8126 \]
Ceftizoxime

\[ y = 11.533x^{0.5878} \]
\[ R^2 = 0.9922 \]

\[ y = 0.3846x^{0.8263} \]
\[ R^2 = 0.9991 \]
\[ y = 0.3629x^{0.8391} \]
\[ R^2 = 0.9988 \]

\[ y = 10.423x^{0.6041} \]
\[ R^2 = 0.989 \]
Cefalexine

\[ y = 7.347x^{0.8024} \]
\[ R^2 = 0.9509 \]

\[ y = 0.731x^{0.6237} \]
\[ R^2 = 0.9798 \]
Clavulanic Acid

\[ y = 11.628x^{0.5783} \]
\[ R^2 = 0.988 \]

\[ y = 0.9843x^{0.4787} \]
\[ R^2 = 0.7685 \]
Cefpiramide

\[ y = 4.5927x^{0.5079} \]
\[ R^2 = 0.6891 \]

\[ y = 0.1204x^{1.1826} \]
\[ R^2 = 0.9447 \]
$y = 6.6346x^{0.6144}$  
$R^2 = 0.9029$

$y = 0.297x^{0.941}$  
$R^2 = 0.9598$
$y = 2.6512x^{0.5355}
R^2 = 0.6077$
Cephaloridine

\[ y = 7.8423x^{0.8027} \]
\[ R^2 = 0.9953 \]

- Rat
- Dog
- Human

\[ y = 0.4063x^{0.9677} \]
\[ R^2 = 0.9969 \]

- Rat
- Dog
- Human
VITA

Prajakta Badri was born on September 04, 1979 in Thane, India and is an Indian citizen. She graduated from Bombay College of Pharmacy, University of Mumbai, India with a Bachelor in Pharmaceutical Sciences in 2001 and a Masters in Pharmaceutical Sciences in 2005. She worked as a Research Associate (Analytical Division, Novel Drug Deliver Systems) at Nicholas Piramal Research Center, Mumbai, India before joining the PK-PD Research Group at Department of Pharmaceutics, Virginia Commonwealth University (VCU) in 2006.

During the course of her Ph.D. studies, Prajakta has published five abstracts. She has presented her research at Annual Meetings of the American Association of Pharmaceutical Scientists (AAPS, 2008, 2009) and American Society of Clinical Pharmacology and Therapeutics (ASCPT, 2009, 2010), in addition to the poster presentations within the School of Pharmacy and VCU. She received AAPS-Clinical Pharmacology and Translation Research (CPTR) Section Travelship Award in 2008 and AAPS-Pharmacokinetics, Pharmacodynamics and Drug Metabolism (PPDM) Section Travelship Award in 2009. Prajakta also received Presidential Trainee Award for the abstract submitted for the ASCPT 2010 Annual Meeting. In addition to this, she has also received VCU School of Pharmacy Jyotsna and Mavji Thacker Award for academic excellence in Department of Pharmaceutics in 2007, VCU Graduate School Phi Kappa Phi Scholarship in 2009, School of Pharmacy – Schwartz Travel Award in 2010 and VCU Graduate School Dissertation Award for spring and summer 2010.

Prajakta served as the GSA President in Department of Pharmaceutics from 2008-2009 and GSA webmaster in Department of Pharmaceutics from 2007-2009. She also served as VCU-AAPS Student Chapter Chair-elect (2008-2009) and VCU-AAPS Student Chapter Chair (2009-2010). In addition, she also serves as a member of ASCPT Scientific Programming Committee since 2009. She is a member of AAPS, ASCPT and Phi Kappa Phi Honor Society.

Abstracts:


