Pharmacokinetics and Pharmacodynamics of Ethanol in Healthy Volunteers: Effects of Input-Rate and Degree of Ethanol Exposure on Subjective and Objective Measures of Impairment

Vijay A. Ramchandani
This is to certify that the dissertation prepared by Vijay A. Ramchandani entitled "Pharmacokinetics and Pharmacodynamics of Ethanol in Healthy Volunteers: Effect of Input-Rate and Degree of Ethanol Exposure on Subjective and Objective Measures of Impairment" has been approved by his committee as satisfactory completion of the dissertation requirement for the degree of Doctor of Philosophy.

Date: August 13, 1996
PHARMACOKINETICS AND PHARMACODYNAMICS OF ETHANOL IN HEALTHY VOLUNTEERS: EFFECT OF INPUT-RATE AND DEGREE OF ETHANOL EXPOSURE ON SUBJECTIVE AND OBJECTIVE MEASURES OF IMPAIRMENT

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

by

Vijay A. Ramchandani
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Virginia Commonwealth University
Richmond, Virginia
August 1996
Addendum to

PHARMACOKINETICS AND PHARMACODYNAMICS OF ETHANOL IN HEALTHY VOLUNTEERS: EFFECT OF INPUT-RATE AND DEGREE OF ETHANOL EXPOSURE ON SUBJECTIVE AND OBJECTIVE MEASURES OF IMPAIRMENT.
Ph.D. Dissertation by Vijay A. Ramchandani
Virginia Commonwealth University, Richmond, Virginia - August 1996

On April 22, 1997, a memorandum was received from the Investigational Pharmacy of MCV Hospitals stating that there was an error in the preparation of the intravenous ethanol solutions for the IV study (see Attachment 1). It appears that the Pharmacy prepared and dispensed 10%v/v ethanol solutions instead of the 10%w/v solutions that we had requested. In other words, the intravenous ethanol solutions that were used in the study contained 8%w/v ethanol, and not 10%w/v ethanol.

As a result of this, the ethanol doses administered during Leg 0 and the active legs of the randomized phase of the study were 20% lower that what had been calculated for administration.

After careful review and repeating the pharmacokinetic and pharmacodynamic analysis of the data, as well as the statistical analysis, it was determined that this error did not affect the main conclusions of the study. The primary differences were in the estimates of the volumes of distribution, Vdc and Vdss, which were about 20% higher than the estimates obtained using the actually administered doses. The estimates of the other PK and PD parameters did not change significantly.

As a result of the error and the subsequent re-analysis of the data, there are some corrections to some of the tables and text in the dissertation. These are limited to chapter 4. The corrections include:

1. Changes to Figure 4.1 and Tables 4.7, 4.8, 4.11, 4.13 and 4.14. The corrected figures and tables are attached to this addendum (Attachment 2).

2. Section 4.3.2B on page 136 should read:

4.3.2B Drug preparation and administration
On the morning of dosing, subjects received a one-hour IV infusion of ethanol. A total dose of \(0.48 \text{ g} \) ethanol/kg body weight for male subjects and \(0.40 \text{ g} \) ethanol/kg body weight for female subjects was administered as a 10%v/v (8%w/v) solution in normal saline over 1 hour. The infusion was administered...
3. Section 4.3.4B on page 147 should read:

**4.3.4B Drug preparation and administration**

During each study period, subjects received one of the following treatments according to the sequence he/she was randomized to. Dosing consisted of two infusions: Infusion I was administered for 1 hour, followed by Infusion II which will be administered over the next 5 hours. The total dose of ethanol, which was individualized for each subject based on his/her pharmacokinetic parameters, was administered as a **10% v/v (8% w/v)** solution in normal saline. Placebo doses consisted of normal saline. The infusions were administered...

4. The last paragraph on page 192 (continuing on to page 194) should read:

The mean intrinsic PK parameters, estimated by compartmental methods across subjects and treatments, along with the inter-individual and intra-individual variability measures (%COV) are presented in table 4.14, by gender. The mean (± S.D.) $V_{\text{max}}$ was **347 (± 77) mg/L/hr** across subjects and treatments. The mean (± S.D.) $K_m$ was **254 (± 83) mg/L** across subjects and treatments. The mean ± SD $V_dss$ was **41 (± 7) L** across treatments for male subjects, and **30 (± 6) L** across treatments for female subjects. The mean (± S.D.) $k_{12}$ was **0.95 (± 0.45) hr^{-1}** across subjects and treatments. The mean (± S.D.) $k_{21}$ was **2.41 (± 1.55) hr^{-1}** across subjects and treatments. This corresponds to a distribution half-life of around 0.23 hours (or around 14 minutes), indicating that the distribution phase for ethanol is quite rapid.

5. The sentence (starting on the fourth line) on page 257 should read:

The mean (± S.D.) $V_{\text{max}}$ was **347 (± 77) mg/L/hr** across subjects and treatments; the mean (± S.D.) $K_m$ was **254 (± 83) mg/L** across subjects and treatments; the mean ± SD $V_dss$ was **41 (± 7) L** across treatments for male subjects, and **30 (± 6) L** across treatments for female subjects. The mean (± S.D.) $k_{12}$ was **0.95 (± 0.45) hr^{-1}** across subjects and treatments and the mean (± S.D.) $k_{21}$ was **2.41 (± 1.55) hr^{-1}** across subjects and treatments. This corresponds to a distribution half-life of around 0.23 hours (or around 14 minutes).
Date: 22 April 1997

To: Patricia Slattum, PharmD

From: Amy Phillips, PharmD

Re: Dilution for Ethanol Study

This memo is to document the telephone conversation that we had previously regarding the concentration of ethanol for the study conducted in 1994 and 1995 with Vijay Ramchandani as well as your study that is currently ongoing.

It has been brought to my attention that the 10% ethanol solution that was expected to be made for both of these studies has actually been 8.01%. Enclosed you will find a copy of the MCV instruction card that was used in preparing the doses for each patient in both studies.

You will see that the USP/NF was incorrectly interpreted to be % by weight as w/v, when it should have been % w/w. You will also see that the density of pure alcohol was not used in calculating the final concentration. We picked the density at 15.56 degrees because that is what the Bureau of Standards recommends. So, you will see that the density of pure alcohol that we used is 0.7936 g/ml.

The calculations for the preparations that were given to the subjects enrolled in this study are as follows:

We used-- 98% v/v ethanol = 98ml of pure alcohol
100ml of total solution

The density of pure alcohol (see enclosed alcoholectroic table) is = 0.7936 g/ml

So, a 98% v/v is 98ml x 0.7936g/ml = 77.8% w/v
100ml

Now the solution that was made used 103ml of 98% v/v ethanol, so the actual concentration is determined to be:

\[
\frac{77.8g}{100ml} = \frac{x g}{103ml of 98\% v/v} = 80.13g
\]

\[
\frac{80.13g}{1000ml} = \frac{x g}{100ml} = 8.01% w/v
\]

As we discussed, we will continue making the solution as we have in the past. The solution will be labeled as an 8% solution and not a 10% solution from this point on. I understand that you will be in touch with Vijay Ramchandani regarding this issue, please forward him this information. Copies of this will be kept in our files as well. Please call me if you need any further information for our records at 8-7901.
ATTACHMENT 2
I

**Medical Screening**

Pharmacokinetic Screen and Familiarization Period
Leg 0
Males: 0.48 g/kg IV Ethanol infused over 1 hour
Females: 0.4 g/kg IV Ethanol infused over 1 hour

Assessment of PK parameters
$V_{max}$, $K_m$, $V_d$
Dose Individualization

**RANDOMIZATION**
Four-way Crossover (Legs 1 - 4)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Infusion I</th>
<th>Infusion II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1 hour)</td>
<td>(5 hours)</td>
</tr>
<tr>
<td>A</td>
<td>ethanol</td>
<td>placebo</td>
</tr>
<tr>
<td>B</td>
<td>placebo</td>
<td>ethanol</td>
</tr>
<tr>
<td>C</td>
<td>ethanol</td>
<td>ethanol</td>
</tr>
<tr>
<td>D</td>
<td>placebo</td>
<td>placebo</td>
</tr>
</tbody>
</table>

Figure 4.1 Study Design Flow Chart
Table 4.7  Mean (%COV) Pharmacokinetic parameters by gender for Leg 0 for intravenous ethanol study

<table>
<thead>
<tr>
<th>Dose [g/kg]</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; [mg/L]</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; [mg/L/(g/kg)]&lt;sup&gt;1&lt;/sup&gt;</th>
<th>V&lt;sub&gt;max&lt;/sub&gt; [mg/L/hr]</th>
<th>K&lt;sub&gt;m&lt;/sub&gt; [mg/L]</th>
<th>Vd [L]</th>
<th>Vd [L/kg]&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n=8)</td>
<td>0.48</td>
<td>924 (19%)</td>
<td>1924 (19%)</td>
<td>241 (27%)</td>
<td>163 (41%)</td>
<td>47 (16%)</td>
</tr>
<tr>
<td>Females (n=8)</td>
<td>0.40</td>
<td>821 (20%)</td>
<td>2052 (20%)</td>
<td>250 (13%)</td>
<td>164 (37%)</td>
<td>35 (18%)</td>
</tr>
<tr>
<td>All (n=16)</td>
<td></td>
<td>1988 (19%)</td>
<td></td>
<td>245 (20%)</td>
<td>164 (38%)</td>
<td>41 (22%)</td>
</tr>
</tbody>
</table>

1: Dose-corrected C<sub>max</sub>  2: body-weight corrected Vd
Table 4.8  Doses calculated from Leg 0 PK parameters for crossover phase of intravenous ethanol study.

<table>
<thead>
<tr>
<th></th>
<th>Trt A [g/kg]</th>
<th>Trt B [g/kg]</th>
<th>Trt C [g/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n=8)</td>
<td>0.60 (12%)</td>
<td>0.96 (8%)</td>
<td>1.11 (8%)</td>
</tr>
<tr>
<td>Females (n=8)</td>
<td>0.53 (13%)</td>
<td>0.85 (12%)</td>
<td>1.00 (11%)</td>
</tr>
<tr>
<td>All (n=16)</td>
<td>0.57 (14%)</td>
<td>0.91 (11%)</td>
<td>1.05 (11%)</td>
</tr>
<tr>
<td>Population¹</td>
<td>0.56</td>
<td>1.00</td>
<td>1.11</td>
</tr>
</tbody>
</table>

¹: Doses predicted for treatments A, B and C based on previously published parameter estimates ($V_{max} = 232$ mg/L/hr, $K_m = 82.1$ mg/L, $V_d = 0.53$ L/kg)
Table 4.11 Mean (%COV) Non-compartmental Pharmacokinetic parameters by gender for crossover phase of intravenous ethanol study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$</th>
<th>$T_{\text{max}}$</th>
<th>$AUC_{\infty}$</th>
<th>$V_{\text{max}}$</th>
<th>$K_m$</th>
<th>$V_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[mg/L]</td>
<td>[mg/L/(g/kg)]²</td>
<td>[hr]</td>
<td>[mg/L*hr]</td>
<td>[mg/L]</td>
<td>[mg/L]</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1182 (16%)</td>
<td>2000 (21%)</td>
<td>1.0 (0.8-1.0)</td>
<td>4854 (64%)</td>
<td>8631 (75%)</td>
<td>147 (27%)</td>
</tr>
<tr>
<td>Females</td>
<td>1056 (14%)</td>
<td>2021 (21%)</td>
<td>1.0 (1.0-1.3)</td>
<td>3731 (24%)</td>
<td>7018 (21%)</td>
<td>157 (18%)</td>
</tr>
<tr>
<td>All</td>
<td>1119 (16%)</td>
<td>2010 (20%)</td>
<td>1.0 (0.8-1.3)</td>
<td>4292 (53%)</td>
<td>7690 (58%)</td>
<td>152 (22%)</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1048 (16%)</td>
<td>1094 (15%)</td>
<td>6.0 (5.0-6.3)</td>
<td>5960 (22%)</td>
<td>6243 (23%)</td>
<td>195 (15%)</td>
</tr>
<tr>
<td>Females</td>
<td>1011 (18%)</td>
<td>1189 (13%)</td>
<td>6.0 (6.0-6.3)</td>
<td>5396 (24%)</td>
<td>6397 (25%)</td>
<td>176 (15%)</td>
</tr>
<tr>
<td>All</td>
<td>1029 (16%)</td>
<td>1142 (17%)</td>
<td>6.0 (5.0-6.3)</td>
<td>5678 (23%)</td>
<td>6320 (23%)</td>
<td>185 (15%)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1286 (16%)</td>
<td>1172 (20%)</td>
<td>1.0 (1.0-6.0)</td>
<td>9835 (25%)</td>
<td>8984 (29%)</td>
<td>203 (29%)</td>
</tr>
<tr>
<td>Females</td>
<td>1253 (12%)</td>
<td>1269 (16%)</td>
<td>1.0 (0.8-6.0)</td>
<td>10253 (26%)</td>
<td>10283 (25%)</td>
<td>197 (34%)</td>
</tr>
<tr>
<td>All</td>
<td>1269 (14%)</td>
<td>1220 (18%)</td>
<td>1.0 (0.8-6.0)</td>
<td>10044 (25%)</td>
<td>9633 (27%)</td>
<td>200 (30%)</td>
</tr>
</tbody>
</table>

1: $T_{\text{max}}$ expressed as Median (Range)  
2: Dose-corrected $C_{\text{max}}$  
3: Dose-corrected $AUC_{\infty}$
Table 4.13 Mean (% COV) Compartmental Pharmacokinetic parameters by gender for crossover phase of intravenous ethanol study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_{m}$ [mg/L]</th>
<th>$V_{dc}$ [L]</th>
<th>$k_{12}$ [hr$^{-1}$]</th>
<th>$k_{21}$ [hr$^{-1}$]</th>
<th>$V_{dss}$ [L]</th>
<th>$V_{dss}$ [L/kg]$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>318 (28%)</td>
<td>267 (39%)</td>
<td>25 (26%)</td>
<td>1.00 (27%)</td>
<td>1.45 (51%)</td>
<td>44 (15%)</td>
<td>0.59 (15%)</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>314 (16%)</td>
<td>215 (37%)</td>
<td>21 (22%)</td>
<td>0.96 (43%)</td>
<td>2.53 (65%)</td>
<td>32 (23%)</td>
<td>0.50 (9%)</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>316 (22%)</td>
<td>241 (39%)</td>
<td>23 (25%)</td>
<td>0.98 (34%)</td>
<td>1.99 (68%)</td>
<td>38 (25%)</td>
<td>0.54 (15%)</td>
</tr>
<tr>
<td>(n=16)</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>356 (24%)</td>
<td>284 (37%)</td>
<td>29 (8%)</td>
<td>0.68 (55%)</td>
<td>2.45 (59%)</td>
<td>40 (17%)</td>
<td>0.54 (13%)</td>
</tr>
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<tr>
<td>Females</td>
<td>356 (22%)</td>
<td>232 (31%)</td>
<td>23 (27%)</td>
<td>1.06 (69%)</td>
<td>3.92 (52%)</td>
<td>30 (15%)</td>
<td>0.47 (9%)</td>
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</tr>
<tr>
<td>All</td>
<td>356 (22%)</td>
<td>257 (35%)</td>
<td>26 (21%)</td>
<td>0.87 (68%)</td>
<td>3.18 (59%)</td>
<td>35 (22%)</td>
<td>0.51 (14%)</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Males</td>
<td>361 (24%)</td>
<td>284 (26%)</td>
<td>25 (14%)</td>
<td>0.82 (26%)</td>
<td>1.85 (58%)</td>
<td>38 (16%)</td>
<td>0.51 (13%)</td>
</tr>
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<td>(n=8)</td>
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</tr>
<tr>
<td>Females</td>
<td>378 (17%)</td>
<td>240 (22%)</td>
<td>18 (25%)</td>
<td>1.19 (41%)</td>
<td>2.28 (53%)</td>
<td>28 (15%)</td>
<td>0.45 (11%)</td>
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<tr>
<td>All</td>
<td>370 (20%)</td>
<td>262 (25%)</td>
<td>22 (24%)</td>
<td>1.00 (41%)</td>
<td>2.06 (55%)</td>
<td>33 (21%)</td>
<td>0.48 (14%)</td>
</tr>
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<td>(n=16)</td>
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1: body weight-corrected $V_{dss}$
Table 4.14  Mean Compartmental PK parameter estimates across treatments for males (M) and Females (F) for intravenous ethanol study

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
<th>$k_{12}$ [hr$^{-1}$]</th>
<th>$k_{21}$ [hr$^{-1}$]</th>
<th>$V_{dss}$ [L]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>All</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Overall Mean</td>
<td>345</td>
<td>350</td>
<td>347</td>
<td>279</td>
<td>229</td>
</tr>
<tr>
<td>Inter-Individual variability (%COV)</td>
<td>25%</td>
<td>19%</td>
<td>22%</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td>Intra-Individual variability (Mean %COV)</td>
<td>11%</td>
<td>13%</td>
<td>12%</td>
<td>15%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Dedicated to

my family

This dissertation is a testimony

of their love and hopes and sacrifices
ACKNOWLEDGEMENTS

I would like to acknowledge the contribution and express my gratitude to the following people and organizations for all their help and support in the completion of this project:

Jürgen Venitz ("Dr. J"), my research advisor, an excellent teacher, and more importantly, a wonderful person.

Members of my graduate committee, Drs. Elswick, Garnett, Kirkwood, Porter, Rosecrans, and Smith, for their help and support throughout the project.

Patty Slattum, for her friendship and support.

Past and present members of the PK-PD Lab, Patty, Vanitha, Roshni, Susan, Chun and Ruma - great colleagues and wonderful friends.

The General Clinical Research Center, for funding part of the clinical portions of the studies.

Cognitive Drug Research Ltd., particularly Dr. Keith Wesnes, for providing the CDR battery, as well as for their technical and data support.

Drs. Johns, Towne, Naimoli, and Gatiwala, for serving as medical monitors for the studies.

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The office staff of the department (especially Sue Brown), for all their assistance.

The staff of the GCRC, who performed an excellent job, going beyond their call of duty to make the entire study experience wonderful.

Past and present staff of the Center for Drug Studies (formerly BioClin), especially one very special person, Sabina Hatchell.

Some very special people, Vanitha, Sekar, and Jaya, as well as all my other friends in Richmond, who helped make the past six years an memorable experience.

My family, for always believing in me. Mere words cannot express how I feel about their faith and support and sacrifices.

Last, but not least, a very special person who has always stood beside me and supported me, through good times and bad - unselfishly and unconditionally - my best friend and my wife, Roshni.
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<td>1.1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.2 BACKGROUND</td>
<td></td>
</tr>
<tr>
<td>1.2.1 Pharmacokinetics of Ethanol</td>
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<td>1.2.2 Pharmacodynamics of Ethanol</td>
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<td>Concentration of hypothetical metabolite</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;ant50&lt;/sub&gt;</td>
<td>Potency of the antagonist, concentration required to produce 50% antagonism</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;avgSS&lt;/sub&gt;</td>
<td>Average steady-state concentrations</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum concentration</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;n&lt;/sub&gt;</td>
<td>Last measured concentration</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;SS&lt;/sub&gt;</td>
<td>Steady-state concentration</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;target&lt;/sub&gt;</td>
<td>Target concentration</td>
<td></td>
</tr>
<tr>
<td>CL</td>
<td>Total body clearance</td>
<td></td>
</tr>
<tr>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;/F</td>
<td>Apparent total body clearance</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous system</td>
<td></td>
</tr>
<tr>
<td>CST</td>
<td>Card-Sorting Task</td>
<td></td>
</tr>
<tr>
<td>COV&lt;sub&gt;avg&lt;/sub&gt;</td>
<td>Coefficient of variation of average steady-state concentrations</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Total administered dose</td>
<td></td>
</tr>
<tr>
<td>Dase</td>
<td>Diaphorase</td>
<td></td>
</tr>
<tr>
<td>DEQ</td>
<td>Drug Effects Questionnaire</td>
<td></td>
</tr>
<tr>
<td>Dose&lt;sub&gt;I&lt;/sub&gt;&lt;sub&gt;A&lt;/sub&gt;</td>
<td>Dose for infusion I, treatment A</td>
<td></td>
</tr>
<tr>
<td>Dose&lt;sub&gt;II&lt;/sub&gt;&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Dose for infusion II, treatment B</td>
<td></td>
</tr>
<tr>
<td>Dose&lt;sub&gt;I&lt;/sub&gt;&lt;sub&gt;C&lt;/sub&gt;</td>
<td>Dose for infusion I, treatment C</td>
<td></td>
</tr>
<tr>
<td>Dose&lt;sub&gt;II&lt;/sub&gt;&lt;sub&gt;C&lt;/sub&gt;</td>
<td>Dose for infusion II, treatment C</td>
<td></td>
</tr>
<tr>
<td>DSST</td>
<td>Digit Symbol Substitution Test</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Effect</td>
<td></td>
</tr>
<tr>
<td>E&lt;sub&gt;D&lt;/sub&gt;</td>
<td>Direct drug effect</td>
<td></td>
</tr>
<tr>
<td>E&lt;sub&gt;FB&lt;/sub&gt;</td>
<td>Feedback effect</td>
<td></td>
</tr>
<tr>
<td>E&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Baseline effect</td>
<td></td>
</tr>
<tr>
<td>E&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal effect</td>
<td></td>
</tr>
</tbody>
</table>
$E_{\text{max obs}}$ Maximum observed response
$E_{\text{min obs}}$ Minimum observed response
$EC_{50}$ Concentration required to produce an effect that is 50% of the maximal effect
EEG Electroencephalography
EKG Electrocardioencephalography
ELOQ Experimental Limit of Quantitation
ETOH Ethanol
FT Finger Tapping
GABA Gaba Amino Butyric Acid
GCRC General Clinical Research Center
$K^+$ Potassium
$k_{12}$ First order distribution rate constant
$k_{21}$ First order redistribution rate constant
$k_{i1}$ First order input rate constant for the hypothetical metabolite
$k_i$ (or $K_i$) Absorption rate constant
$k_{\text{off10}}$ First order exit rate constant for the hypothetical metabolite
$K_m$ Michaelis Menten constant
$k_0$ Infusion rate
$k_{\text{off}}$ Rate constant for offset of tolerance
$k_{\text{on}}$ Rate constant for onset of tolerance
MRT Mean Residence Time
MSC Model Selection Criteria
MTT Monotetrazolium dye
$n$ Hill coefficient
$Na^+$ Sodium
NAD Nicotinamide Adenenine Dinucleotide
NADH Nicotinamide Adenine Dinucleotide reduced
NMMDA N-methyl d-aspartate
NR Non-Responder
ORI Observer-Rated Impairment
PD Pharmacodynamics
PK Pharmacokinetics
PK-PD Pharmacokinetic-Pharmacodynamic
POMS Profile of mood states
PPT Psychometric Performance Tests
$r^2$ Coefficient of determination
REA Radiation Energy Attenuation
REML Restricted maximum likelihood
S Slope or sensitivity factor for effect-concentration relationship
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.D.</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>S.E.</td>
<td>Standard Error</td>
</tr>
<tr>
<td>SHAS</td>
<td>Subjective High Assessment Scale</td>
</tr>
<tr>
<td>SRI</td>
<td>Subject-Rated Impairment</td>
</tr>
<tr>
<td>SRI-AE</td>
<td>Subject Rated Impairment - Alcohol Effects score</td>
</tr>
<tr>
<td>STAI</td>
<td>State Trait Anxiety Inventory</td>
</tr>
<tr>
<td>T</td>
<td>Duration of input</td>
</tr>
<tr>
<td>T_{infI}</td>
<td>Time of duration of infusion I</td>
</tr>
<tr>
<td>T_{infII}</td>
<td>Time of duration of infusion II</td>
</tr>
<tr>
<td>T_{max}</td>
<td>Time to achieve maximum concentration</td>
</tr>
<tr>
<td>t_{max}</td>
<td>Time of maximal observed response</td>
</tr>
<tr>
<td>t_{min}</td>
<td>Time of minimal observed response</td>
</tr>
<tr>
<td>T_{a}</td>
<td>Time of the last measured concentration</td>
</tr>
<tr>
<td>V_d</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>V_d/F</td>
<td>Apparent volume of distribution</td>
</tr>
<tr>
<td>V_{dss}</td>
<td>Volume of distribution at steady-state</td>
</tr>
<tr>
<td>V_{max}</td>
<td>Maximum elimination rate</td>
</tr>
<tr>
<td>%AUC_{extrap}</td>
<td>% extrapolated area under the concentration-time curve</td>
</tr>
<tr>
<td>%AUMC_{extrap}</td>
<td>% extrapolated area under the moment curve</td>
</tr>
<tr>
<td>%DFN</td>
<td>% Difference From Nominal</td>
</tr>
<tr>
<td>%DFT</td>
<td>% Difference from target</td>
</tr>
<tr>
<td>%RSD</td>
<td>% Relative Standard Deviation</td>
</tr>
<tr>
<td>%COV</td>
<td>% Coefficient of Variation</td>
</tr>
<tr>
<td>α</td>
<td>Level of significance</td>
</tr>
<tr>
<td>β-hCG</td>
<td>β-human chorionic gonadotropin</td>
</tr>
<tr>
<td>λ</td>
<td>Terminal elimination rate constant</td>
</tr>
</tbody>
</table>
PHARMACOKINETICS AND PHARMACODYNAMICS OF ETHANOL IN HEALTHY VOLUNTEERS: EFFECT OF INPUT-RATE AND DEGREE OF ETHANOL EXPOSURE ON SUBJECTIVE AND OBJECTIVE MEASURES OF IMPAIRMENT

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

Virginia Commonwealth University, 1996

DIRECTOR: Jürgen Venitz, M.D., Ph.D., Associate Professor and Director of Pharmacokinetics-Pharmacodynamics Laboratory, Department of Pharmacy and Pharmaceutics

The goal of this project was to investigate the effect of input-rate (oral and intravenous) and degree of exposure on the pharmacokinetics of ethanol and on subjective and objective measures of impairment, as well as on the development of acute tolerance to the effects of ethanol in young, healthy volunteers.

The primary objective of this research was to test the following hypotheses:

1) the rate and degree of ethanol exposure (oral and intravenous) in normal healthy males and females affect the pharmacokinetics (PK) and pharmacodynamics (PD) of ethanol in a non-linear fashion; 2) the EEG changes after ethanol administration correlate with changes in psychometric performance and subject-rated impairment, as well as serum
ethanol concentrations; and 3) acute tolerance develops to the subjective effects of ethanol which is not reflected in changes in electroencephalographic (EEG) activity or psychometric performance.

This study was conducted in two parts. Part I was a five-way crossover pilot study in six healthy male volunteers to evaluate the effect of dose and dose-rate on the PK and PD of ethanol. This study evaluated changes in EEG activity, psychometric performance and subjective impairment to evaluate the relationship between these subjective and objective measures, and the relationship between these measures and serum ethanol concentrations. Part II was a 4-way crossover study in 16 healthy male and female subjects to study the PK-PD relationship for intravenous (IV) ethanol and acute tolerance development to the effects of ethanol. In this study, subjects were administered individualized intravenous ethanol infusions, to achieve a target concentration of 1000 mg/L after different durations of exposure. This study was designed to investigate the PK of ethanol, as well as to assess changes in EEG activity, psychometric performance and subjective impairment. This study evaluated the relationship between these measures, and the relationship between these measures and serum ethanol concentrations, as well as the development of acute tolerance to the effects of ethanol.

Results from both studies showed that: 1) Ethanol, after oral and intravenous administration, follows capacity-limited pharmacokinetics. Intrinsic PK parameters, $V_{\text{max}}$, $K_m$ and $V_d$ were independent of dose and input-rate, but were associated with fairly high inter-individual variability. 2) Ethanol, after oral and intravenous administration, induced
a transient slowing of the EEG and impairment in psychometric performance. The magnitude of the changes in these measures appeared to be dose-related as well as input-rate-related (observed in the IV study), however there was a fairly large degree of variability in response between individuals. 3) Ethanol, after oral and intravenous administration, induced transient subjective impairment, which was dose-related and input-rate-related, and correlated with serum ethanol concentrations across treatments. 4) A subset of subjects (2/6 males in the oral ethanol study, and 2/8 males and 4/8 female subjects in the IV study) were classified as "non-responders" based on their lack of subjective response to ethanol, despite serum ethanol concentrations, psychometric impairment and EEG changes that were consistent with the other subjects. 5) There was significant exposure-related acute tolerance development to the subjective effects of ethanol observed in both studies. This acute tolerance development could be characterized by a PK-PD model incorporating tolerance as a compensatory feedback mechanism to counter-regulate the direct subjective impairment effect of the drug. Acute tolerance was not observed for the psychometric impairment or changes in EEG activity, indicating that there was a temporal disparity between objective and subjective impairment following ethanol administration. 6) The EEG changes were not correlated with the psychometric or subjective impairment. 7) There was a significant gender difference observed in the Cmax and Vdss for ethanol, probably due to gender differences in body weight and body water content. There was also a significant gender difference observed in the magnitude of ethanol-induced subjective impairment, with females showing a lower
degree of subjective impairment, despite achieving similar concentrations and
demonstrating similar psychometric impairment and EEG changes. This gender difference
may be partly confounded by the larger proportion of female "non-responders" compared
to the male "non-responders" in the study.
CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 INTRODUCTION

Ethanol is probably the most widely used drug in the world. It is commonly self-prescribed rather than prescribed by a clinician and the dose determined either by tradition, social context or the achievement of a pharmacological end-point (self-titration) (Holford, 1987). Almost no other substance has been as comprehensively investigated as ethanol, not only because it is one of the oldest and most ubiquitous abused "drugs" in human history, but also because of its unique dynamic and kinetic behavior (Martin et al., 1984). Although considered at one time (in the Middle Ages) as the "elixir of life", it is now recognized that the therapeutic value of ethanol is extremely limited and that chronic ingestion of excessive amounts presents a major social and medical problem (Rall, 1990).

1.2 BACKGROUND

1.2.1 Pharmacokinetics of Ethanol

Ethanol is unusual among drugs in several aspects of its pharmacokinetics. Particularly
striking is the great biological inter-subject variability in alcohol consumption patterns as well as in alcohol elimination, in the pattern of short-term fluctuations of serum ethanol concentrations, and in the partitioning of alcohol between the blood and other body fluids and tissues even at equilibrium (Dubowski, 1985).

**Absorption**

After oral ingestion, it is almost completely absorbed, primarily from the small intestine, by passive diffusion (Holford, 1987; Wilkinson et al., 1977). Ethanol ingested on an empty stomach is very rapidly absorbed with peak serum concentrations occurring between 30 to 90 minutes. The rate of alcohol absorption after oral administration is greatly influenced by the nature and concentration of the alcoholic beverage (O’Neill et al., 1983; Dubowski, 1987; Wilkinson, 1977), the rate of ingestion (O’Neill et al., 1983), the fed or fasted state (Sedman et al., 1978), the nature and composition of food (Sedman et al., 1978), as well as a multitude of other physical, biological, psychological, and temporal factors. Several studies have investigated the effect of these factors, either individually or in combination, on the peak concentration of ethanol achieved as well as the time of peak concentration. These studies have revealed the following:

1) Highly concentrated solutions of ethanol, when ingested, are relatively slowly absorbed, because of the inhibitory effect of these high concentrations on gastric emptying, thus delaying the arrival of the ethanol in the small intestine where most of the absorption occurs (Dubowski, 1983; Wilkinson et al., 1977).
2) Large volumes of very dilute solutions are also absorbed relatively slowly, possibly due to the slowing effect of the volume on gastric emptying rate (Hunt and Macdonald, 1954; Wilkinson et al., 1977).

3) Food has a large effect on ethanol absorption. Both the nature of the food (solid or liquid), as well as the composition of the food (carbohydrate or fat or protein) are important determinants of the peak ethanol concentration. The concomitant ingestion of various foods with ethanol results in lower peak concentrations and increased time to peak concentration. It is postulated that this effect is also mediated by the delaying of gastric emptying time resulting from the intake of carbohydrate or fatty foods (Sedman et al., 1978).

Wilkinson et al. (1977) have successfully developed a PK model, incorporating gastric emptying as a first-order process from the stomach to the small intestine along with first-order absorption from the intestine into the body compartment and capacity-limited elimination from the body compartment, to describe the ethanol-concentration profiles obtained following oral administration of ethanol to healthy male volunteers.

**Distribution**

The distribution of ethanol throughout the body is largely governed by the water content of various organs and tissues, especially at equilibrium, since it is a small, polar, completely water soluble molecule. The volume of distribution of ethanol is comparable to total body water, which is about 60% of body weight (Marshall et al., 1984; Holford,
Elimination

Elimination of ethanol occurs primarily through metabolism with minute fractions of the administered dose being excreted in the breath (0.7%), sweat (0.1%), and urine (0.3%) (Holford, 1987). Metabolism primarily occurs in the liver via enzymatic oxidation by alcohol dehydrogenase to acetaldehyde (Lunquist and Wolthers, 1958; Wagner et al., 1976; Rall, 1990).

For the first half of this century, the classical view of ethanol kinetics in humans was that the elimination of ethanol occurred at a constant rate and was independent of the concentration of ethanol in the body. In 1933, Widmark developed an equation, based on zero-order kinetics, to describe the concentration-time relationship for ethanol (Wilkinson, 1980). The use of this zero-order model was widespread until 1958, when Lunquist and Wolthers (1958) first proposed that the Michaelis-Menten model for enzyme kinetics could be used to describe the elimination of ethanol in humans. In this model, elimination by a particular enzyme system is characterized by the elimination capacity, i.e., the maximum elimination rate ($V_{max}$), and the concentration at which the enzyme system metabolizes its substrate at 50% of the elimination capacity ($K_m$). For many drugs that are metabolized, typical (therapeutic) concentrations are low relative to the $K_m$, and the elimination can be parameterized by a single PK parameter, i.e., clearance (apparent first-order elimination). Ethanol is unusual because "typical" concentrations are in excess
of the $K_m$, and both $V_{\text{max}}$ and $K_m$ must be known to determine the elimination rate. The elimination rate is non-linearly related to the concentration, and the elimination is considered to be capacity-limited. When concentrations are much higher than the $K_m$, the elimination approaches $V_{\text{max}}$ and the elimination rate is approximately zero-order, i.e., the elimination rate is independent of the ethanol concentration. When concentrations are below the $K_m$, the elimination rate approximates a first-order process.

Several investigators (Wagner et al., 1976, Wilkinson et al., 1976, Wilkinson et al., 1977, Rangno et al., 1981) have used PK models incorporating capacity-limited elimination models, using PK parameters, $V_{\text{max}}$ and $K_m$, to describe the overall elimination process for ethanol. Some investigators have attempted to fit models incorporating parallel first-order pathways of elimination to ethanol-concentration-time data to include the contribution of the fractions excreted in urine, breath, and sweat to the overall elimination process (O’Neill et al., 1984; Wilkinson, 1980; Holford, 1987). One-compartment models with capacity-limited elimination are most commonly used to describe the ethanol concentration vs. time profile, although investigators have used two-compartment models to incorporate the rapid distribution phase that is observed, especially after intravenous infusions of ethanol (Hartman et al., 1988).

Mean population estimates for the PK parameters for ethanol elimination, from studies done in young healthy males, are 8.5 g/hr/70 kg for $V_{\text{max}}$, 80 mg/L for $K_m$, and 37 L/70kg for $V_d$ (Holford, 1987). There is considerable variability in the estimates of $K_m$.
from different studies (Holford, 1987). This may be a consequence of the differences in sampling schedules of terminal sampling time points, when concentrations are less than or equal to the $K_{m}$. This may also be due to differences in the limit of quantitation of the different analytical methods used for the analysis of ethanol in various biological fluids, such as gas chromatography (Wilkinson et al., 1975), enzymatic methods (Poklis and Mackell, 1979), immunoassay methods (Cary et al., 1984; Abbott TDx Manual, 1995), as well as the estimation of ethanol concentrations in breath (Harger et al., 1950; Mason and Dubowski, 1976).

**Factors affecting ethanol pharmacokinetics**

In addition to the factors affecting the absorption of ethanol listed above, the oral absorption of ethanol depends on other factors including the dose (Wagner et al., 1976; Pikaar et al., 1988; Wagner and Patel, 1972) and the rate of ingestion (Dubowski, 1985; O’Neill et al., 1983) as well as individual factors such as gender, body-weight and body composition (Sutker et al., 1987; Marshall et al., 1983). Since ethanol follows capacity-limited elimination kinetics, an increase in dose results in a disproportionate increase in serum concentration and area under the curve (a measure of systemic exposure). However, the intrinsic pharmacokinetic parameters $V_{\text{max}}$ and $K_{m}$ are thought to be independent of dose. The rate of input can also affect the peak concentration and time of peak concentration as described earlier. However, the rate of ingestion would not be expected to influence the intrinsic pharmacokinetic parameters for ethanol.
Factors that influence ethanol elimination include ethanol intake, food, other drugs, gender, body weight, body composition, as well as genetic influences (Wilson et al., 1984; Thurman et al., 1989; Frezza et al., 1990; Sedman et al., 1978; Pikaar et al., 1988; Lane et al., 1985; Holford, 1987; Marshall et al., 1983).

Acute ethanol intake can affect the elimination rate of ethanol as shown by the study by Wilson et al. (1984) who demonstrated an increase in the elimination rate for ethanol following the administration of a second dose during the elimination phase of the first dose administered a few hours earlier. This may be explained in part by an increase in hepatic blood flow since ethanol has been shown to increase hepatic blood flow and therefore could increase its own elimination (Mendeloff, 1954). The effect of chronic ethanol use on the pharmacokinetics of ethanol has been the subject of some debate because studies in humans are difficult to interpret due to inadequately controlled factors such as duration and quantity of chronic exposure. One study that observed the effect of several weeks of ethanol consumption in non-alcoholic subjects on the pharmacokinetics of ethanol found that the elimination rate was not significantly altered after 45 g/day ethanol consumption for 3 weeks (Holtzman et al., 1985). However, since the authors used zero-order pharmacokinetic models to estimate the ethanol elimination rates, these results should be interpreted with some caution.

Food, especially that rich in fat or carbohydrates, also appears to reduce the elimination parameters for ethanol, as demonstrated by Sedman et al. (1978). However, since these foods may also affect hepatic blood flow which could have affected the estimates of $K_m$.
and $V_{\text{max}}$, this may be a confounding factor in the interpretation of the studies done by Sedman et al. (1978).

Although there are several studies investigating the effect of ethanol on other drugs administered concurrently (Lane et al., 1985), there are few studies evaluating the effect of other drugs on ethanol pharmacokinetics or pharmacodynamics. Studies have demonstrated the lack of effect of drugs such as cimetidine and ranitidine on ethanol elimination (Holtzman, 1985), while studies evaluating the influence of nicotine and smoking on ethanol elimination have demonstrated that ethanol elimination rates were increased by 20% in subjects who drank but did not smoke, and by 45% in subjects who drank and smoked compared with subjects who did neither (Kopun and Poping, 1977). One study evaluating the effect of oral contraceptives on ethanol pharmacokinetics reported that ethanol elimination rates in women who used oral contraceptives were about 20% lower than in women who did not use oral contraceptives (Jones and Jones, 1984). Although the subjects in both groups were matched for weight, the subjects in the contraceptive group had 11% lower peak concentrations. This may reflect differences in volumes of distribution between the two groups and may account, in part, for the differences in elimination rates observed between the two groups in this study. In general, the influence of interacting drugs and diseases on ethanol disposition has not been studied systematically, and the only studies performed to date have several limitations that makes the interpretation of the results somewhat problematic.

Gender and body-weight differences have been implicated as significant determinants of
ethanol disposition in several studies (Sutker et al., 1987; Marshall et al., 1983; Radlow and Hurst, 1985). A study by Marshall and his colleagues in 1983 investigating the elimination of ethanol in male and female subjects reported that females achieved significantly higher peak serum ethanol concentrations and areas under the curve than males following oral administration of 0.5 g/kg ethanol. The authors also reported that women had a significantly lower volume of distribution than male subjects, although their elimination rates were similar. However, this study used zero-order kinetic analysis. In this study, the investigators demonstrated that the apparent volume of distribution was significantly correlated with total body water (measured using a tritiated-water dilution method) suggesting that the gender differences in ethanol pharmacokinetics are secondary to gender differences in body water content. Since ethanol distributes into total body water, women have smaller volumes of distribution for ethanol than men and therefore achieve higher peak concentrations for a given dose of ethanol than men.

Another study reported that differences in peak concentrations following equivalent doses of ethanol administered to men and women were due to differences in first-pass metabolism of ethanol in the gastrointestinal tract, which was significantly correlated with gastric alcohol dehydrogenase activity (Frezza et al., 1990). The investigators concluded that females have lower gastric alcohol dehydrogenase activity resulting in a lower degree of first-pass metabolism and therefore in higher concentrations compared to males. However, some studies have demonstrated no differences in the first-pass metabolism of ethanol between males and females (Ammon et al., 1996).
1.2.2 Pharmacodynamics of Ethanol

Pharmacodynamics, or the relationship between drug concentration in the systemic circulation and pharmacological effect(s), has been the subject of numerous studies. Understanding this relationship is important because it contributes to the inter-individual variability observed in drug response. In general, determining the relationship between drug concentration and response is also necessary for optimization of drug therapy. Studies of the pharmacodynamics of centrally acting drugs have been limited by the difficulty in obtaining quantitative measures of CNS response (Dingemanse et al., 1988). In general, measures of drug effect used in pharmacodynamic studies should be quantitative, objective, non-invasive, reproducible (both within and between individuals), and sensitive to changes in drug concentration. The measure should also have some relationship to the therapeutic or toxic clinical effects of the drug (Slattum, 1992). The following sections discuss some of the pharmacodynamic measures that have been used to characterize the pharmacodynamics of ethanol.

1.2.2a Neuropharmacology of Ethanol

Ethanol is considered to be a central nervous system (CNS) depressant and its responses characteristically include euphoria, impaired thought processes, and decreased mechanical efficiency (Evan et al., 1974). Although alcoholic drinks are viewed as stimulating, this apparent stimulation is a result of depression of the inhibitory control mechanisms of the brain (Rall, 1990). However, as intoxication becomes more advanced, there is
progressive depression of CNS function that can ultimately lead to respiratory depression, coma and even death.

For many years it has been thought that ethanol, like volatile anesthetics exerts its depressant effects on the CNS by perturbation of the neuronal membrane lipids (Rall, 1990; Tabakoff and Hoffman, 1987; Dietrich et al., 1989). This membrane hypothesis of the mechanism of action of ethanol has been widely accepted, and other studies have since refined this hypothesis resulting in the view that the interactions of ethanol are specific to certain regions of the membrane, reflecting the nonuniform distribution of integral membrane proteins (Tabakoff and Hoffman, 1987). Ethanol also has selective effects on specific membrane bound enzyme systems, such as selective inhibition of the monoamine oxidase enzyme system (Tabakoff et al., 1985), and enhanced sensitivity of neuronally localized Na⁺, K⁺-ATPase (Marks et al., 1984). Ethanol has also been shown to interact with specific neurotransmitters and receptor-effector coupling systems, including activation of catecholamine receptor-associated adenylate cyclase in the brain (Luthin and Tabakoff, 1984; Saito et al., 1985), inhibition of binding of ligands associated with the chloride channel complex of the GABA receptor (but not the binding of GABA or benzodiazepines to their receptors) (Thyagarajan and Ticku, 1985), and suppression of the excitatory effects of endogenous glutamate at the NMDA receptor (Deitrich et al., 1989). However, all these effects were observed in animal models or in-vitro systems, and the relationship between the effect of ethanol on these systems and the observed
behavioral effects of ethanol in humans are somewhat unclear and remain to be unravelled.

1.2.2b Effects on psychometric performance

Psychometric performance tests have been used to assess the pharmacodynamics of several centrally-acting drugs, including ethanol (Hindmarch, 1980). These psychomotor tests provide a non-invasive and quantitative measure of motor and cognitive function and allow comparison between different drugs or between different doses of the same drug (Hindmarch, 1980). Studies evaluating these effects of centrally-acting drugs measure drug-induced changes in various aspects of human performance, including cognition, attention, memory and motor aspects. These studies also attempt to determine the physiological mechanisms that have been altered by these drugs, including neurochemical effects, changes in cerebral blood flow and alterations in patterns of neuroelectric activity (Wesnes et al., 1987). A large number of tasks have been used to evaluate the cognitive effects of drugs ranging from the ability to rapidly tap a stylus to simulated car driving. The introduction of computerized psychometric testing procedures has resulted in a wider range of tests that are able to measure different aspects of performance with a high degree of sensitivity (Wesnes et al., 1987). In order for these tests to be optimally used in pharmacodynamic studies of psychoactive drugs, they should be sensitive to both impairment as well as improvement in performance produced by the drug, provide quantitative measures of effect, be sensitive to small changes in drug concentration, and
should be reproducible, both within and between subjects. The tests should measure both
cognitive and motor aspects of psychometric performance and should include some
aspects of functioning that have relevance and importance for daily behavior (Slattum,

However, psychometric tests can sometimes be limited in that they may be prone to
subjective influences such as learning, motivation, and fatigue, which can affect their
reproducibility and sensitivity. Also, the relationship between changes in performance on
the psychometric tasks and the behavioral and psychological effects of the drug are

There is considerable interest in evaluating the effects of ethanol on human performance,
especially as it relates to the problems associated with drunk driving (Irving and Jones,
1992). Some studies have been done to correlate the dose or concentration of ethanol
with impairment in reaction time and cognitive ability to determine what amounts or
concentrations would be considered unsafe and illegal from a medicolegal perspective
(Dubowski, 1977; Irving and Jones, 1992).

Alcohol has been shown in several studies to produce impairment of psychometric
function assessed by various tests including tracking, digit symbol substitution, reaction
time, body sway, hand steadiness and finger tapping (Evan et al., 1974; Sidell and Pless,
1971; Fagan et al., 1987; Idestrom and Cadenius, 1968; Wittenborn, 1987). In these
studies alcohol has been shown to decrease speed and accuracy of performance and
increase errors in performance consistent with psychomotor impairment.
In a review of psychometric tests in psychopharmacology (Wittenborn, 1987), the author has summarized the different tests used to study the psychometric performance effects of ethanol. The results show that alcohol showed impairment effects in 20 out of 22 tests that were compared, indicating that alcohol produces significant impairment of psychomotor performance and that psychometric tests are sensitive measures of the effects of ethanol.

There are very few studies, however, that have attempted to determine the temporal relationship between alcohol concentration and psychometric impairment. Also, there are very few studies evaluating the effect of factors such as dose, rate of input (or ingestion), or degree of exposure, as well as factors such as age, gender, or interacting drugs, on this relationship (Moskowitz et al., 1976, Taberner, 1980).

1.2.2c Effects on mood and subjective state

Most psychoactive drugs, including ethanol, produce changes in mood and perception of subjective states. These changes in mood and perception can be measured using various scales. These scales are primarily of two types: self-rated or observer-rated, depending on the user. These scales can be constructed as questionnaires with multiple choice responses, or as visual analog scales. Visual analog scales usually consist of a line with its ends defined by the extremes of the variable to be measured, for e.g., "not at all" to "extremely" for the variable "DRUNK" on an alcohol impairment scale, and individuals makes a mark on the line corresponding to his/her present state with respect to that
variable. Visual analog scales have been used in several studies to measure drug-induced changes in mood and subjective states (Bond and Lader, 1974). They have the advantage in that they are easy and quick to complete, easy for the investigator to score, can be used repeatedly and reproducibly (Bond and Lader, 1974; Slattum, 1992). They are less subject to motivational and learning effects, although they can be subject to fatigue or boredom effects if measured too frequently. They do require subject co-operation and thus could be difficult to complete in very sedated to hyperactive subjects (Slattum, 1992).

Ethanol has been studied by investigators interested in its behavioral effects. The detrimental effects of alcohol on human performance as well as on subjective measures of impairment are well documented (Begleiter and Platz, 1972; Jones and Vega, 1973; Moskowitz and Burns, 1976; Schuckit, 1984). Ethanol produces numerous mood effects ranging from increased alertness to relaxation and a state of well-being or euphoria (Ekman et al., 1963; Lukas et al., 1986). These behavioral effects have been measured by various subjective visual analog scales including the Subjective High Assessment Scale (SHAS) (Shuckit and Gold, 1983; Lex et al., 1988), Drug Effects Questionnaire (DEQ) (de Wit et al., 1990), various versions of the Profile of Mood states (POMS) (McNair et al., 1971; deWit et al., 1990; Nagoshi et al., 1992), the State-Trait Anxiety Inventory (STAI) (Sutker et al., 1987), various versions and sub-scales of the Addiction Research Center Inventory (Hill et al., 1963; Turkkan et al., 1988), and a multitude of empiric scales derived from the above-listed scales (Kaplan et al., 1985; Radlow and Hurst,
These studies also show that ethanol produces dose-related changes in subjective measures of intoxication, perceived impairment and sedation. These scales have been shown to be fairly sensitive to the effects of ethanol on subjective state and mood.

1.2.2d Effects on electroencephalography

Quantitative EEG is being increasingly used to study the pharmacodynamics of psychoactive drugs (Dingemanse et al., 1988; Fink, 1982; Kroboth et al., 1988; Slattum, 1992; Jagannathan, 1995). The EEG provides an ongoing record of the neuroelectric activity of the brain, either in the resting state or under different activation procedures (e.g., repetitive photic stimulation, drug administration etc.). Although the scalp-recorded EEG is an overall measure of brain activity, it provides one of the best and most direct measures available for assessing the functional state of the CNS (Begleiter and Platz, 1972). Quantitative EEG is objective and non-invasive, and derived parameters change gradually with changes in plasma drug concentrations. Repeated or continuous measures of the EEG can be made, although a familiarization session before the study is advisable to avoid a first-session effect due to anxiety (Fink and Irwin, 1983; Slattum, 1992; Jagannathan, 1995). There are several environmental factors that can influence the results of studies evaluating the EEG as a quantitative measure of drug effect (Sannita, 1990). The ability to monitor ongoing neuroelectric activity allows for the investigation of the relationship between subjective states, behavioral changes, and electrophysiological
activity of the CNS at baseline as well after administration of a psychoactive drug such as ethanol. Of particular interest is the question whether alcohol-induced EEG changes parallel the gradual ethanol-induced changes in subjective and behavioral responses (Begleiter and Platz, 1972).

Studies investigating the effects of acute ethanol administration on the adult human electroencephalogram (EEG) have been generally consistent (Ehlers et al., 1989; Ehlers and Shuckit, 1990). Most studies report an increase in EEG amplitude, particularly in the alpha band (8 to 12 Hz) and a slowing of the dominant alpha frequency following low to moderate doses of ethanol (Begleiter and Platz, 1972; Lukas et al., 1986; Ehlers and Shuckit, 1989, Ehlers and Shuckit, 1991, Kaplan et al., 1988). After the ingestion of larger doses, an increase in lower frequencies (delta: 0 to 4 Hz, and theta: 4 to 8 Hz) is observed and is associated with profound sedation (Ehlers and Shuckit, 1991; Lukas et al., 1986, Lukas and Mendelson, 1986). Studies have also emphasized a large degree of individual variability in responses to alcohol (Lehtinen, 1978, 1985). The studies evaluating the effects of ethanol on the EEG are limited in that they were primarily aimed at evaluating EEG responses as objective measures to identify populations at risk for alcoholism rather than evaluating the EEG as a pharmacodynamic measure. Thus, these studies did not evaluate the complete time course of the ethanol-induced EEG changes. Most studies evaluated initial effects during the first two hours after ethanol administration.

Several factors have been shown to modify the acute response in individuals following
ethanol administration including quantity and frequency of drinking (Cloninger et al., 1984), family history of alcoholism (Shuckit, 1984; Pollock et al., 1986), individual differences in ethanol metabolism (Zeiner et al., 1979), as well as the baseline (pre-drug) EEG activity (Ehlers et al., 1989). There are several reports of studies evaluating differences in EEG activity (both at baseline and following ethanol administration) in subjects at risk for alcoholism, but these studies have generally been inconclusive and inconsistent (Cohen et al., 1990; Ehlers et al., 1990; Pollock et al., 1983).

1.2.3 Acute tolerance development to effects of ethanol

The phenomenon of decreased effect with prolonged exposure to a drug is called tolerance (Porchet et al., 1988). When the tolerance develops within the time course of a single dose, it is called acute tolerance or tachyphylaxis. Development of acute tolerance has been recognized for a number of drugs, including centrally-acting drugs such as cocaine (Chow et al., 1985; Ambre et al., 1988), caffeine (Shi et al., 1993), morphine (Ekblom et al., 1993, Ouellet and Pollack, 1995)) and nicotine (Porchet et al., 1988). Tolerance development may be related to changes in the number of receptors in the target tissue (down-regulation), decreased receptor-effector coupling, depletion of secondary endogenous messengers, and/or a physiological adaptation by counter-regulatory feedback systems (Danhof and Mandema, 1994).

Acute tolerance to alcohol was first described by Mellanby, who reported a lower impairment at a given ethanol concentration in the descending limb of the ethanol
concentration-time curve than at the same concentration in the ascending limb of the curve (Gengo et al., 1990). Since then, several studies have characterized the development of acute tolerance to single doses of ethanol (Goldberg, 1943; Moskowitz et al., 1976; Vogel-Sprott, 1979; Radlow and Hurst, 1985; Jones and Vega, 1972). However, there are also reports describing the lack of tolerance to alcohol’s effects (Gengo et al., 1990; Wilson et al., 1984; Kaplan et al., 1985; Sidell et al., 1971; Linnoila et al., 1978; Pishkin et al., 1983; Rohrbaugh et al., 1987).

One explanation for this inconsistency may be the endpoint used to measure the pharmacological effects of ethanol. Endpoints that measure subjective perception of intoxication, such as those used by Radlow and Hurst (1985) and Jones and Vega (1972), indicate the development of acute tolerance. In general, data from studies measuring subjective assessments are consistent with the development of acute tolerance. The opposite conclusion is reached when objective psychological functions are assessed, such as the psychometric tests used by Kaplan et al. (1985) and Rohrbaugh et al. (1987), among others. Gengo et al. (1990) observed that subjective impairment effects following ethanol administration were lower during the declining phase of the concentration-time profile relative to the effects during the ascending phase of the concentration-time profile, whereas scores on the Digit Symbol Substitution Test (DSST), a psychometric test, were similar at comparable concentrations on the ascending and descending limbs of the concentration-time profile. Generally, studies measuring psychomotor performance fail to show significant acute tolerance to ethanol.
Other factors that may influence the development of acute tolerance include the rate and
direction of change of concentration and the degree and rate of prior exposure to ethanol.
Gender, age and previous ethanol use may also be contribution factors, however, they
have not been studied in a rigorous manner.

Several paradigms can be used to study the development of acute tolerance to the effects
of drugs, especially alcohol. One method is to compare effects at the same concentrations
during the ascending and descending limbs of the alcohol concentration-time curve (Jones
et al., 1972; Gengo et al., 1990). Another method is to compare the responses following
the administration of paired IV infusions of the drug separated by different intervals of
time, such as the method used by Porchet et al. (1988) for nicotine and by Shi et al.
(1993) for caffeine. In such a paradigm, a decrease in the response following the second
infusion relative to the first infusion can be interpreted as the development of acute
tolerance.

Yet another method is to study the time course of the effects of ethanol at "steady-state",
i.e., when concentrations in the body are constant. In such a paradigm, a diminution of
the effects of ethanol, despite maintenance of constant plasma (or serum) concentrations,
can be interpreted as the development of acute tolerance. A dosing regimen can be
designed to control the rate of input such that levels can be maintained fairly constant
over prolonged durations. Intravenous administration of ethanol can provide good control
of the input rate, which is critical to the achievement of these constant levels. The study
by Kaplan et al. (1985) is the only study found that used this approach. In this study,
ethanol was administered orally to achieve a breath ethanol concentration equivalent to a serum ethanol concentration between 800 and 1000 mg/L, then a maintenance dose was given every 30 minutes to maintain the alcohol concentration at that level for 6 hours. Several measures, including postural sway, manual tracking, word recall test (a measure of cognitive ability), as well as subjective measures of intoxication using visual analog scales, were evaluated. The results from this study indicated that ethanol resulted in psychometric impairment and subjective impairment, but no acute tolerance development was observed to the motor or physiological effects; however, acute tolerance was observed for the word recall test.

Although there are several studies demonstrating the development of acute tolerance to the effects of ethanol, there are no studies assessing the quantitative aspects of acute tolerance to ethanol. In order to model the rate and extent of tolerance development, modifications of the classical effect model may be used (Holford, 1992). Ideally, such a model would allow the characterization of both full and partial tolerance as well as any rebound effects, as well as the characterization of the time course of effect upon continuous as well as repeated intermittent administration. Quantitative information on the rate and extent of acute tolerance development can provide a description of the pharmacodynamic properties of particular drugs to which tolerance develops. This description can be used to choose drug regimens minimizing the development of tolerance. Since many drugs of abuse, including ethanol are subject to tolerance development, quantitation of this tolerance development may improve the understanding
of the specific temporal patterns of drug abuse and related complications.

Various pharmacokinetic-pharmacodynamic (PK-PD) models have been developed to quantitate the tolerance development for several drugs, including furosemide (Hammarlund et al., 1985), nitroglycerin (Bauer and Fung, 1994), cocaine (Chow et al., 1985; Ambre et al., 1988), caffeine (Shi et al., 1993), morphine (Ekblom et al., 1993, Ouellet and Pollack, 1995)) and nicotine (Porchet et al., 1988). There are however no studies which have attempted to model the development of tolerance to the effects of ethanol.
CHAPTER 2
RESEARCH HYPOTHESES

2.1 HYPOTHESIS

The hypotheses guiding this research project are:

1. the rate and degree of ethanol exposure (oral and intravenous) in young healthy males and females affect the pharmacokinetics and pharmacodynamics of ethanol in a non-linear fashion.

2. the EEG changes after ethanol administration (oral and intravenous) correlate with changes in psychometric performance and subject-rated impairment, as well as serum ethanol concentrations.

3. acute tolerance develops to the subjective effects of ethanol which is not reflected in changes in EEG activity or psychometric performance.

This study was conducted in two parts. Part I was a pilot study in healthy male volunteers to study the effect of dose and input-rate on the pharmacokinetics and pharmacodynamics after oral administration of ethanol. This study was a double-blind, placebo-controlled, five-way crossover study in six healthy male subjects. Subjects were administered two doses of oral ethanol (0.3 g/kg and 0.6 g/kg), each at two input-rates
(20 minutes and 50 minutes), and placebo. This study was designed to investigate the pharmacokinetics of ethanol, as well as to assess changes in pharmacodynamic measures, such as EEG, psychometric performance and changes in subjective measures of impairment, following oral ethanol administration. This study evaluated the relationship between these subjective and objective measures of impairment, and the relationship between these measures and serum ethanol concentrations.

Part II was a study in healthy male and female subjects evaluating the pharmacokinetic-pharmacodynamic relationship after intravenous administration of ethanol and acute tolerance development to the effects of ethanol. This study was a double-blind, placebo-controlled, four-way crossover study in sixteen healthy subjects (8 males and 8 females). Subjects were administered individualized intravenous ethanol infusions, at different rates to achieve a target concentration of 1000 mg/L at the end of 1 hour (treatment A), at the end of 6 hours (treatment B), as well as to achieve the target concentration at the end of the first hour and to maintain that concentration at "steady-state" for the next five hours (treatment C).

This study was designed to investigate the pharmacokinetics of ethanol, as well as to assess changes in pharmacodynamic measures, such as EEG, psychometric performance and changes in subjective measures of impairment, following individualized intravenous ethanol infusions in a concentration-controlled fashion. This study evaluated the relationship between these subjective and objective measures of impairment, and the relationship between these measures and serum ethanol concentrations. This study also
evaluated the development of acute tolerance to the effects of ethanol, and attempt to demonstrate the temporal disparity between objective impairment and subjective impairment. This study also examined gender differences in ethanol pharmacokinetics and pharmacodynamics.

2.2 RATIONALE AND SIGNIFICANCE

This research aims to assess the relationship between serum ethanol concentrations, EEG changes, changes in psychometric performance and changes in subjective measures of impairment after administration of ethanol, both oral and intravenous, at different rates. This research is also aimed at examining the development of acute tolerance to the pharmacological effects of ethanol, as measured by these pharmacodynamic end-points. Of special interest is to characterize the temporal disparity between the performance impairment and perceived impairment following ethanol administration to healthy subjects, as well as to evaluate whether ethanol-induced EEG changes correlate with performance impairment or with subjective impairment.

The relevance of acute tolerance, particularly in subjective effects is considerable. The temporal disparity between objective impairment and subjective impairment can result in an inability to accurately self-assess sobriety at a time when blood ethanol levels begin to decline. This may result in the person judging his/her impairment at the time of performance of tasks such as driving as not significant enough to influence their skills and could have a significant impact on serious problems such as drunk driving. This
research would allow the evaluation of a clinical paradigm to assess the time-course of acute tolerance development to the pharmacological effects of ethanol, including effects on the EEG, on psychometric performance and on perceived impairment. This paradigm would also allow the evaluation of the effect of input-rate and degree of acute exposure on the pharmacokinetics, pharmacodynamics and tolerance development. This approach can be used to study the development of acute tolerance, not only to these effects, but also to other pharmacological effects of ethanol, such as neuro-endocrine or cardiovascular effects in various populations such as healthy elderly volunteers, alcoholics, as well as subjects at high risk for alcoholism such as children of alcoholics. Comparison of the differences in pharmacokinetics and pharmacodynamics of ethanol as well as to acute tolerance development in these populations may help to further increase our understanding of the inter-individual differences in sensitivity to ethanol’s effects. Recognition of the complexity of the relationships between ethanol dose, time and pharmacological effects is essential for the development of a paradigm for measuring the influence of factors such as gender, age and concomitant drugs on the effects of ethanol. Ethanol can also be viewed as a model CNS depressant for the evaluation of objective PD end-points, such as EEG, psychometric tests and subjective measures of mood and behavior, as well as other end-points such as neuro-endocrine concentrations and cardiovascular responses for ethanol and other psychoactive drugs in order to correlate these surrogate measures with concentration or dose.
CHAPTER 3
ORAL ETHANOL STUDY

3.1 SPECIFIC AIMS

The specific aims of this study were:

(1) To investigate the pharmacokinetics and pharmacodynamics following administration of two single, escalating doses, each at two different dose rates, of oral ethanol in healthy male subjects.

(2) To assess changes in objective measures of impairment viz., EEG and psychometric performance, as well as subjective measures of impairment after oral ethanol administration.

(3) To examine the relationship between changes in the objective measures and subjective measures of impairment, and the relationship between these measures and serum ethanol concentrations.

3.2 STUDY DESIGN

This study was a randomized, double-blind, placebo-controlled, five-period crossover study in six (6) healthy male volunteers. The start of each study period was separated by a washout period of at least 1 week. Subjects received one of the following five...
treatments during each study period:

Treatment A: ethanol 0.3 g/kg body weight administered over 20 minutes (low-fast);
Treatment B: ethanol 0.6 g/kg body weight administered over 20 minutes (high-fast);
Treatment C: ethanol 0.3 g/kg body weight administered over 50 minutes (low-slow);
Treatment D: ethanol 0.6 g/kg body weight administered over 50 minutes (high-slow);
and
Treatment E: placebo.

Each subject was assigned to one of the three randomization sequences listed in table 3.1 by an unblinded pharmacist, and received each treatment exactly once. Six subjects were scheduled to be enrolled into the study with two subjects assigned to each sequence.

3.3 EXPERIMENTAL METHODS

3.3.1 SUBJECTS

Six healthy male volunteers participated in the study. Subjects were considered for inclusion if they were healthy male non-smokers between the ages of 21 and 35 years. All subjects were determined to be healthy based on the results of medical screening consisting of: (a) medical history, (b) physical examination, (c) vital signs (supine and standing systolic and diastolic blood pressure, heart rate and body temperature) as well as an orthostatic test, (d) 12-lead EKG including a 30 second rhythm strip, (e) laboratory screen consisting of SMAC-20, CBC and urinalysis, as well as a urine drug test and
Table 3.1  Randomization sequences for oral ethanol study

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>Period 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>E</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>II</td>
<td>C</td>
<td>D</td>
<td>E</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>III</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
</tbody>
</table>

A: Ethanol 0.3 g/kg body weight over 20 minutes
B: Ethanol 0.6 g/kg body weight over 20 minutes
C: Ethanol 0.3 g/kg body weight over 50 minutes
D: Ethanol 0.6 g/kg body weight over 50 minutes
E: Placebo
Subjects were excluded from the study if (a) they were smokers, (b) they had a clinically significant history of renal, hepatic, cardiovascular, gastro-intestinal, neurological, pulmonary, or hematologic disease, (c) they had a history of alcohol abuse, drug addiction, psychological dependence on drugs, or psychiatric illness, (d) they had first degree relatives (mother, father, or siblings) with a history of mental illness or alcohol/drug abuse, (e) they took any medications chronically or had taken any prescription medication or investigational drugs for at least 4 weeks before entering the study, (f) had an average daily caffeine intake greater than the equivalent of two cups of coffee, or (g) had an average weekly alcohol intake greater than 6 oz. (180 ml) of ethanol (approximately twelve 12 oz. beers).

Before enrolling in the study, each subject signed an informed consent form attesting that the study procedures were explained to him and that his participation in the study was voluntary.

After successfully completing the medical screening, all subjects underwent an EEG and psychometric test familiarization period. During this period, EEG recordings were made for about 4 hours to familiarize subjects to the EEG procedures to minimize any first-session anxiety effects. Subjects also learned and practiced the psychometric tests to optimize their performance and to minimize any learning effects during the study. Within one week after each subject completed the study, the physical examination and vital signs, laboratory tests, and EKG were repeated.
3.3.2 PROCEDURES

The clinical study was conducted at the General Clinical Research Center (GCRC) unit at the Medical College of Virginia Hospitals, Medical College of Virginia-Virginia Commonwealth University. The Committee on the Conduct of Human Research at MCV-VCU reviewed and approved the study protocol, and the informed consent form (August 1991) prior to the start of the study. The protocol, including revisions, as well as the consent form are in Appendix A. The study was conducted from February through July of 1992.

During each of the five study periods, the following procedures were followed:

3.3.2A Admission to Clinical Research Unit

Subjects were admitted to the GCRC unit on the evening of the day prior to each day of ethanol or placebo dosing and were discharged on the morning after the day of ethanol or placebo dosing. Subjects were instructed not to consume any medications (including OTC medications and vitamins) or caffeine for 72 hours before each study period and during each study period. Subjects also had to abstain from alcohol starting 72 hours before the first treatment period through the end of the study. All subjects had a negative urine drug screen and breath alcohol test on admission for each study period. All subjects completed a verbal probe concerning recent medical history as well as alcohol and medication use on admission for each study period.
3.3.2B Drug Preparation and Administration

During each treatment period, the subjects received one of the following five treatments:

Treatment A: ethanol 0.3 g/kg body weight given in four equal "drinks" every 5 minutes at 0, 5, 10 and 15 minutes, followed by 2 placebo "drinks" at 30 and 45 minutes after the start of dosing;

Treatment B: ethanol 0.6 g/kg body weight given in four equal "drinks" every 5 minutes at 0, 5, 10 and 15 minutes, followed by 2 placebo "drinks" at 30 and 45 minutes after the start of dosing;

Treatment C: ethanol 0.3 g/kg body weight given in four equal "drinks" every 15 minutes at 0, 15, 30 and 45 minutes, with 2 placebo "drinks" at 5 and 10 minutes after the start of dosing;

Treatment D: ethanol 0.6 g/kg body weight given in four equal "drinks" every 15 minutes at 0, 15, 30 and 45 minutes with 2 placebo "drinks" at 5 and 10 minutes after the start of dosing;

Treatment E: Placebo given in 6 equal "drinks" at 0, 5, 10, 15, 30 and 45 minutes.

Each treatment was given exactly once and in random order according to the randomization sequence (table 3.1). Both the subjects and the investigators were blinded with respect to treatment. During each treatment period, subjects consumed six "drinks" according to the dosing schedule in table 3.2, in an attempt to blind subjects to the different rates of input.

Ethanol was administered as a 25% solution of 90.4 proof Vodka (Smirnoff Vodka, Ste
Table 3.2 Dosing schedule for oral ethanol study

<table>
<thead>
<tr>
<th>Time [min]</th>
<th>Treatment¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>0</td>
<td>X²</td>
</tr>
<tr>
<td>5</td>
<td>X</td>
</tr>
<tr>
<td>10</td>
<td>X</td>
</tr>
<tr>
<td>15</td>
<td>X</td>
</tr>
<tr>
<td>30</td>
<td>P³</td>
</tr>
<tr>
<td>45</td>
<td>P</td>
</tr>
</tbody>
</table>

1: A = Ethanol 0.3 g/kg over 20 minutes, B = Ethanol 0.6 g/kg over 20 minutes, C = Ethanol 0.3 g/kg over 50 minutes, D = Ethanol 0.6 g/kg over 50 minutes, E = Placebo.
2: X = Ethanol "drink".
3: P = Placebo "drink".
Pierre Smirnoff Fls, Hartford, CT) in fruit juice (equal parts orange and grapefruit). The "drink" was given ice-cold in an opaque container with a lid and was sipped with a straw. A vodka-soaked gauze pad was placed under the lid in an attempt to blind the subject to the contents. The placebo "drink" consisted of fruit juice and contained a small amount of ethanol (5% of the dose) in a further attempt to blind the subject.

Doses were prepared by an unblinded pharmacist, who assigned subjects randomly to one of the randomization sequences. A sealed copy of the randomization schedule was available at the research unit in case of an emergency.

3.3.2C Blood Sampling

Prior to dosing, a heparin containing catheter was inserted into a forearm vein for access to blood sampling.

Six ml blood samples for determination of serum ethanol concentration were collected in red-top tubes with no additives at the following times: pre-dose and 10 min, 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing. The blood was allowed to clot, centrifuged (within 1 hour of sampling) for 10 minutes, serum harvested and stored at -20°C until analysis by the TDx Analyzer (Abbott Laboratories, N. Chicago, IL).

The total volume of blood drawn for ethanol determination during the study was about 540 ml over the five-week period of the study.
3.3.2D Electroencephalography (EEG)

Five minute segments of 28-channel EEG, using a Neuroscience Brain Imager (NeuroScience Services, Mesa, AZ), were recorded for each subject with eyes closed at the following times: pre-dose and 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing. Subjects were asked to count back from 500 by threes in an attempt to maintain vigilance during the recordings. Omni-prep (D.O.Weaver and Co., Aurora, CO) was used to prepare the scalp prior to electrode placement and Electro-gel (Electro-Cap International Inc., Dallas, TX) was used as the conducting gel. The electrodes were placed using an Electro-cap (Electro-Cap International Inc., Dallas, TX) according to the 10/20 International System (Spehlman R, 1981) with 8 additional electrodes located 50% between the standard 10/20 placement. Linked ears were used as the reference. Four additional channels were used to monitor for vertical and lateral eye movements and electromyographic activity. All electrodes were made of tin. The electrode impedances were checked before each recording, and maintained at less than 5.6 kΩ and similar between electrodes. The raw EEG was stored on an optical disk until later analysis. Any disturbances in the room or subject movement during the EEG recording were documented. The Brain Imager filers were set as follows: Low filter - 0.3 Hz, High filter - 40 Hz, Notch filter - off. System integrity checks were performed biweekly throughout the study to ensure stability of channel calibration and proper filter settings.
3.3.2E Psychometric Performance Tests (PPT)

A battery of three psychometric tests was completed by each subject at the following times: pre-dose and 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing. The battery consisted of a computerized card-sorting task (CST), computerized motor performance task, finger tapping (FT) and a 90 second pencil-and-paper digit symbol substitution test (DSST) (Lezak, 1976). The computerized psychometric tests were part of the STIM software package (Neuroscan Inc., Herndon, VA). In the morning before dosing for each period, subjects practiced the psychometric test battery twice.

3.3.2F Subject-Rated Impairment (SRI) Scales

A 100 mm visual analog scale, based on the Subjective High Assessment Scale (SHAS) (Shuckit, 1984), was completed by each subject at the following times: pre-dose and 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing. The scale had 11 items: HIGH, DRUNK, CONFUSED, DIZZY, CLUMSY, FLOATING, SLURRED SPEECH, UNCOMFORTABLE, FEEL GREAT, FEEL TERRIBLE and ALCOHOL EFFECTS. Subjects indicated their perceived level of intoxication response for each item by placing a mark on an unnumbered 100 mm scale that ranged from "not at all" to "extremely".

3.3.2G Observer-Rated Impairment (ORI) Scales
A 100 mm visual analog scale was completed by a blinded investigator (VAR) for each subject at the following times: pre-dose and 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing. The scale had 3 items: HIGH, DRUNK and CONFUSED. The blinded investigator indicated his perception of the subject's level of intoxication by placing a mark on an unnumbered 100 mm scale that ranged from "not at all" to "extremely".

3.3.2H Safety Measurements

Vital signs, i.e., blood pressure (sitting) and heart rate, were measured, using a Dynamap (Critikon Inc., Tampa, FL), at the following times: pre-dose and 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing.

All subjects were observed for symptoms and signs of clinical intolerance to the drug or procedures and asked to report any adverse effects. These were evaluated by the Medical Monitor (MJ) for their clinical significance and potential need for treatment.

3.3.2I Diet

On the evening prior to dosing, subjects received a light snack. Subjects fasted from midnight on the evening before ethanol or placebo dosing until six hours after drug administration. Water was permitted ad libitum throughout each study period. Dinner and a snack were served 10 and 14 hours after dosing respectively. Caffeine-free beverages were served with meals. The same menu was served on corresponding days
of each study period.

3.3.2J Discharge from Clinical Research Unit

Subjects were discharged on the morning of the day after ethanol or placebo dosing. A breath alcohol test was done prior to discharge at the end of each treatment period to ensure that the subjects did not have detectable ethanol levels.

A study flow sheet is presented in table 3.3. When the study measurements were scheduled at the same time, they were conducted in the following sequence: 1) blood samples 2) EEG 3) PPT 4) SRI and ORI scales and 5) safety measurements, with the blood sample being collected at exactly the scheduled time.

When each subject completed the study, he was asked to assess which treatment he believed he had received during each period of the study.

3.3.3 SAMPLE ANALYSIS

Analysis of serum samples for ethanol concentrations was performed in the Biopharmaceutical Analysis Laboratory at the Department of Pharmacy and Pharmaceutics at MCV-VCU. Performance validation and sample analysis were conducted with the guidance of Clark March in the Biopharmaceutical Analysis Laboratory at the Department of Pharmacy and Pharmaceutics at MCV-VCU.

3.3.3A Analytical Method for Ethanol in Serum
Table 3.3 Study period flow sheet for oral ethanol study

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>-12</th>
<th>-10</th>
<th>-1</th>
<th>0</th>
<th>0.17</th>
<th>0.33</th>
<th>0.83</th>
<th>1.25</th>
<th>1.5</th>
<th>1.75</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
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SAC: Serum Samples for Alcohol Determination, EEG: Electroencephalography, PPT: Psychometric Performance Battery, SRI/ORI: Subject Rated Impairment & Observer Rated Impairment Scale, VS: Vital Signs (blood pressure, heart rate, temperature)
The analytical method used to measure ethanol concentrations in serum was fluorescence polarization immunoassay using the TDx Analyzer (Abbott Laboratories Inc., N. Chicago, IL). The TDx ethanol assay is a reagent system for the quantitative measurement of ethanol in human whole blood, serum, plasma or urine.

The assay utilizes radiative energy attenuation (REA) technology. The ethanol concentration is determined by the combined catalytic reactions of alcohol dehydrogenase (ADH) and diaphorase (Dase) to generate a dye. The reaction scheme is as follows:

\[
\text{ADH} \\
\text{EtOH} + \text{NAD} \rightarrow \text{Acetaldehyde} + \text{NADH} + \text{H}^+ \\
\text{Dase} \\
\text{NADH} + \text{MTT} \rightarrow \text{NAD} + \text{MT-Formazan}
\]

where NAD: Nicotinamide Adenine Dinucleotide

NADH: Nicotinamide Adenine Dinucleotide reduced

MTT: Monotetrazolium dye

The relationship between the concentration of ethanol and measured fluorescence intensity is established by generating a standard curve. Six calibrators of known concentrations (0, 250, 500, 1000, 2000 and 3000 mg/L) are run and the resulting attenuated fluorescence signal is measured. The calibration is then stored in the instrument. When an unknown is read, the concentration is calculated directly from the stored calibration curve (TDx Manual, 1995).
Materials and Reagents: The ethanol calibrators (standards), serum controls and reagent packs were obtained from Abbott Labs. The calibrator pack consists of six vials of accurately measured amounts of ethanol in an aqueous solution at the following concentrations: 0, 250, 500, 1000, 2000 and 3000 mg/L. The serum controls pack consisted of three vials of ethanol in human serum at the following concentrations: Control L: 500 mg/L (range: 425 - 575 mg/L), Control M: 1000 mg/L (range: 900 - 1100 mg/L), and Control H: 2500 mg/L (range: 2250 - 2750 mg/L). The reagent pack consisted of three vials, labelled S, T and P. Vial S was the substrate solution containing <5% Nicotinamide adenine dinucleotide in sodium citrate buffer. Vial T was the enzyme solution containing <5% yeast alcohol dehydrogenase and <1% diaphorase in a protein stabilizer solution containing components of whole blood in buffer. Vial P was the indicating solution containing <1% monotetrazolium dye and <0.01% fluorescein in solvent. The TDx dilution buffer, sample cartridges and sample cuvettes were purchased from Abbott Labs.

Calibration: A six-point calibration curve was generated by running six calibrators of known concentrations (0, 250, 500, 1000, 2000 and 3000 mg/L) and measuring the resulting attenuated fluorescence signal. The calibration was then stored in the instrument. When a sample was run, the concentration was calculated directly from the stored calibration curve (TDx Manual, 1995).

Summary of Method: The sample cartridges and cuvettes were placed in the carousel.
The carousel has a capacity to run up to 20 samples in a single run. Individual samples or controls were pipetted into the sample wells of the sample cartridges. The carousel was then placed in the analyzer and the run was initiated. The samples were pipetted into the dilution well and diluted with the TDx buffer. The diluted sample was pipetted into the cuvette and the reagents were sequentially added, allowed to incubate and the resulting attenuated fluorescence measured by the fluorometer within the instrument. The concentration was calculated directly from the stored calibration curve and printed.

3.3.3C Performance Characteristics for Ethanol in Serum

The performance characteristics, including specificity, sensitivity, precision, and accuracy by recovery were determined by Abbott Labs, as detailed in the TDx Manual (1995). The following is a brief description of these characteristics.

Specificity: Specificity was determined by assaying several compounds of interest (ethanol, n-butanol, n-propanol, isopropanol, ethylene glycol, propylene glycol, methanol, acetone) in concentrations up to 10000 mg/L. The only compounds that showed reactivity greater than 0.1% were Ethanol (100%), n-butanol (10.7%) and n-propanol (36%) (TDx Manual, 1995).

Sensitivity: Sensitivity was defined in the TDx manual (1995) as the lowest measurable concentration distinguishable from zero with 95% confidence. The reported limit of quantitation (LOQ) was 100 mg/L.

Precision: Reproducibility was reported in the TDx manual (1995) to be acceptable when
5 replicates of ethanol solutions at 400, 1000 and 2500 mg/L were run on 10 different occasions over a period of 2 weeks. Between run and within run variability was reported to be less than 6%.

Accuracy by Recovery: Recovery was determined by adding known quantities of ethanol to serum and saline to levels of 200, 500, 1000, 2000 and 3000 mg/L. The TDx was calibrated with the serum-based controls and the saline-based controls were assayed relative to that calibration. % Recovery was calculated as:

\[
\% \text{ recovery} = \frac{\text{Conc in saline}}{\text{target conc}} \times 100
\]

Results indicated an average recovery of 100.3 ± 2.7% (TDx Manual, 1995).

3.3.3D Performance Validation for Ethanol in Serum

Sensitivity: To experimentally test the reported sensitivity limit, as well as to determine if concentrations below the limit set by Abbott Labs could be accurately and reliably quantitated, the experimental limit of quantitation (ELOQ) was estimated. For this, standards were prepared at concentrations of 50 mg/L and 100 mg/L by diluting 1 ml of the appropriate calibrators (500 mg/L and 1000 mg/L respectively) to 10 ml with blank serum. These were run in replicates of 5 each along with controls. Precision was estimated by calculating the %Relative Standard Deviation (%RSD) and accuracy was estimated by calculating the %Difference From Nominal (%DFN, calculated as \([\text{observed-nominal}/\text{nominal} \times 100]) for each run. The lowest concentration that gave %RSD and %DFN less than 20% was determined to be the ELOQ.
Results: The 100 mg/L standard gave an RSD of 4% and DFN of 6%. The 50 mg/L standard solution was prepared five times and each time the RSD and DFN were greater than 20%. Therefore 100 mg/L was determined to be the ELOQ.

Precision and Accuracy: In this study, the precision and accuracy were determined by pooling the data from the controls run during the sample analysis and calculating the %RSD and %DFN respectively. In addition to the three controls supplied by Abbott Labs (L, M and H), a control at 100 mg/L (Control X) was prepared by diluting the 1000 mg/L standard and run along with the other controls during sample runs.

Results: Table 3.4 lists the %RSD and %DFN calculated from values pooled from controls run along with samples during the analysis of subject samples. The %DFN for all controls is ≤ 15% which is within acceptable limits. The %RSD for controls L, M and H were ≤ 9% which is within acceptable limits. The %RSD for Control X was 27% which is larger than the pre-set criteria of 20%. This may be consequence of using two different batches of controls during sample analysis. In an attempt to overcome this problem, the instrument was re-calibrated for a smaller concentration range (100 to 2000 mg/L) and the sample volume was increased from 2 µl to 4 µl, but the results from these attempts were inconsistent and resulted in %RSD and %DFN larger then 20%. Finally, it was decided to re-calibrate the instrument for the original concentration range (100 to 3000 mg/L), then re-run all samples in the concentration range of 100 to 250 mg/L. Controls X and L were run with the samples, and these values were pooled with the values obtained from earlier runs. Estimates of the sample concentration from both runs
Table 3.4  Measures of precision and accuracy of analytical method for ethanol

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<th>Experimental Limit of Quantitation (ELOQ)</th>
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<td>Valid Concentration Range</td>
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| Precision (%RSD)                         | Control X (100 mg/L): 19%  
Control L (500 mg/L): 9%  
Control M (1000 mg/L): 7%  
Control H (2500 mg/L): 4% |
| Accuracy (%DFN)                          | Control X (100 mg/dL): 15%  
Control L (500 mg/dL): 11%  
Control M (1000 mg/dL): 1%  
Control H (2500 mg/dL): 3% |
were used in the pharmacokinetic analysis to account for the high assay variability at lower concentrations. The overall %RSD and %DFN for Control X were 19% and 15%, respectively. Using the results of duplicate sample runs effectively decreased the %RSD by a factor of $\sqrt{2}$ (Chamberlain, 1985).

3.3.3E Analysis of subject samples

The TDx assay was used to determine ethanol concentrations in serum from the six subjects that completed the clinical study. There were a total of 18 samples per subject per period and four active treatment periods per subject (Total samples = 432). Calibration was performed prior to performance validation. All four controls (X, L, M and H) were run at the start of subject sample analysis to ensure that the calibration curve was stable and valid. The samples for a single study period for each subject were split, and nine samples were run on each carousel along with 2 of the controls (X, L, M and H).

This analytical method for the determination of ethanol concentrations in serum was simple, specific, adequately sensitive, precise and accurate within acceptable limits for the purposes of this study.

3.3.4 PHARMACOKINETIC ANALYSIS

Pharmacokinetic analysis of the serum ethanol concentration-time data was performed by noncompartmental and compartmental methods.
Serum ethanol concentration vs. time profiles were constructed for each subject and treatment on both linear and semi-logarithmic scales. The following PK parameters were estimated from the concentration-time data for each subject and treatment: maximum concentration ($C_{\text{max}}$), time to achieve maximum concentration ($T_{\text{max}}$), area under the concentration-time curve extrapolated to infinity ($AUC_{\infty}$), apparent total body clearance ($CL_{\text{tot}}/F$), apparent volume of distribution ($Vd/F$), maximum elimination rate ($V_{\text{max}}$) and Michaelis-Menten constant ($K_m$). $C_{\text{max}}$ was estimated as the maximum observed serum concentration and $T_{\text{max}}$ as the time (relative to the start of dosing) that $C_{\text{max}}$ occurred.

$AUC_{\infty}$ was calculated as:

$$AUC_{\infty} = AUC_{\text{imp}} + \frac{C_a}{\lambda}$$

where $AUC_{\text{imp}}$ is the AUC from 0 to the time ($t_a$) of the last measured concentration ($C_a$) calculated by the trapezoidal rule (Gibaldi and Perrier, 1982) and $C_a/\lambda$ is the AUC extrapolated from $t_a$ to infinity ($AUC_{\text{extrap}}$). $\lambda$, which is the terminal slope of the log concentration vs. time profile, was estimated as $V_{\text{max}}/K_m$.

$CL_{\text{tot}}/F$ was calculated as:

$$CL_{\text{tot}}/F = \frac{D}{AUC_{\infty}}$$

where $D$ is the total administered dose.

$Vd/F$ was calculated as:
\[ V_d/F = CL_{tot} / F \times MRT \]

where MRT is the mean residence time calculated as:

\[ MRT = \frac{AUMC_{\infty}}{\text{AUC}_{\infty}} - \frac{T}{2} \]

where T is the duration of input (20 minutes or 50 minutes), and AUMC\(_{\infty}\) is the area under the moment curve extrapolated to infinity, calculated by determining the area under the moment curve (AUMC) from 0 to the time (\(t_n\)) of the last measured concentration (\(C_n\)) by the trapezoidal rule by summing individual areas calculated by

\[ AUMC = \frac{(C_1 \times t_1 + C_2 \times t_2) \times (t_2 - t_1)}{2} \]

and then extrapolating to infinity as follows (Gibaldi and Perrier, 1982):

\[ AUMC_{\infty} = AUMC_{\text{trp}} + \frac{C_n \times t_n}{\lambda} + \frac{C_n}{\lambda^2} \]

Although the MRT calculated in this manner is adjusted for the input time into the absorption compartment, it is not the systemic MRT since it includes the mean absorption time, which cannot be subtracted out from the estimate of MRT. Also, the estimation of the terminal exponential slope of the concentration-time profile implicitly assumes a first-order process (Gibaldi and Perrier, 1982). Although, the elimination of ethanol does approximate a first-order process at low concentrations (relative to the \(K_m\)), the elimination is best characterized by a capacity-limited process and presents a limitation in the interpretation of the MRT and subsequent estimation of the \(Vd/F\).
\( V_{\text{max}} \) was estimated from the slope (slope1) of the linear regression performed on the initial apparent linear declining phase of the concentration-time profiles as:

\[
V_{\text{max}} = - \text{slope1}
\]

\( K_m \) was estimated from the slope (slope2) of the linear regression performed on the terminal apparent linear declining phase of the log concentration-time profiles as:

\[
K_m = - \frac{V_{\text{max}}}{2.303 \times \text{slope2}}
\]

Descriptive statistics, including mean, standard deviation, coefficient of variation (%COV), median and range were calculated for each parameter by treatment and subject as well as across treatments.

3.3.4B Compartmental Methods

Compartmental analysis was performed for individual serum concentration-time data in order to estimate the intrinsic pharmacokinetic parameters, maximum elimination rate (\( V_{\text{max}} \)), Michaelis-Menten constant (\( K_m \)), apparent volume of distribution (\( V_d/F \)) and first-order absorption rate constant (\( k_a \)). Model fitting was performed using Scientist (version 2.0 for Windows, MicroMath Inc., Salt Lake City, UT). Several PK models were evaluated, such as models with first-order or zero-order input functions, models with one or two compartments, incorporating capacity-limited elimination with and without a parallel first-order elimination pathway. Weighing schemes of 1 and 1/y were evaluated. Noncompartmental PK parameter estimates were used as initial estimates for \( V_{\text{max}}, K_m \).
and Vd/F, and a population mean estimate of 2.0 hr\(^{-1}\) was used as the initial estimate for \(k_a\) (Rangno et al., 1981). The model which best fit the data was selected based on several goodness of fit criteria: maximization of the coefficient of determination and Model Selection Criteria (Scientist Manual, 1994), minimization of the standard deviation of the parameter estimates, random scatter in the plots of residuals vs. independent variables, normal distribution of the residuals and visual inspection of observed values and fitted curves.

The final PK model selected was a one compartment body model with zero-order input into the absorption compartment and first-order absorption into the central compartment, with capacity-limited elimination (figure 3.1). The best fits were obtained with a weight of 1, i.e., unweighted. Descriptive statistics, including mean, standard deviation, %COV, median and range were calculated for each PK parameter by treatment and subject as well as across treatments.

In addition to compartmental analysis of individual subjects and treatments, the final PK model, based on individual treatments and subjects, was fit simultaneously to concentration-time data across all four active treatments for each subject. This approach allowed better estimation of the intrinsic PK parameters for each subject, by incorporating the intra-subject variability in PK; however, it did not allow separate estimation of the inter-individual and intra-individual variability for the PK parameters. In this approach, the dose and duration of input (T) were incorporated as independent variables along with time, and concentration was the dependent variable. Weighing
Figure 3.1 Final PK model for oral ethanol
schemes of 1 and 1/y were compared, with unweighted fitting resulting in better fits. The mean PK parameter estimates obtained for each subject from the individual model fits were used as initial estimates. Goodness of fit was assessed using the same criteria as described above for the individual model fits. Descriptive statistics, including mean, standard deviation, %COV, median and range were calculated for each PK parameter across subjects.

3.3.5 PHARMACODYNAMIC ANALYSIS
Pharmacodynamic analysis included the analysis of data from the EEG recordings, psychometric performance tests, as well as the SRI and ORI scales.

3.3.5A EEG Analysis
EEG recordings were stored on optical disks and analyzed off-line. Each of the 5-minute recordings was reviewed and edited to remove each 2.5 second epoch that was contaminated with artifacts (eye movement, muscle movement, electrode artifacts, or other disturbances noted during the recording). The remaining artifact-free epochs were averaged to form an average topographical map for each recording using the statistical operations program on the Brain Imager. The file containing the average amplitude in each of the five classical frequency bands (delta: 0.39 - 3.0 Hz; theta: 4.3 - 7.8 Hz; alpha: 8.2 - 11.7 Hz; beta I: 12.1 -16.0 Hz; and beta II: 16.4 - 30 Hz) at each of the 28 electrodes was transferred from the Brain Imager to an IBM compatible 80486 computer.
and imported into a spreadsheet program (Quattro Pro, Borland International, Scotts Valley, CA) developed by Dr. Slattum (1992) for further processing.

From each average recording, the following PD measures were obtained: total power (in $\mu V^2$) across all electrodes and across all frequency bands, total power across all electrodes within each frequency band, relative power across all electrodes within each frequency band, and spectral edge (in Hz).

Power was determined for each average recording by squaring the amplitude (in $\mu V$) of the EEG signal at each electrode in each frequency band. Total power in each frequency band was calculated by summing the power across all electrodes for the given frequency band. Total power across all frequency bands was calculated by summing the total power across all five frequency bands. Relative power in each frequency band was calculated by dividing the total power of the frequency band by the total power across all 5 frequency bands. The spectral edge, which is the frequency below which 87% of the EEG activity is located, was also determined.

3.3.5B Psychometric Performance Test Analysis

For each of the psychometric tests, the following measures were obtained:

1. Card Sorting Task (CST): total categories completed and number of erroneous responses determined at each time-point;

2. Finger Tapping Task (FT): the average rate (taps per second) of finger tapping for both the dominant and non-dominant hands determined based on three trials at each time
point;

3. Digit Symbol Substitution Task (DSST): the total number of substitutions completed in the 90 second testing interval as well as the number of erroneous responses determined at each time point.

3.3.5C Impairment Scales Analysis

For the SRI and ORI scales, a score between 0 and 100 was obtained for each item, by measuring the number of millimeters between the left end of the scale and the mark placed by the subject at each time point. Since two of the six subjects in the study were classified as "non-responders" and did not show consistent responses on the SRI scales (maximal observed response less than 20 mm for treatments B and D), even though they showed consistent psychometric impairment and EEG changes, subjects were given a "non-responder" score (NR) of 0 if they were non-responders or 1 if they were responders.

3.3.5D Pharmacodynamic Analysis

Response-time profiles, i.e., plots of change in response measure from pre-dose baseline vs. time plots, for each subject during each treatment period were plotted for each response measure. The PD response measures evaluated were:

- **EEG measures**: total power across all bands, total power in each of the 5 frequency bands (delta, theta, alpha, beta I, beta II), relative power in each of the 5 frequency
bands (delta, theta, alpha, beta I, beta II), spectral edge;

**PP measures**: total categories and number of errors for CST, average tap-rate for dominant and non-dominant hands for FT, total attempts and number of errors for DSST;

**Impairment Scales**: score for each of the 11 items on the SRI scales and 3 items of the ORI scales.

Pharmacodynamic parameters including baseline response ($E_o$), maximal or minimal observed response ($E_{\text{max}}^{\text{obs}}$ or $E_{\text{min}}^{\text{obs}}$) and time of maximal or minimal observed response ($t_{\text{max}}$ or $t_{\text{min}}$) were derived for each PD measure. The baseline response ($E_o$) was defined as the response prior to drug administration at 0 hour. $E_{\text{max}}^{\text{obs}}$ was determined as the highest response observed during the first 6 hours after drug administration, and $E_{\text{min}}^{\text{obs}}$ was determined as the lowest response observed during the first 6 hours after drug administration. The $E_{\text{max}}^{\text{obs}}$ and $E_{\text{min}}^{\text{obs}}$ were determined from data obtained only during the first 6 hours after drug administration because the responses were expected to be the greatest during this period. The $t_{\text{max}}$ (or $t_{\text{min}}$) was determined as the time after the start of dosing that $E_{\text{max}}^{\text{obs}}$ (or $E_{\text{min}}^{\text{obs}}$) occurred.

Descriptive statistics, including mean, standard deviation, %COV, median and range were calculated for each PD parameter by treatment and subject as well as across treatments.

In addition, response vs. serum concentration profiles were plotted for each response measure for each subject at each treatment, to evaluate the effect-concentration relationship as well as the development of acute tolerance to the effects. The presence
of a clockwise hysteresis loop in the response-time profiles would be consistent with
development of acute tolerance for that response.

3.3.6 STATISTICAL ANALYSIS

Statistical analysis was performed to 1) evaluate the dose-related and rate-related changes
in the pharmacokinetic and pharmacodynamic end-points, EEG, psychometric
performance and subjective impairment following administration of two escalating single
oral doses of ethanol at two different rates in healthy male subjects; and 2) to determine
the relationship between the EEG changes after oral ethanol administration and changes
in psychometric performance and subjective impairment.

Because there are many variables of interest in this statistical analysis, the multiplicity
of desired inferential statements about the data become problematic. Adjusting the level
of significance ($\alpha$) for the multiple statistical comparisons, as made in traditional
confirmatory analysis, would result in extremely small $\alpha$ values and virtually no
likelihood of detecting any statistically significant differences considering the small
sample size. Therefore, using the concept of descriptive data analysis, expected
differences between treatments based on previously reported studies and patterns apparent
from examining the data were evaluated statistically without adjusting the level of
significance (Abt, 1987, Abt, 1990). The results of these analyses were used to make
descriptive inferential statements about the data, but not to reject the null hypothesis.
Hypotheses generated by this study would have to be confirmed by prospective studies
involving a larger number of subjects.

Primary pharmacokinetic parameters that were evaluated using descriptive data analysis included apparent volume of distribution (Vd/F), absorption rate constant (k_a), maximum elimination rate (V_{max}), and Michaelis-Menten constant (K_m). These PK parameters were selected to evaluate the effect of dose and dose-rate on these intrinsic PK parameters for ethanol. Primary pharmacodynamic measures that were evaluated included peak changes (E_{max}^{obs}-E_o or E_{min}^{obs}-E_o) in total EEG power, changes in relative EEG power in the theta, and alpha bands, peak changes in tap-rate for the non-dominant hand for FT, peak changes in the items, "DRUNK", and "ALCOHOL EFFECTS" on the SRI scales, and peak changes in the item "DRUNK" on the ORI scales. These PD parameters were selected based on changes seen in these measures in previously reported studies (Ehlers and Shuckit, 1991; Lukas et al., 1986; Wittenborn, 1987; Shuckit, 1984) as well as patterns apparent from preliminary examination of the data. Statistical comparisons for the other PD end-points (including changes in relative EEG power in the delta, beta I and beta II bands, changes in EEG spectral edge, changes in tap-rate for the dominant hand for FT, changes in the item "HIGH" on the SRI as well as ORI scales) were treated as exploratory data analysis. These were used to generate hypothesis rather than to make formal conclusions based on the data.

The significance of the baseline (E_o) as a covariate was examined to evaluate the relationship between the baseline of the response and the change in PD response. Also, the NR score was used as a covariate in the statistical comparison of PD measures to
evaluate its effect on the PD response.

To evaluate the treatment effects on the PK and PD measures, the PK parameters and summary PD parameters \( \left( \text{E}_{\max}^{\text{obs-E}_o}, \text{E}_{\min}^{\text{obs-E}_o}, \text{t}_{\max} \right) \) or \( \left( \text{t}_{\min} \right) \) for the primary PD measures for each treatment were compared across treatments using statistical techniques appropriate for a 5-way crossover design. The model used to fit the data was of the form:

\[
Y_{ijkl} = \mu + \delta_i + \pi_j + \zeta_{k(i)} + \alpha_l + \epsilon_{ijkl}
\]

\( i = 1, II, III \) (sequences);
\( j = 1, 2, 3, 4, 5 \) (periods);
\( k = 1, 2, 3, 4, 5, 6 \) (subjects);
\( l = A, B, C, D, E \) (treatments) (only active treatments A, B, C, D for PK parameters);

where \( Y_{ijkl} \) is the response for the kth subject in the ith sequence in the jth period after the lth treatment, \( \mu \) is the overall mean, \( \delta_i \) is the effect of the ith sequence, \( \pi_j \) is the effect of the jth period, \( \zeta_{k(i)} \) is the effect of the kth subject nested within the ith sequence, \( \alpha_l \) is the effect of the lth treatment, and \( \epsilon_{ijkl} \) is the random error associated with \( Y_{ijkl} \). The \( \epsilon_{ijkl} \) are assumed to be normally distributed random variables with a mean of 0 and variance \( \sigma^2 \). It is also assumed that the nested effects for subject are randomly and independently distributed with a mean of 0 and common variance of \( \sigma^2 \), and independent of \( \epsilon_{ijkl} \).

Model fitting was performed using PROC MIXED in SAS (version 6.07, SAS Institute,
Cary, NC). Table 3.5 lists the sample SAS code for PROC MIXED. This procedure allows the modelling of the mean of the dependent variable, y, as well as the variance of y. The estimation method used for the covariance parameters was restricted maximum likelihood (REML). The variance of y was modelled by evaluating two variance structure matrices, simple (random effect) and autoregressive. For most variables, the simple structure resulted in better model fits based on maximization of the Akaike's Information Criterion (SAS/STAT User's Guide, 1990, SAS Technical Report P-229, 1992).

The level of significance (α) was set at 0.05. In case of significant differences (p < 0.05), multiple comparisons were performed using the ESTIMATE procedure in SAS (SAS/STAT User's Guide, 1990).

Residuals were tested for normality using PROC UNIVARIATE in SAS (SAS/STAT User's Guide, 1990). This procedure generates box plots and normal probability plots, which were examined to test for normality of the residuals. This procedure also computes the Shapiro-Wilk statistic, W, to test the null hypothesis that the residuals are normally distributed. The null hypothesis of normality was rejected if the probability of a smaller value of W was less than 0.05.

One of the aims of this study was to assess the relationship between the EEG changes and changes in PP as well as the relationship between the EEG changes and SRI. In order to achieve this, linear regression of the EEG parameters ($E_{max}^{obs}$ for relative theta power) on the PP parameters ($E_{min}^{obs}$ for non-dominant hand tap-rate), and on the SRI
Table 3.5 Sample SAS code for PROC MIXED

```
proc mixed data=save.DATAl;
   class trt period seq sub;
   model y=seq period trt covar1 covar2 / predicted;
   random sub(seq);
   * estimate 'A vs. B' trt 1 -1 0 0;
   * estimate 'A vs. C' trt 1 0 -1 0;
   * estimate 'A vs. D' trt 1 0 0 -1;
   * estimate 'B vs. C' trt 0 1 -1 0;
   * estimate 'B vs. D' trt 0 1 0 -1;
   * estimate 'C vs. D' trt 0 0 1 -1;
make 'predicted' out=pred;
make 'fitting' out=fit;
```

DATA1: data set
trt: treatment, seq: sequence, sub: subject
covar1, covar2: covariates
*: estimate statements used for multiple comparisons only for overall significance
parameters (\(E_{\text{max}}^{\text{obs}}\) for SRI-ALCOHOL EFFECTS score) were performed individually to assess the significance of the relationship between the EEG changes and changes in PP and SRI. The coefficient of determination was determined for each of the regressions as an index of the association between the two variables. Since this was a crossover study and results obtained for different treatments in the same subject are not independent, the regression was only performed for observations for treatment B (high-fast), since the greatest change in the PD measures would be expected for this treatment. Regression was performed using Microsoft Excel (version 5, Microsoft Inc., WA). This test allowed us to determine if the EEG changes were more closely related to changes in PP or to changes in subject-rated impairment measures.

3.4 RESULTS AND DISCUSSION

3.4.1 CLINICAL RESULTS

3.4.1A Subject Demographics

Six male subjects were entered into the study after successfully passing the medical screening, and all six subjects completed all five periods of the study. Demographic and physical characteristics of the subjects are shown in table 3.6. The subjects were between 21 and 32 years of age. Their weight ranged from 68 to 98 kg with an mean of 78 kg. Subjects were low to moderate alcohol drinkers with alcohol use ranging from less
Table 3.6  Demographic and physical characteristics of subjects in oral ethanol study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age [yrs]</th>
<th>Weight [kg]</th>
<th>Height [cm]</th>
<th>Race</th>
<th>Handedness</th>
<th>Alcohol consumption [#drinks/week]</th>
<th>Responder/Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>73.6</td>
<td>170.0</td>
<td>Caucasian</td>
<td>Right</td>
<td>1</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>68.4</td>
<td>171.3</td>
<td>African-American</td>
<td>Right</td>
<td>$&lt;1^1$</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>73.6</td>
<td>172.5</td>
<td>Caucasian</td>
<td>Right</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>98.2</td>
<td>177.5</td>
<td>Caucasian</td>
<td>Right</td>
<td>7</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>81.0</td>
<td>178.8</td>
<td>Caucasian</td>
<td>Right</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>71.8</td>
<td>175.0</td>
<td>Caucasian</td>
<td>Right</td>
<td>6</td>
<td>R</td>
</tr>
<tr>
<td>Mean</td>
<td>26</td>
<td>77.8</td>
<td>174.2</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>S.D.</td>
<td>4</td>
<td>10.8</td>
<td>3.5</td>
<td></td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>COV%</td>
<td>16%</td>
<td>14%</td>
<td>2%</td>
<td></td>
<td></td>
<td>84%</td>
<td></td>
</tr>
</tbody>
</table>

1: Subject 2 had alcohol consumption of 1-2 drinks/month  2: R: Responder, NR: Non-Responder
than 1 to 11 alcoholic beverages per week.

3.4.1B Adverse Events

In general, all subjects tolerated the study procedures and study drug well. There were no adverse events reported for the placebo (treatment E) and low-dose treatments (treatments A and C). One subject (subject 2) reported mild nausea about 1.5 hours after receiving each of the high-dose treatments (B and D), which lasted for about 1 hour and resolved without any treatment. One subject (subject 1) had mild nausea accompanied by vomiting at about 1.5 hours after receiving each of the high-dose treatments (B and D), which lasted for about 1 hour and resolved without any treatment.

3.4.2 PHARMACOKINETICS

3.4.2A Noncompartmental Analysis

Serum ethanol concentration vs. time profiles for each treatment and subject are shown in Appendix B1. Figure 3.2 shows the serum ethanol concentration vs. time for all subjects by treatment. As figure 3.2 illustrates, the high-dose treatments B and D resulted in higher concentrations, about twice the concentrations observed after the low-dose treatments A and C. Also, the time of peak concentrations appear to be later for the slow-input treatments C and D compared to the fast-input treatments A and B. Elimination profiles are consistent with capacity-limited elimination, showing an initial
Figure 3.2 Serum ethanol concentration vs. time for all subjects by treatment for oral ethanol study
linear (apparent zero-order) decline, and a later exponential (apparent first-order) decline. Mean pharmacokinetic parameters determined by noncompartmental analysis are presented in table 3.7. $C_{\text{max}}$ increased approximately two-fold with a two-fold increase in the dose (from 0.3 g/kg to 0.6 g/kg); the population variability appeared to decrease with the increase in dose. This was seen for both fast and slow input treatments. $C_{\text{max}}$ (mean ± S.D.) values were 401 ± 133 mg/L and 347 ± 82 mg/L for treatments A and C, respectively, and 754 ± 114 mg/L and 724 ± 108 mg/L for treatments B and D, respectively. Dose-corrected $C_{\text{max}}$ values were not significantly different across treatments (see figure 3.3).

Figure 3.4 shows a plot of the mean (S.E.) $T_{\text{max}}$ by treatment. $T_{\text{max}}$ was not significantly different between treatments, although there was a trend toward larger $T_{\text{max}}$ values for slow-input treatments compared to the fast-input treatments, especially at the high dose (median $T_{\text{max}}$ of 1.0 hrs for treatment B versus 1.6 hrs for treatment D). Since $T_{\text{max}}$ was determined as the time at which the $C_{\text{max}}$ was observed, its determination was limited by the sampling schedule, and since concentrations were not measured continuously but at discrete time-points, this resulted in some censoring of the data.

$AUC_{\infty}$ increased approximately three-fold with a two-fold increase of the dose (from 0.3 g/kg to 0.6 g/kg); the population variability appeared to decrease with an increase in dose (see figure 3.5). This was seen for both fast and slow input treatments. $AUC_{\infty}$ (mean ± S.D.) values were 991 ± 258 mg/L*hr and 835 ± 209 mg/L*hr for treatments A and C, respectively, and 3185 ± 354 mg/L*hr and 3045 ± 357 mg/L*hr for treatments B.
Table 3.7  Mean (%COV) Non-compartmental pharmacokinetic parameters by treatment across subjects for ethanol oral study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$ [mg/L]</th>
<th>$C_{\text{max}}$ [mg/L/(g/kg)]²</th>
<th>$T_{\text{max}}$ [hr]</th>
<th>$AUC_{\infty}$ [mg/L*hr]</th>
<th>$AUC_{\infty}$ [mg/L*hr/(g/kg)]³</th>
<th>$V_{\max}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
<th>$Vd/F$ [L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=6)</td>
<td>401 (33%)</td>
<td>1338 (33%)</td>
<td>1.0 (0.6-1.8)</td>
<td>991 (26%)</td>
<td>3303 (26%)</td>
<td>136 (31%)</td>
<td>240 (30%)</td>
<td>71 (49%)</td>
</tr>
<tr>
<td>B (n=6)</td>
<td>754 (15%)</td>
<td>1256 (15%)</td>
<td>1.0 (0.6-1.8)</td>
<td>3185 (11%)</td>
<td>5308 (11%)</td>
<td>138 (22%)</td>
<td>173 (57%)</td>
<td>42 (21%)</td>
</tr>
<tr>
<td>C (n=6)</td>
<td>347 (24%)</td>
<td>1157 (24%)</td>
<td>1.3 (0.6-1.5)</td>
<td>922 (32%)</td>
<td>3072 (32%)</td>
<td>160 (36%)</td>
<td>189 (52%)</td>
<td>87 (37%)</td>
</tr>
<tr>
<td>D (n=6)</td>
<td>724 (15%)</td>
<td>1206 (15%)</td>
<td>1.6 (0.6-2.0)</td>
<td>3045 (12%)</td>
<td>5075 (12%)</td>
<td>146 (26%)</td>
<td>229 (45%)</td>
<td>51 (20%)</td>
</tr>
</tbody>
</table>

1: $T_{\text{max}}$ expressed as Median (Range)  
2: Dose-corrected $C_{\text{max}}$  
3: Dose-corrected $AUC_{\infty}$  
4: $p < 0.05$ vs. treatments A and C
Figure 3.3 Dose-corrected Cmax (Mean ± S.E.) by treatment for oral ethanol study

Figure 3.4 T_max (Median ± Range) by treatment for oral ethanol study

Figure 3.5 Dose-corrected AUC∞ (Mean ± S.E.) by treatment for oral ethanol study
and D, respectively. Dose-corrected AUC_{\infty} estimates were statistically different between low-dose treatments and high-dose treatments (p=0.0004). This finding is consistent with non-linear, capacity-limited pharmacokinetics for ethanol. The precision of the AUC_{\infty} estimates was estimated by calculating the percent AUC extrapolated (%AUC_{\text{extrap}}) by dividing the AUC_{\text{extrap}} by the AUC_{\infty}. The %AUC_{\text{extrap}} ranged from <1% to 22% across individual AUC_{\infty} calculations. CL_{\infty}/F (mean ± S.D.) estimates were 414 ± 107 ml/min and 463 ± 162 ml/min for treatments A and C respectively, and 249 ± 53 ml/min and 265 ± 67 ml/min for treatments B and D respectively. CL_{\infty}/F showed a statistically significant decrease with the increase in dose (p=0.0118), although the estimates did not appear to change with an increase in input-rate. This is consistent with non-linear elimination of ethanol. As table 3.7 indicates, the intrinsic PK parameters, V_{\text{max}}, K_{m} and Vd/F estimated by noncompartmental analysis did not appear to be different across treatments. Table 3.8 lists the intrinsic PK parameter estimates by subject across treatments, along with the %COV for each subject which is a measure of intra-subject variability. The mean intrinsic PK parameters, estimated by non-compartmental methods across subjects and treatments, along with the inter-individual and intra-individual variability measures (%COV) are presented in table 3.9. The mean (± S.D.) V_{\text{max}} was 145 (± 41) mg/L/hr across subjects and treatments. The mean (± S.D.) K_{m} was 208 (± 92) mg/L across subjects and treatments. The mean (± S.D.) Vd/F was 63 (± 29) L across subjects and treatments. As table 3.9 indicates, the inter-individual variability, as measured by the %COV, was considerable for the PK parameters, especially for the
Table 3.8  Mean (%COV) Non-compartmental intrinsic pharmacokinetic parameters by subject across treatments for oral ethanol study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=4)</td>
<td>117 (25%)</td>
<td>144 (70%)</td>
</tr>
<tr>
<td>2 (n=4)</td>
<td>92 (16%)</td>
<td>171 (48%)</td>
</tr>
<tr>
<td>3 (n=4)</td>
<td>140 (18%)</td>
<td>208 (46%)</td>
</tr>
<tr>
<td>4 (n=4)</td>
<td>182 (27%)</td>
<td>219 (39%)</td>
</tr>
<tr>
<td>5 (n=4)</td>
<td>184 (5%)</td>
<td>292 (19%)</td>
</tr>
<tr>
<td>6 (n=4)</td>
<td>156 (4%)</td>
<td>211 (52%)</td>
</tr>
</tbody>
</table>
Table 3.9  Non-compartmental intrinsic pharmacokinetic parameters across subjects and treatments for oral ethanol study

<table>
<thead>
<tr>
<th></th>
<th>(V_{\text{max}}) [mg/L/hr]</th>
<th>(K_{m}) [mg/L]</th>
<th>(V_d/F) [L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Mean (n=24)</td>
<td>145</td>
<td>208</td>
<td>63</td>
</tr>
<tr>
<td>Inter-Individual variability (%COV) (n=24)</td>
<td>29%</td>
<td>45%</td>
<td>47%</td>
</tr>
<tr>
<td>Intra-Individual variability (Mean %COV) (n=6)</td>
<td>16%</td>
<td>45%</td>
<td>32%</td>
</tr>
</tbody>
</table>
Among other things, this may be a consequence of the sparse terminal sampling schedule and the relatively poor precision in the analytical methods, particularly at low concentrations. For all parameters, intra-individual variability was lower than the inter-individual variability.

In summary, noncompartmental analysis of the serum ethanol concentration-time data indicated that ethanol follows dose-dependent, capacity-limited elimination. The intrinsic PK parameters, $V_{\text{max}}$, $K_{m}$, and $V_d/F$ were independent of dose and dose-rate, and the mean parameter estimates are consistent with values observed in other studies evaluating ethanol PK following oral administration of doses ranging from 0.14 to 1.25 g/kg (Wilkinson et al., 1977; Holford, 1987). The noncompartmental parameter estimates provided good initial estimates for the compartmental analysis of the serum ethanol concentration-time data.

### 3.4.2B Compartmental Analysis

A one-compartment body model with zero-order input into the absorption compartment and first-order absorption into the central compartment, with capacity-limited elimination was fit to the individual serum ethanol concentration vs. time profiles. The fits were considered to be adequate based on the coefficient of determinations ($r^2$), which ranged from 0.792 to 0.978 and Model Selection Criteria (MSC), which ranged from 1.036 to 3.313, random scatter in the plots of residuals vs. independent variable, normal distribution of the residuals as well as visual inspection of observed and fitted curves.
The standard deviations and calculated %COVs of the parameter estimates were high, especially for $V_{\text{max}}$ with %COVs ranging from 34% to 1365%, and for $K_m$ with %COVs ranging from 135% to 2380%, indicating significant imprecision in the parameter estimates.

Individual concentration vs. time profiles illustrating the observed values and fitted curves are shown in Appendix B2. Figure 3.6 shows the serum ethanol concentration vs. time profile (observed values and fitted curves) by treatment for a representative subject (subject 2). Table 3.10 lists the compartmental PK parameter estimates by treatment. Statistical comparison of the intrinsic PK parameters indicated no significant differences across treatments or subjects. Table 3.11 lists the intrinsic PK parameter estimates by subject across treatments, along with the %COV for each subject which is a measure of intra-subject variability. The mean intrinsic PK parameters, estimated by compartmental methods across subjects and treatments, along with the inter-individual and intra-individual variability measures (%COV) are presented in table 3.12. The mean ($\pm$ SD) $V_{\text{max}}$ was 226 ($\pm$ 92) mg/L/hr across subjects and treatments. The mean ($\pm$ SD) $K_m$ was 176 ($\pm$ 59) mg/L across subjects and treatments. The mean ($\pm$ SD) $V_d/F$ was 52 ($\pm$ 15) L across subjects and treatments. The mean ($\pm$ SD) $k_a$ was 3.8 ($\pm$ 2.4) hr$^{-1}$ across subjects and treatments corresponding to an absorption half-life of 0.18 hrs (or about 11 minutes). As table 3.12 indicates, the inter-individual variability, as measured by the %COV, was considerable for the PK parameters, especially for the $k_a$ and $K_m$. This may be a consequence of the sampling schedule and the relatively poor precision in the
Figure 3.6 Serum Ethanol Concentration vs. time profile by treatment for a representative subject (subject 3) for oral ethanol study (symbols are observed values and lines are fitted curves from individual fits)
Table 3.10  Mean (%COV) Compartmental pharmacokinetic parameter estimates by treatment across subjects for oral ethanol study

<table>
<thead>
<tr>
<th>Trt</th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
<th>$V_d/F$ [L]</th>
<th>$K_s$ [hr$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=6)</td>
<td>270 (41)</td>
<td>176 (23)</td>
<td>49 (27)</td>
<td>4.2 (57)</td>
</tr>
<tr>
<td>B (n=6)</td>
<td>188 (40)</td>
<td>153 (34)</td>
<td>54 (33)</td>
<td>3.4 (54)</td>
</tr>
<tr>
<td>C (n=6)</td>
<td>255 (40)</td>
<td>174 (37)</td>
<td>50 (22)</td>
<td>4.5 (72)</td>
</tr>
<tr>
<td>D (n=6)</td>
<td>192 (33)</td>
<td>200 (40)</td>
<td>57 (36)</td>
<td>3.1 (76)</td>
</tr>
</tbody>
</table>
Table 3.11  Mean (%COV) Compartmental pharmacokinetic parameters by subject across treatments for oral ethanol study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_{\text{m}}$ [mg/L]</th>
<th>$V_d/F$ [L]</th>
<th>$K_a$ [hr$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=4)</td>
<td>148 (25)</td>
<td>136 (31)</td>
<td>57 (19)</td>
<td>2.6 (31)</td>
</tr>
<tr>
<td>2 (n=4)</td>
<td>141 (12)</td>
<td>142 (36)</td>
<td>50 (19)</td>
<td>2.4 (27)</td>
</tr>
<tr>
<td>3 (n=4)</td>
<td>257 (15)</td>
<td>177 (31)</td>
<td>54 (14)</td>
<td>2.7 (29)</td>
</tr>
<tr>
<td>4 (n=4)</td>
<td>236 (56)</td>
<td>208 (31)</td>
<td>71 (36)</td>
<td>3.8 (15)</td>
</tr>
<tr>
<td>5 (n=4)</td>
<td>312 (36)</td>
<td>205 (28)</td>
<td>42 (10)</td>
<td>8.4 (23)</td>
</tr>
<tr>
<td>6 (n=4)</td>
<td>263 (9)</td>
<td>186 (41)</td>
<td>41 (12)</td>
<td>2.9 (59)</td>
</tr>
</tbody>
</table>
Table 3.12  Compartmental pharmacokinetic parameters across subjects and treatments for oral ethanol study

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
<th>$V_d/F$ [L]</th>
<th>$K_a$ [hr$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Mean (n=24)</td>
<td>226</td>
<td>176</td>
<td>52</td>
<td>3.8</td>
</tr>
<tr>
<td>Inter-Individual variability (%COV) (n=24)</td>
<td>41%</td>
<td>34%</td>
<td>29%</td>
<td>63%</td>
</tr>
<tr>
<td>Intra-Individual variability (Mean %COV) (n=6)</td>
<td>26%</td>
<td>33%</td>
<td>18%</td>
<td>31%</td>
</tr>
</tbody>
</table>
analytical methods, particularly at low concentrations. For all parameters, intra-individual variability was lower than the inter-individual variability.

In summary, a one-compartment model with zero-order input into the absorption compartment and first-order absorption into the central compartment, with capacity-limited elimination was adequately fit to the individual concentration-time data. The mean and inter-individual variability estimates of the intrinsic PK parameters $V_{\text{max}}, K_m$ and $V_d/F$ are consistent with values estimated in other studies of the PK of oral ethanol using capacity-limited elimination models (Wagner and Patel, 1972; Wilkinson, 1980; Sedman et al., 1978; Holford, 1987). The estimate of $k_\text{a}$ obtained in this study was within the range of absorption rate constants estimated in other studies (Rangno et al., 1981; Holford, 1987). The $k_\text{a}$ estimated in this study is probably not a reflection of a true first-order process, since its value is expected to be influenced by the zero-order rate of input into the absorption compartment. The variability in $k_\text{a}$ is consistent with the inter-individual variability in absorption of ethanol observed in other studies (Wagner and Patel, 1972; Rangno et al., 1981; Wilkinson et al., 1977) and may be a consequence of the inherent variability in physiological processes such as gastric emptying observed between individuals.

In addition to fitting the individual concentration vs. time profiles, the final PK model, as described above, was also fit simultaneously to concentration-time data across all four active treatments for each subject.
Results of the simultaneous fit of individual subject concentration-time data across treatments indicated that the fits were adequate based on the coefficients of determinations ($r^2$), which ranged from 0.716 to 0.968 and Model Selection Criteria (MSC), which ranged from 1.047 to 3.243, random scatter in the plots of residuals vs. independent variable, normal distribution of the residuals as well as visual inspection of observed and fitted curves. The standard deviations and calculated %COVs of the parameter estimates were somewhat high, especially for $V_{\text{max}}$ with %COVs ranging from 17% to 235%, and for $K_m$ with %COVs ranging from 53% to 305%.

Individual concentration vs. time profiles illustrating the observed values and fitted curves are shown in Appendix B3. Table 3.13 lists the PK parameter estimates obtained by subject, for the simultaneous fit. The PK parameter estimates were not significantly different across subjects. The mean ($\pm$ S.D.) $V_{\text{max}}$ was 193 ($\pm$ 46) mg/L/hr, the mean ($\pm$ S.D.) $K_m$ was 174 ($\pm$ 79) mg/L, the mean ($\pm$ S.D.) $V_d/F$ was 53 ($\pm$ 12) mg/L and the mean ($\pm$ S.D.) $k_s$ was 3.3 ($\pm$ 2.5) hr$^{-1}$. The inter-individual variability was comparable to that observed from compartmental analysis of individual data.

Table 3.14 compares the mean (%COV) PK parameter estimates obtained from all three methods of PK analysis: non-compartmental, individual compartmental and simultaneous compartmental analysis. As table 3.14 indicates, the parameter estimates and their variability measures were comparable across the different methods. Figure 3.7 (a-d) illustrates the correlation between the parameter estimates obtained by the individual compartmental and simultaneous compartmental methods. The plots show a high degree
Table 3.13  Compartmental intrinsic pharmacokinetic parameters from simultaneous fitting of treatments by subject for oral ethanol study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
<th>$V_{d/F}$ [L]</th>
<th>$k_{a}$ [hr$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>143</td>
<td>57</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>139</td>
<td>125</td>
<td>48</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>234</td>
<td>83</td>
<td>47</td>
<td>2.6</td>
</tr>
<tr>
<td>4</td>
<td>209</td>
<td>281</td>
<td>76</td>
<td>3.0</td>
</tr>
<tr>
<td>5</td>
<td>230</td>
<td>153</td>
<td>44</td>
<td>8.4</td>
</tr>
<tr>
<td>6</td>
<td>214</td>
<td>260</td>
<td>49</td>
<td>1.9</td>
</tr>
<tr>
<td>Mean</td>
<td>193</td>
<td>174</td>
<td>53</td>
<td>3.3</td>
</tr>
<tr>
<td>S.D.</td>
<td>46</td>
<td>79</td>
<td>12</td>
<td>2.5</td>
</tr>
<tr>
<td>%COV</td>
<td>24%</td>
<td>45%</td>
<td>23%</td>
<td>76%</td>
</tr>
</tbody>
</table>
Table 3.14  Comparison of pharmacokinetic parameter estimates from non-compartmental, compartmental and simultaneous compartmental analysis

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
<th>$Vd/F$ [L]</th>
<th>$k_a$ [hr$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-compartmental</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis ($n=24$)</td>
<td>145 (29%)</td>
<td>208 (45%)</td>
<td>63 (47%)</td>
<td>NE$^1$</td>
</tr>
<tr>
<td><strong>Compartmental</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis ($n=24$)</td>
<td>226 (41%)</td>
<td>176 (34%)</td>
<td>52 (29%)</td>
<td>3.8 (63%)</td>
</tr>
<tr>
<td><strong>Simultaneous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compartmental Analysis</td>
<td>193 (24%)</td>
<td>174 (45%)</td>
<td>53 (23%)</td>
<td>3.3 (76%)</td>
</tr>
<tr>
<td>Analysis ($n=6$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1: NE = not estimated
Figure 3.7a  Plot of $V_{\text{max}}$ obtained from simultaneous fits vs. mean (S.E.) $V_{\text{max}}$ obtained from individual fits by subject for oral ethanol study.

Figure 3.7b  Plot of $K_m$ obtained from simultaneous fits vs. mean (S.E.) $K_m$ obtained from individual fits by subject for oral ethanol study.
Figure 3.7c  Plot of Vd/F obtained from simultaneous fits vs. mean (S.E.) Vd/F obtained from individual fits by subject for oral ethanol study

Figure 3.7d  Plot of $k_a$ obtained from simultaneous fits vs. mean (S.E.) $k_a$ obtained from individual fits by subject for oral ethanol study
of correlation and random scatter of points about the line of identity, indicating that the
two methods result in comparable parameter estimates. The individual compartmental
analysis allows the estimation of inter-individual variability as well as intra-individual
variability if the same subject receives active treatment on more than one occasion.
Although the simultaneous compartmental method provides only an estimate of inter-
individual variability, it has the advantage in that it incorporates the intra-individual
variability, which results in more accurate parameter estimates for each subject.

3.4.3 PHARMACODYNAMICS

3.4.3A EEG

Baseline-corrected response vs. time profiles for the EEG measures evaluated, including
total power across all frequency bands, total and relative power within each of the five
frequency bands (delta, theta, alpha, beta I and beta II) and spectral edge are shown in
Appendix C. A review of these plots reveal the following: 1) a transient increase in total
power across all treatments, including placebo, 2) no consistent changes in relative delta
power across subjects and treatments, 3) increases in relative alpha power seen only for
treatment D (high-slow), 4) increases in relative power in theta, beta I and beta II bands
seen only for the high-dose treatments (B and D), and 5) increases in spectral edge seen
only for the high-dose treatments (B and D).

The means and %COV of the baseline EEG measures are presented in table 3.15. The
Table 3.15  Pharmacodynamic parameters (Means and %COV) for EEG measures across treatments and subjects

<table>
<thead>
<tr>
<th></th>
<th>Total Power</th>
<th>Relative Delta Power</th>
<th>Relative Theta Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$E_o \ [\mu V^2]$</td>
<td>$E_{max} \ [\mu V^2]$</td>
<td>$E_{max}-E_o \ [\mu V^2]$</td>
</tr>
<tr>
<td>A</td>
<td>15508 (48%)</td>
<td>30138 (62%)</td>
<td>14630 (111%)</td>
</tr>
<tr>
<td>B</td>
<td>14210 (51%)</td>
<td>25663 (54%)</td>
<td>11453 (79%)</td>
</tr>
<tr>
<td>C</td>
<td>14565 (45%)</td>
<td>26279 (51%)</td>
<td>11714 (80%)</td>
</tr>
<tr>
<td>D</td>
<td>14746 (47%)</td>
<td>27273 (61%)</td>
<td>12982 (90%)</td>
</tr>
<tr>
<td>E</td>
<td>17520 (83%)</td>
<td>28544 (62%)</td>
<td>11023 (67%)</td>
</tr>
<tr>
<td></td>
<td>$E_o \ [-]$</td>
<td>$E_{max} \ [-]$</td>
<td>$E_{max}-E_o \ [-]$</td>
</tr>
<tr>
<td>A</td>
<td>0.488 (38%)</td>
<td>0.695 (20%)</td>
<td>0.207 (109%)</td>
</tr>
<tr>
<td>B</td>
<td>0.510 (37%)</td>
<td>0.699 (6%)</td>
<td>0.188 (101%)</td>
</tr>
<tr>
<td>C</td>
<td>0.463 (42%)</td>
<td>0.654 (31%)</td>
<td>0.191 (110%)</td>
</tr>
<tr>
<td>D</td>
<td>0.538 (43%)</td>
<td>0.677 (10%)</td>
<td>0.139 (135%)</td>
</tr>
<tr>
<td>E</td>
<td>0.470 (44%)</td>
<td>0.619 (40%)</td>
<td>0.149 (94%)</td>
</tr>
</tbody>
</table>

1: $T_{max}$ expressed as Median (range)
Table 3.15 contd.

<table>
<thead>
<tr>
<th>Relative Alpha Power</th>
<th>Trt</th>
<th>$E_o$ [-]</th>
<th>$E_{\text{max}}$ [-]</th>
<th>$E_{\text{max}} - E_o$ [-]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.260 (71%)</td>
<td>0.501 (37%)</td>
<td>0.241 (79%)</td>
<td>0.6 (0.3-5.0)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.247 (89%)</td>
<td>0.452 (40%)</td>
<td>0.205 (72%)</td>
<td>0.6 (0.3-0.8)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.286 (70%)</td>
<td>0.443 (42%)</td>
<td>0.157 (113%)</td>
<td>1.6 (0.6-6.0)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.215 (92%)</td>
<td>0.460 (39%)</td>
<td>0.245 (77%)</td>
<td>3.6 (0.6-6.0)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>0.276 (74%)</td>
<td>0.422 (50%)</td>
<td>0.147 (116%)</td>
<td>0.9 (0.3-6.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Beta I Power</th>
<th>Trt</th>
<th>$E_o$ [-]</th>
<th>$E_{\text{max}}$ [-]</th>
<th>$E_{\text{max}} - E_o$ [-]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.031 (45%)</td>
<td>0.042 (37%)</td>
<td>0.012 (76%)</td>
<td>1.6 (0.3-5.0)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.030 (42%)</td>
<td>0.065 (35%)</td>
<td>0.034 (67%)</td>
<td>2.3 (0.3-4.0)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.031 (54%)</td>
<td>0.043 (35%)</td>
<td>0.012 (77%)</td>
<td>2.0 (0.8-4.0)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.029 (67%)</td>
<td>0.062 (42%)</td>
<td>0.033 (54%)</td>
<td>2.5 (0.8-4.0)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>0.035 (66%)</td>
<td>0.043 (60%)</td>
<td>0.008 (252%)</td>
<td>4.0 (0.3-6.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Beta II Power</th>
<th>Trt</th>
<th>$E_o$ [-]</th>
<th>$E_{\text{max}}$ [-]</th>
<th>$E_{\text{max}} - E_o$ [-]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.034 (30%)</td>
<td>0.058 (34%)</td>
<td>0.023 (93%)</td>
<td>0.6 (0.3-1.8)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.032 (37%)</td>
<td>0.067 (40%)</td>
<td>0.035 (73%)</td>
<td>1.0 (0.3-6.0)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.043 (44%)</td>
<td>0.055 (33%)</td>
<td>0.012 (91%)</td>
<td>2.4 (0.3-5.0)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.035 (72%)</td>
<td>0.060 (23%)</td>
<td>0.025 (83%)</td>
<td>1.0 (0.3-6.0)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>0.041 (60%)</td>
<td>0.053 (54%)</td>
<td>0.012 (70%)</td>
<td>0.3 (0.3-5.0)</td>
<td></td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{max}}$ expressed as Median (range)
Table 3.15 contd.

<table>
<thead>
<tr>
<th>Trt</th>
<th>$E_o$ [Hz]</th>
<th>$E_{max}$ [Hz]</th>
<th>$E_{max}-E_o$ [Hz]</th>
<th>$T_{max}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9.7 (10%)</td>
<td>11.3 (11%)</td>
<td>1.7 (89%)</td>
<td>0.3 (0.3-1.8)</td>
</tr>
<tr>
<td>B</td>
<td>9.6 (12%)</td>
<td>12.0 (11%)</td>
<td>2.4 (77%)</td>
<td>0.3 (0.3-0.8)</td>
</tr>
<tr>
<td>C</td>
<td>10.3 (14%)</td>
<td>11.3 (11%)</td>
<td>1.0 (98%)</td>
<td>2.9 (0.3-5.0)</td>
</tr>
<tr>
<td>D</td>
<td>9.5 (25%)</td>
<td>11.6 (13%)</td>
<td>2.1 (47%)</td>
<td>1.0 (0.8-6.0)</td>
</tr>
<tr>
<td>E</td>
<td>10.2 (23%)</td>
<td>11.4 (17%)</td>
<td>1.1 (66%)</td>
<td>0.7 (0.3-6.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{max}$ expressed as Median (range)
baseline measures were not different across subjects and treatments, but showed considerable variability, except for relative theta power and spectral edge.

Figures 3.8 - 3.14 show the mean (± S.E.) peak changes in the EEG measures, including total power, relative power in each of the five frequency bands, delta, theta, alpha, beta I and beta II), and spectral edge, by treatment.

Statistical comparison of the $E_{max}^{obs}$ or $E_{min}^{obs}$ and $t_{max}$ or $t_{min}$ for the EEG measures revealed significant treatment differences only for relative theta power ($p=0.04$). Multiple comparisons indicated that the high-dose treatments were significantly different from the low-dose treatments and placebo, however the low-dose treatments were indistinguishable from placebo. Also, there were no differences between fast and slow input treatments both at low and high doses. Residuals were found to be normally distributed for these variables. There were no significant sequence or period effects on any of the EEG variables evaluated. The p values for the significance of the baseline response as a covariate was less than 0.05 for all the EEG variables evaluated except for relative theta power. This indicates that the baseline differences account for a significant proportion of the variability in EEG response between treatments.

The increases in theta power, along with the increases in beta power and decrease in the spectral edge are consistent with the increase in EEG power and a generalized slowing of the EEG that have been previously reported in the literature following administration of oral doses of ethanol comparable to doses administered in this study (Begleiter and Platz, 1972; Ehlers et al., 1989; Lukas et al., 1986). The large individual variability in
Figure 3.8 Baseline-corrected $E_{\text{max}}$ for Total power by treatment for oral ethanol study

Figure 3.9 Baseline-corrected $E_{\text{max}}$ for Relative delta power by treatment for oral ethanol study
Figure 3.10 Baseline-corrected $E_{\text{max}}$ for Relative theta power by treatment for oral ethanol study

Figure 3.11 Baseline-corrected $E_{\text{max}}$ for Relative alpha power by treatment for oral ethanol study
Figure 3.12 Baseline-corrected $E_{\text{max}}$ for Relative beta I power by treatment for oral ethanol study

Figure 3.13 Baseline-corrected $E_{\text{max}}$ for Relative beta II power by treatment for oral ethanol study
Figure 3.14 Baseline-corrected $E_{\text{min}}$ for spectral edge by treatment for oral ethanol study
EEG responses following ethanol administration observed in this study are also in agreement with the published literature (Lehtinen et al., 1978; Lehtinen et al., 1985). The EEG did not prove to be a very sensitive measure of the CNS effects of ethanol, showing changes only at the high dose relative to placebo. There did not appear to be an effect of input-rate on the EEG measures evaluated.

3.4.3B Psychometric Performance Tests

Baseline-corrected response vs. time profiles for the PPT measures evaluated, including categories completed and number of errors for the CST, average tap-rate for the dominant and non-dominant hands for FT and total attempts and number of errors for DSST are shown in Appendix D. Table 3.16 lists the baseline ($E_0$), maximum or minimum observed response ($E_{\text{max}}^{\text{obs}}$ or $E_{\text{min}}^{\text{obs}}$) and time of $E_{\text{max}}^{\text{obs}}$ or $E_{\text{min}}^{\text{obs}}$ ($t_{\text{max}}$ or $t_{\text{min}}$) for each of the PPT measures evaluated. Figures 3.15 - 3.17 show the peak changes in the PPT measures evaluated by treatment, including total attempts and number of errors for DSST and peak change in dominant and non-dominant hand tap-rate for FT. Results for the CST indicate that there were no consistent changes in either of the measures. There was a high degree of variability in baseline responses as well as in the peak responses measured. Also, a learning effect was observed across periods with improvement in performance over time independent of treatment. There appeared to be a transient decrease in the total attempts followed by a later increase in total attempts for the DSST, as well as a transient increase in the number of
Table 3.16  Pharmacodynamic parameters (Means and %COV) for PPT measures across treatments and subjects

<table>
<thead>
<tr>
<th>DSST-Total Attempts</th>
<th>Trt</th>
<th>E₀ [-]</th>
<th>Eₘᵢₙ [-]</th>
<th>E₀-Eₘᵢₙ [-]</th>
<th>Tₓₜₓₓ [hr]¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>62 (16%)</td>
<td>53 (19%)</td>
<td>8 (58%)</td>
<td>1.6 (0.8-6.0)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>55 (25%)</td>
<td>51 (24%)</td>
<td>6 (92%)</td>
<td>1.6 (0.8-4.0)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>59 (21%)</td>
<td>52 (21%)</td>
<td>7 (73%)</td>
<td>1.5 (0.8-2.5)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>58 (25%)</td>
<td>46 (25%)</td>
<td>12 (71%)</td>
<td>1.6 (1.5-3.0)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>55 (24%)</td>
<td>52 (22%)</td>
<td>4 (87%)</td>
<td>1.8 (1.5-5.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DSST-Number of Errors</th>
<th>Trt</th>
<th>E₀ [-]</th>
<th>Eₘᵢₙ [-]</th>
<th>Eₘᵢₙ-E₀ [-]</th>
<th>Tₓₜₓₓ [hr]¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3 (169%)</td>
<td>7 (55%)</td>
<td>5 (86%)</td>
<td>2.8 (1.8-5.0)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>2 (159%)</td>
<td>7 (78%)</td>
<td>6 (60%)</td>
<td>2.1 (0.8-3.0)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>3 (121%)</td>
<td>7 (112%)</td>
<td>4 (119%)</td>
<td>1.9 (1.8-2.0)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>2 (185%)</td>
<td>8 (85%)</td>
<td>6 (57%)</td>
<td>2.8 (1.5-4.0)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>3 (122%)</td>
<td>6 (103%)</td>
<td>3 (99%)</td>
<td>2.3 (0.8-6.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.1 (14%)</td>
<td>5.6 (16%)</td>
<td>0.5 (99%)</td>
<td>3.5 (0.3-6.0)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>6.2 (15%)</td>
<td>5.1 (21%)</td>
<td>1.0 (56%)</td>
<td>0.7 (0.3-6.0)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>6.0 (14%)</td>
<td>5.5 (17%)</td>
<td>0.5 (98%)</td>
<td>1.4 (0.8-4.0)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>6.2 (15%)</td>
<td>5.5 (18%)</td>
<td>0.7 (47%)</td>
<td>1.6 (0.8-4.0)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>5.7 (17%)</td>
<td>5.6 (12%)</td>
<td>0.2 (117%)</td>
<td>4.0 (1.5-5.0)</td>
<td></td>
</tr>
</tbody>
</table>

¹: Tₓₜₓₓ expressed as Median (range)
Table 3.16 contd.

<table>
<thead>
<tr>
<th>Trt</th>
<th>$E_0$ [taps/sec]</th>
<th>$E_{\text{min}}$ [taps/sec]</th>
<th>$E_0 - E_{\text{min}}$ [taps/sec]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.0 (12%)</td>
<td>5.5 (13%)</td>
<td>0.6 (66%)</td>
<td>0.7 (0.3-1.5)</td>
</tr>
<tr>
<td>B</td>
<td>6.0 (14%)</td>
<td>5.1 (18%)</td>
<td>0.9 (46%)</td>
<td>0.6 (0.3-1.8)</td>
</tr>
<tr>
<td>C</td>
<td>5.7 (18%)</td>
<td>5.4 (16%)</td>
<td>0.3 (62%)</td>
<td>0.8 (0.3-3.0)</td>
</tr>
<tr>
<td>D</td>
<td>5.7 (18%)</td>
<td>5.0 (21%)</td>
<td>0.8 (56%)</td>
<td>1.9 (0.6-2.5)</td>
</tr>
<tr>
<td>E</td>
<td>5.5 (10%)</td>
<td>5.4 (14%)</td>
<td>0.2 (95%)</td>
<td>2.5 (0.6-3.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{max}}$ expressed as Median (range)
Figure 3.15 Baseline-corrected $E_{min}$ for Total attempts for DSST by treatment for oral ethanol study

Figure 3.16 Baseline-corrected $E_{max}$ for number of errors for DSST by treatment for oral ethanol study
Figure 3.17a Baseline-corrected $E_{\text{min}}$ for non-dominant hand tap-rate by treatment for oral ethanol study

Figure 3.17b Baseline-corrected $E_{\text{min}}$ for dominant hand tap-rate by treatment for oral ethanol study
errors for the DSST. The greatest effect was seen for treatment D, however, the variability in the responses was considerable. The response for the DSST measures was also confounded by learning effects, however, baseline variability in DSST measures was low. Statistical comparison of PD parameters for DSST did not reveal any significant differences between treatments. There was, however, a significant period effect observed for the $E_{\text{min}}^{\text{obs}}$ for the total attempts ($p=0.001$).

Although the effects of ethanol on the card-sorting test and on the DSST have been demonstrated in other studies (Wittenborn, 1987, Gengo et al., 1990), the lack of effect seen in this study may be attributed to task difficulty and inadequate training of the subjects prior to drug administration.

There appeared to be a dose-related decrease in the tap-rate for both hands for the FT, with a greater effect seen for the non-dominant hand. Baseline variability was relatively low across subjects and treatments. Statistical comparison of $E_{\text{min}}^{\text{obs}}$ for the non-dominant hand as well as for the dominant hand indicated significant differences across treatments ($p=0.014$ for dominant hand tap-rate and $p=0.023$ for non-dominant hand tap-rate). Multiple comparisons revealed that the two high-dose treatments (B and D) were significantly different from the two low-dose treatments (treatments A and C) and placebo (treatment E), but were not different from each other. The low-dose treatments were indistinguishable from each other and from placebo. The $p$ values for the significance of the baseline response as a covariate was less than 0.05 for the $E_{\text{min}}^{\text{obs}}$ for both hands. This indicates that the baseline response is a significant determinant of the
FT response to ethanol. The NR score (see section 3.3.5E) was also a significant covariate in the statistical analysis of the $E_{\text{min,obs}}$ values across treatments. This indicates that there may be a correlation between the lack of subjective response of the non-responders and the degree of psychomotor impairment as measured by FT. Statistical comparison of $T_{\text{min}}$ values revealed no significant differences across treatments. There did not appear to be any effect of input-rate on the FT measures.

The decrease in total attempts and increase in number of errors for the DSST as well as the decrease in tap-rate for FT are consistent with psychometric impairment. The psychomotor impairment appeared to be dose-related, but showed consistent, and in some cases statistically significant changes only for the high-dose treatments. The impairment in psychometric performance is consistent with the published literature on performance impairment following oral administration of ethanol doses to achieve concentrations in the range of 800 to 1000 mg/L (Evan et al., 1984, Moskowitz et al., 1976, Wittenborn, 1987).

Also, there did not appear to be any effect of input-rate on the PPT measures evaluated. The effect of input-rate on psychometric performance was evaluated by Moskowitz et al. (1976), who found that subjects who consumed the dose of ethanol rapidly (ingestion time: 15 minutes) performed more poorly than subjects who consumed the dose of ethanol slowly (ingestion time: 1 hour). The lack of effect of input-rate on psychometric performance observed in our study may be due to the relatively small difference in the slow and fast input-rates (20 minutes vs. 50 minutes) used in our study, as well as the
fairly high variability due to individual differences in performance impairment.

3.4.3C Impairment Scales

Baseline-corrected response vs. time profiles for the SRI and ORI measures evaluated, including scores for the items "HIGH", "DRUNK" AND "ALCOHOL EFFECTS" on the SRI scale, as well as scores for the items "HIGH" and "DRUNK" on the ORI scale are shown in Appendix E. Response vs. time profiles for the other items on the SRI and ORI scales are not included since they did not show a consistent response across subjects and treatments.

Table 3.17 lists the baseline ($E_0$), maximum observed response ($E_{\text{max obs}}$) and time of $E_{\text{max obs}}$ ($t_{\text{max}}$) for each of the SRI and ORI items listed above. Figures 3.18 - 3.22 show the peak changes in the SRI and ORI measures evaluated by treatment, including "HIGH", "DRUNK" and "ALCOHOL EFFECTS" for the SRI scales, and "HIGH" and "DRUNK" for the ORI scales.

The SRI and ORI scales were very sensitive to the effects of ethanol, with the most sensitive items being "HIGH", "DRUNK" and "ALCOHOL EFFECTS" on the SRI scale and "HIGH" and "DRUNK" on the ORI scale. There were dose-related increases in the $E_{\text{max obs}}$ for these items, with both low and high doses showing statistically significant increases in $E_{\text{max obs}}$ from placebo. Some subjects also showed a delayed $t_{\text{max}}$, especially at the high dose, indicating that there was an input-rate-related effect on the SRI and ORI scales.
Table 3.17  Pharmacodynamic parameters (Means and %COV) for SRI/ORI measures across treatments and subjects

<table>
<thead>
<tr>
<th>SRI - HIGH Score</th>
<th>Trt</th>
<th>$E_o$ [mm]</th>
<th>$E_{max}$ [mm]</th>
<th>$E_{max-E_o}$ [mm]</th>
<th>$T_{max}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>1 (140%)</td>
<td>13 (86%)</td>
<td>12 (90%)</td>
<td>0.5 (0.3-0.6)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1 (126%)</td>
<td>32 (64%)</td>
<td>31 (65%)</td>
<td>0.6 (0.3-1.3)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1 (175%)</td>
<td>10 (67%)</td>
<td>9 (75%)</td>
<td>0.8 (0.3-1.5)</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1 (126%)</td>
<td>33 (73%)</td>
<td>32 (77%)</td>
<td>1.2 (0.3-3.0)</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1 (113%)</td>
<td>1 (77%)</td>
<td>0 (155%)</td>
<td>0.3 (0.3-0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SRI - DRUNK Score</th>
<th>Trt</th>
<th>$E_o$ [mm]</th>
<th>$E_{max}$ [mm]</th>
<th>$E_{max-E_o}$ [mm]</th>
<th>$T_{max}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>1 (122%)</td>
<td>8 (59%)</td>
<td>7 (60%)</td>
<td>0.9 (0.3-2.5)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1 (126%)</td>
<td>25 (60%)</td>
<td>24 (61%)</td>
<td>0.6 (0.3-1.3)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1 (167%)</td>
<td>5 (103%)</td>
<td>4 (111%)</td>
<td>1.3 (0.3-2.0)</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1 (100%)</td>
<td>29 (81%)</td>
<td>27 (86%)</td>
<td>1.5 (0.3-3.0)</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1 (126%)</td>
<td>2 (73%)</td>
<td>1 (122%)</td>
<td>0.6 (0.3-6.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SRI - ALCOHOL EFFECTS Score</th>
<th>Trt</th>
<th>$E_o$ [mm]</th>
<th>$E_{max}$ [mm]</th>
<th>$E_{max-E_o}$ [mm]</th>
<th>$T_{max}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>A</td>
<td>1 (89%)</td>
<td>17 (50%)</td>
<td>16 (54%)</td>
<td>0.6 (0.3-2.0)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1 (126%)</td>
<td>40 (47%)</td>
<td>39 (47%)</td>
<td>0.6 (0.3-1.5)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1 (159%)</td>
<td>14 (54%)</td>
<td>14 (57%)</td>
<td>0.8 (0.6-1.5)</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1 (245%)</td>
<td>34 (73%)</td>
<td>34 (75%)</td>
<td>1.4 (0.6-2.5)</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1 (126%)</td>
<td>3 (88%)</td>
<td>2 (144%)</td>
<td>0.5 (0.3-0.8)</td>
</tr>
</tbody>
</table>

1: $T_{max}$ expressed as Median (range)
Table 3.17 contd.

<table>
<thead>
<tr>
<th>Trt</th>
<th>$E_0$ [mm]</th>
<th>$E_{\text{max}}$ [mm]</th>
<th>$E_{\text{max}}-E_0$ [mm]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 (245%)</td>
<td>16 (54%)</td>
<td>16 (53%)</td>
<td>0.9 (0.3-1.5)</td>
</tr>
<tr>
<td>B</td>
<td>0 (0%)</td>
<td>23 (38%)</td>
<td>23 (38%)</td>
<td>1.0 (0.6-1.5)</td>
</tr>
<tr>
<td>C</td>
<td>0 (0%)</td>
<td>11 (65%)</td>
<td>11 (65%)</td>
<td>1.4 (0.3-1.5)</td>
</tr>
<tr>
<td>D</td>
<td>0 (0%)</td>
<td>26 (30%)</td>
<td>26 (30%)</td>
<td>1.8 (0.8-2.0)</td>
</tr>
<tr>
<td>E</td>
<td>0 (0%)</td>
<td>2 (157%)</td>
<td>2 (156%)</td>
<td>0.3 (0.3-1.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trt</th>
<th>$E_0$ [mm]</th>
<th>$E_{\text{max}}$ [mm]</th>
<th>$E_{\text{max}}-E_0$ [mm]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0 (0%)</td>
<td>6 (59%)</td>
<td>6 (59%)</td>
<td>1.1 (0.3-1.5)</td>
</tr>
<tr>
<td>B</td>
<td>0 (0%)</td>
<td>21 (44%)</td>
<td>21 (44%)</td>
<td>1.5 (1.3-2.0)</td>
</tr>
<tr>
<td>C</td>
<td>0 (0%)</td>
<td>5 (111%)</td>
<td>5 (111%)</td>
<td>1.0 (0.3-1.5)</td>
</tr>
<tr>
<td>D</td>
<td>0 (0%)</td>
<td>20 (58%)</td>
<td>20 (58%)</td>
<td>1.9 (0.8-3.0)</td>
</tr>
<tr>
<td>E</td>
<td>0 (245%)</td>
<td>1 (155%)</td>
<td>1 (167%)</td>
<td>0.3 (0.3-1.3)</td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{max}}$ expressed as Median (range)
Figure 3.18 Baseline-corrected $E_{\text{max}}$ for SRI-HIGH score by treatment for oral ethanol study.

Figure 3.19 Baseline-corrected $E_{\text{max}}$ for SRI-DRUNK score by treatment for oral ethanol study.
Figure 3.20 Baseline-corrected $E_{\text{max}}$ for SRI-ALCOHOL EFFECTS score by treatment for oral ethanol study

Figure 3.21 Baseline-corrected $E_{\text{max}}$ for ORI-HIGH score by treatment for oral ethanol study
Figure 3.22 Baseline-corrected $E_{\text{max}}$ for ORI-DRUNK score by treatment for oral ethanol study.
Two of the six subjects (subjects 1 and 3) did not show a consistent response on the SRI and ORI scales, even though they showed EEG changes and psychometric impairment consistent with the other subjects. These two subjects were classified as "non-responders". Figure 3.23 shows the SRI-"ALCOHOL EFFECTS" score vs. time, by treatment, for two representative subjects (subject 1 - non-responder and subject 4 - responder). In order to incorporate this in the statistical analysis, these two subjects were given a "non-responder" score (NR) of 0, while the other four subjects ("responders") were given a score of 1. This score was used as a covariate in the statistical analysis.

Statistical comparison of the $E_{\text{max}}$ and $t_{\text{max}}$ revealed significant treatment differences for all the SRI and ORI variables. Significant differences were observed for all of the five measures evaluated (SRI-"HIGH": $p=0.0006$, SRI-"DRUNK": $p=0.0020$, SRI-"ALCOHOL EFFECTS": $p=0.0013$, ORI-"HIGH": $p=0.0010$, ORI-"DRUNK": $p=0.0001$). Multiple comparisons indicated that, for all the five measures, the low doses (A and C) were indistinguishable from placebo (E) and from each other, while the high doses (B and D) were significantly different from low-doses and placebo. There were no significant differences between the two high dose treatments. The $t_{\text{max}}$ parameter showed significant differences only for one measure, ORI-"DRUNK" ($p=0.0135$). Multiple comparisons revealed significant differences for treatment B (high-fast) vs. placebo and treatment D (high-slow) vs. the other treatments. There were no differences between treatments A, C and E. There were no significant sequence or period effects. The baseline response was not a significant covariate in the analysis, however the NR score
Figure 3.23  SRI-ALCOHOL EFFECTS vs. time profiles by treatment for representative non-responder subject (subject 1) and representative responder subject (subject 4)
was a significant covariate for all the variables tested (p < 0.05), indicating that the NR score was an important determinant of the differences in response on the SRI and ORI scales across treatments.

In summary, the SRI and ORI scales provided sensitive measures of the subjective effects of ethanol. The most sensitive items on the scales were "HIGH", "DRUNK" and "ALCOHOL EFFECTS", showing dose-related as well as input-rate related (at the high dose) changes in scores consistent with perceived impairment. These results are consistent with results obtained by other investigators who have used scales similar to the SRI scales (Shuckit, 1984; Lex et al., 1988; Gengo et al., 1990), indicating that these scales are indeed sensitive measures of the subjective effects of ethanol.

3.4.3D PK-PD Correlation and Tolerance Development

In order to evaluate the PK-PD relationship for ethanol, response vs. serum ethanol concentration profiles were plotted for several of the PD measures evaluated. The PD measures that were plotted vs. serum concentrations included the relative theta power from the EEG measures, tap-rate for the non-dominant hand for FT from the PPT, and the score on the item "ALCOHOL EFFECTS" on the SRI scales. Response vs. concentration plots for each of these measures are presented by subject and treatment in Appendix F.

A review of the plots for baseline-corrected relative theta power vs. serum ethanol concentrations resulted in the following observations:
1) Effect-concentration profiles revealed no consistent patterns across subjects or treatments.

2) For the low-dose treatments A and C, several of the subjects showed an initial decrease in relative theta power followed by a later increase that went above baseline values for some subjects. The changes in relative theta power did not appear to be correlated to concentrations for these treatments.

3) For the high-dose treatments B and D, there was a general increase in relative theta power with concentration. For treatment B, 3 of the 6 subjects showed an initial transient decrease in relative theta power prior to the increases in relative theta power. For treatment D, the initial transient decrease was seen in 3 of the 6 subjects. Only one subject (subject 6) showed the presence of a clockwise hysteresis loop in the response vs. concentration profile.

In summary, there was no consistent effect-concentration correlation for the EEG measures evaluated. There was some correlation between peak concentration and peak effect, but the time-course of changes in concentration and effect were inconsistent.

A review of the plots for baseline-corrected non-dominant hand tap-rate vs. serum ethanol concentrations resulted in the following observations:

1) Increasing concentrations generally were associated with decreases in tap-rate. 2) for treatment A, 2 of the 6 subjects (subjects 1 and 5) actually showed an increase in tap-rate, indicating an improvement rather than impairment in psychomotor performance.
Also, two of the subjects (subject 2 and 4) showed some degree of clockwise hysteresis with a smaller change in tap-rate at later time-points during the descending limb of the profile relative to the change at earlier time-points during the ascending limb of the profile, at similar concentrations.

3) For treatment C, one subject (subject 5) showed an increase in tap-rate, while one subject (subject 6) showed an initial increase in tap-rate followed by a later sustained decrease in tap-rate.

4) For treatment B, one subject (subject 1) showed an initial increase in tap-rate followed by a decrease in tap-rate at later-time points. Three of the subjects (subjects 2, 3, 4) showed a clockwise hysteresis pattern with greater degrees of impairment at earlier time-points during increasing concentrations followed by lower degrees of impairment, and in some cases improvement in performance at later-time points during declining concentrations.

5) For treatment D, one subject (subject 5) showed a consistent increase in performance with no indication of impairment. Three subjects (subjects 2, 4, 6) showed an improvement in performance at later time points, but tap-rates went above baseline values only for one subject at later time-points.

In summary, low-dose treatments showed inconsistent changes in tap-rate, while high doses showed concentration-related impairment. At the high dose, the fast-input treatment (treatment B) showed impairment in performance followed by improvement in performance at later time points in some of the subjects. The slow-input treatment
(treatment D) showed initial impairment, with some improvement in performance at later time-points, however the degree of improvement was smaller than that observed for treatment B. This later improvement in performance may be due to acute tolerance development to the psychometric impairment effects of ethanol. Another explanation for this phenomenon may be the development of acute learning effects. The relatively large variability in the time course of the tap-rate following the different doses and dose-rates of ethanol as well as the learning effects may have precluded the development of a clear relationship between changes in finger-tapping rate and concentration.

A review of the plots for baseline-corrected SRI-Alcohol Effect Scores vs. serum ethanol concentrations resulted in the following observations:

1) There was a consistent increase in SRI scores with concentrations at earlier time points that appeared to be correlated, i.e., higher concentrations were associated with a higher degree of subjective impairment as assessed by the SRI scores.

2) At later time-points, the effect appeared to decline faster than concentrations resulting in the presence of clockwise hysteresis loops in the effect vs. concentration profiles. Clockwise hysteresis loops were observed in 3 of the 6 subjects for treatment A, and in 5 of the 6 subjects for treatments B, C and D. Figure 3.24 shows the SRI-Alcohol effect vs. concentration profiles by treatment for a representative subject (subject 2). The degree of hysteresis was dose-related with higher doses showing larger degrees of hysteresis indicated by a rightward shift in the descending limb by about 300 mg/L with
Figure 3.24 SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentration profiles by treatment for a representative subject (subject 2).
an increase in dose.

3) Only one subject (subject 4) showed consistent concentration-related impairment without the presence of hysteresis.

4) Even the subjects who were classified as non-responders had effect-concentration profiles that showed clockwise hysteresis.

Follow-up analysis for other items of the SRI scale, including the items "HIGH" and "DRUNK", as well as for the ORI scale items "HIGH" and "DRUNK" revealed the same pattern of initial concentration-related impairment and the presence of clockwise hysteresis, although the most profound effect was observed for the SRI-Alcohol Effects scores.

These findings are consistent with the development of acute, exposure-related tolerance development to the subjective impairment effects of ethanol. This means that the degree of subjective impairment perceived by the subject was higher during the ascending limb of the ethanol concentration-time curve than at similar concentrations during the descending limb of the ethanol concentration-time curve. During the drug elimination phase, the effect declined faster than drug concentrations such that subjects did not perceive themselves to be impaired even though they had significant measurable concentrations of ethanol and exhibited psychometric impairment as measured by finger-tapping. This means that there was a temporal disparity between perceived impairment and performance impairment during the descending limb of the ethanol concentration-time curve.
These findings are consistent with the results of other studies evaluating subjective and objective impairment following oral ethanol administration to achieve concentrations comparable to the serum concentrations achieved in this study (Radlow and Hurst, 1985, Jones et al., 1987, Kaplan et al., 1985, Gengo et al., 1990, Rohrbaugh et al., 1987). A review of the results of these studies indicate that, in general, objective measures of impairment, such as psychometric performance measures, show no acute tolerance development, while subjective measures that rely on the subjective perception of impairment appear to show the development of acute tolerance to ethanol. Results of this study also indicate that the tolerance appears to be exposure-related, however, the 2.5 fold increase in input-rate (from 20 minutes to 50 minutes) did not appear to have an effect on the development of acute tolerance to the subjective effects. Considering the large variability in absorption of ethanol as well as in the pharmacodynamics of ethanol, the 2.5 fold difference in the input-rate may not have been large enough to evaluate an input-rate effect on the PK and PD of oral ethanol in this study.

3.4.3E PK-PD Modelling of the Acute Tolerance Development to Subjective Effects of Ethanol

A PK-PD model was developed to describe the tolerance development to the subjective impairment following oral ethanol administration. The SRI-ALCOHOL EFFECTS (SRI-AE) measure was selected since it was shown to be the most sensitive subjective measure of ethanol’s effect. The SRI-AE and concentration data were fit individually for each
subject and treatment. The data sets were imported from a spreadsheet (Microsoft Excel version 5, Microsoft Inc., WA) and directly imported into the program used for the fitting, Scientist (version 2.0 for Windows, MicroMath Inc., Salt Lake City, UT).

**Model Development:** The first model evaluated was the hypothetical antagonistic metabolite model first used to describe tolerance development to the cardiovascular effects of nicotine (Porchet et al., 1988). This model incorporates tolerance as a result of (non-competitive) antagonism produced by a hypothetical metabolite induced by a first order process. The model consists of three parts. The first is a pharmacokinetic model (one compartment model with capacity-limited elimination for ethanol). The second is a pharmacodynamic model linked to the PK model that relates the serum concentration of ethanol (C) to the observed effect E using the linear relationship,

$$E = S \times C$$

where S is the slope or sensitivity factor for the effect-concentration relationship. The third part of the model is the tolerance model consisting of a hypothetical metabolite ($C_{ant}$) which is related to the central PK compartment by a first-order rate constant $k_{ant}$. The metabolite is eliminated by a first order process ($k_{ant}$). The overall PD model equation is:

$$E = \frac{S \times C}{1 + \left(\frac{C_{ant}}{C_{ant50}}\right)}$$

where $C_{ant50}$ is the potency of the antagonist, or the concentration required to produce
50% antagonism.

This model was coded in Scientist. Initial estimates were obtained from simulations using different values of the parameters. The model was fit to the individual concentration-effect (SRI-AE) data. The PK parameters were fixed to the final estimates obtained during the PK modelling of the data (done previously, see section 3.4.2B).

After attempting to fit several data sets, it was realized that this model works best with data with repeated inputs of drug. The onset and offset of effect are governed by a single rate constant, therefore the fastest the effect can decline is at the same rate as the concentration of the metabolite. Since the metabolite concentration is a function of the parent drug, the effect cannot decline faster than the elimination rate of the parent drug (in the case of formation-rate limited metabolite kinetics). Therefore this model is incapable of describing the existing data. It cannot be used to model acute tolerance within the same dose without repeated inputs (as done in the original study by Porchet et al., 1988). Therefore it was determined that other models of tolerance would have to be evaluated. One of the models that was evaluated and finally used for our data was the model originally developed by Bauer and Fung (1994) to describe nitroglycerin-induced hemodynamic tolerance in experimental heart failure. The final model used incorporates the PK model (one compartment with capacity-limited elimination) linked to the PD model which relates concentration (C) to effect (E) (see figure 3.25). The model postulates that the primary (direct) effect, rather than the drug concentration, is the driving force that activates the tolerance mechanism. This assumption implies that the
Figure 3.25 Final PK-PD model for acute tolerance development to subjective effects of oral ethanol
tolerance to the effect is a result of compensatory feedback mechanisms that are produced to counter-regulate the direct effect.

The direct drug effect \( (E_D) \) was modelled as:

\[
E_D = S \cdot C
\]

where \( S \) is the slope factor or Sensitivity.

The feedback effect \( (E_{FB}) \) was modelled using two rate constants \( (k_{on} \) and \( k_{off} \)). The differential equation was

\[
E_{FB}' = k_{on} \cdot E_D - k_{off} \cdot E_{FB}
\]

The net observed effect \( E \) was calculated as

\[
E = E_D - E_{FB}
\]

This model was coded in Scientist. Initial estimates were obtained from simulations using different values of the parameters. The model was fit to the individual concentration-effect (SRI-AE) data. The PK parameters were fixed to the final estimates obtained during the PK modelling of the data (done previously, see section 3.4.2). Weights of 1 and \( 1/y \) were evaluated. Goodness of fit was assessed by evaluating the coefficient of determination \( (r^2) \), Model Selection Criteria (MSC), parameter estimates and their standard deviations, residual analysis, and visual observation of the observed points and fitted effect-time profiles as well as observed and fitted hysteresis loops (in effect-concentration plots).

Results: Individual fits were determined to be acceptable based on goodness of fit criteria described above. Weights of \( 1/y \) did not appear to improve the fit. The
correlations for the final model ranged from 0.860 to 0.997, and MSC ranged from 1.21 to 5.21. Table 3.18 lists the final parameter estimates for the model parameters, \( S, k_{on} \) and \( k_{off} \). Figure 3.26 shows the observed values and fitted curves for the SRI-AE score vs. concentration plots by treatment for a representative subject (subject 2).

As Table 3.18 indicates, the overall \( S \) does not appear to be different across treatments. However, the \( S \) for responders appears to be higher than for non-responders. The slope, \( S \), can be considered as a measure of individual sensitivity to the effect of ethanol for a unit change in concentration, in the absence of tolerance. The finding that the estimate of \( S \) is lower for the non-responders compared to the responders is a result of the classification of the subjects based on their subjective response to ethanol. \( S \) can serve as a valuable measure to evaluate differences in sensitivity to the effects of ethanol (in the absence of tolerance) for other surrogate measures of ethanol’s effect (that can be linearly related to concentration), as well as in different populations of subjects, such as women, elderly subjects and alcoholic subjects.

The rate constants, \( k_{on} \) and \( k_{off} \), did not appear to be different across treatments, and did not differ between responders and non-responders. The relatively large COV\% may be a result of the small sample sizes (\( n = 2 \) for non-responders and \( n = 4 \) for responders). The mean \( k_{on} \) of 0.75 hr\(^{-1}\) translates to an onset half-life of tolerance of 0.9 hours, and the mean \( k_{off} \) of 1.42 hr\(^{-1}\) translates to an onset half-life of tolerance of 0.5 hours.

One observation from the PK-PD modelling is that the model predicts a rebound effect, i.e., the net effect falls below the baseline. This cannot be observed in the data since the

<table>
<thead>
<tr>
<th></th>
<th>Trt A</th>
<th>Trt B</th>
<th>Trt C</th>
<th>Trt D</th>
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</thead>
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<tr>
<td><strong>S</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=6)</td>
<td>0.060 (83%)</td>
<td>0.070 (68%)</td>
<td>0.070 (81%)</td>
<td>0.066 (78%)</td>
</tr>
<tr>
<td>NR¹ (n=2)</td>
<td>0.075 (40%)</td>
<td>0.023 (19%)</td>
<td>0.039 (27%)</td>
<td>0.020 (7%)</td>
</tr>
<tr>
<td>R² (n=4)</td>
<td>0.053 (114%)</td>
<td>0.094 (42%)</td>
<td>0.086 (77%)</td>
<td>0.089 (54%)</td>
</tr>
<tr>
<td><strong>k_{on}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=6)</td>
<td>0.79 (56%)</td>
<td>0.84 (42%)</td>
<td>1.11 (57%)</td>
<td>0.61 (55%)</td>
</tr>
<tr>
<td><strong>k_{off}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=6)</td>
<td>2.69 (105%)</td>
<td>1.30 (31%)</td>
<td>1.72 (45%)</td>
<td>0.95 (41%)</td>
</tr>
</tbody>
</table>

1: NR - Non-Responder  2: R - Responder
Figure 3.26 SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentration profiles (observed values and fitted curves) by treatment for a representative subject (subject 2).
mood scales do not permit measurement of effects below the baseline (zero).

In summary, the feedback model of tolerance that characterizes acute tolerance as a result of compensatory feedback mechanisms that are produced to counter-regulate the direct effect of the drug resulted in an adequate fit to the subjective effect-concentration-time data from this study. This model has been previously used to describe the hemodynamic effects of nitroglycerin (Bauer and Fung, 1994), and to our knowledge, this is the first attempt to use this model to describe tolerance to the CNS effects of a centrally-acting drug. The general form of this model can accommodate changes in drug input, allowing the flexibility of examining the effect of different input regimens (doses and dose-rates) on the development of acute tolerance to the subjective effects of ethanol.

3.4.3F Correlation of Pharmacodynamic Measures

Since one of the aims of this study was to evaluate the EEG as a surrogate measure of the CNS effect of ethanol, and to assess the relationship between the EEG changes and changes in PP as well as the relationship between the EEG changes and SRI, linear regression of the \( E_{\text{max obs}} \) for relative theta power on the \( E_{\text{min obs}} \) for non-dominant hand tap-rate, and on the \( E_{\text{max obs}} \) for SRI-ALCOHOL EFFECTS score were performed individually to assess the significance of the relationship between the EEG changes and changes in PP and SRI. Since this was a crossover study, the regression was only performed for observations for treatment B (high dose-fast input).

Figure 3.27 shows the plot of \( E_{\text{max obs}} \) for relative theta power vs. the \( E_{\text{min obs}} \) for non-
Figure 3.27 Baseline-corrected $E_{max}$ for Relative theta power vs. baseline-corrected $E_{max}$ for Non-dominant hand tap-rate for Treatment B

Figure 3.28 Baseline-corrected $E_{max}$ for Relative theta power vs. baseline-corrected $E_{max}$ for SRI-ALCOHOL EFFECTS score for Treatment B
dominant hand tap-rate for treatment B. The coefficient of determination was 0.159 (n=6), which is not significant, but does indicate a trend toward a weak association between these two objective measures.

Figure 3.28 shows the plot of $E_{\text{max,obs}}$ for relative theta power vs. the $E_{\text{max,obs}}$ for SRI-Alcohol Effects score for treatment B. As figure 3.28 illustrates, there does not appear to be a consistent relationship between the two variables. Also, the coefficient of determination was 0.002 (n=6). This indicates that there does not appear to be an association between changes in EEG measures and changes in subjective impairment measures.

Thus, it appears from comparison of the regressions of EEG measures individually on psychometric performance measures and on subjective impairment measures, that, if anything, the EEG changes are more closely associated with PPT changes rather than with the subject-rated impairment measures. It should be noted, however, that neither of the associations were statistically significant, and that these comparisons were only performed for peak changes in these measures, and that the comparisons were only done for one treatment.

3.5 CONCLUSIONS

The following conclusions can be made from the oral ethanol study which was a pilot study designed to evaluate the effect of dose and dose-rate on the pharmacokinetics and pharmacodynamics of ethanol in six healthy male subjects. Table 3.19 lists the results
Table 3.19. Summary of Inferential Statistical Analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Treatment Effect</th>
<th>Multiple comparisons</th>
<th>Baseline as covariate</th>
<th>NR score as covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{\text{max}}$</td>
<td>NS $^1$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$K_m$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$V_d/F$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$k_a$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pharmacodynamic Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Power</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}} - E_0$</td>
<td>NS $^1$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rel. Theta Power</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}} - E_0$</td>
<td>p=0.041</td>
<td>$A \neq D, E \neq B,C,D$</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>NS $^1$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rel. Alpha Power</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}} - E_0$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>NS $^1$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Left hand Tap-rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_0 - E_{\text{min}}$</td>
<td>p=0.022</td>
<td>$A \neq B,D; C \neq B,D$; $E \neq B,D$</td>
<td>p=0.014</td>
<td>p=0.010</td>
</tr>
<tr>
<td>$t_{\text{min}}$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SRI-Drunk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}} - E_0$</td>
<td>p=0.002</td>
<td>$A \neq B,D; C \neq B,D$; $E \neq B,D$</td>
<td>NS</td>
<td>p=0.017</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>NS $^1$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SRI-Alcohol Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}} - E_0$</td>
<td>p=0.001</td>
<td>$A \neq B,D; C \neq B,D$; $E \neq B,D$</td>
<td>NS</td>
<td>p=0.039</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>NS $^1$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ORI-Drunk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}} - E_0$</td>
<td>p=0.000</td>
<td>$A \neq B,D; C \neq B,D$; $E \neq B,D$</td>
<td>NS</td>
<td>p=0.004</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>NS $^1$</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^1$: NS = not significant
of the inferential statistical analysis performed for the primary PK and PD measures evaluated in this study.

1) Ethanol, after oral administration, follows capacity-limited pharmacokinetics. The serum ethanol concentration vs. time profile was best described by a one-compartment model with zero-order input into the absorption compartment and first-order absorption into the central compartment, and capacity-limited elimination. The intrinsic PK parameters estimated for ethanol were $V_{\text{max}}$, $K_m$, $Vd/F$ and $k_a$. The mean ($\pm$ SD) $V_{\text{max}}$ was 226 ($\pm$ 92) mg/L/hr across subjects and treatments. The mean ($\pm$ SD) $K_m$ was 176 ($\pm$ 59) mg/L across subjects and treatments. The mean ($\pm$ SD) $Vd/F$ was 52 ($\pm$ 15) L across subjects and treatments. The mean ($\pm$ SD) $k_a$ was 3.8 ($\pm$ 2.4) hr$^{-1}$ across subjects and treatments. The intrinsic PK parameters were independent of dose and input-rate, but were associated with considerable inter-individual variability, especially $K_m$ and $k_a$. Inter-individual variability was higher than inter-individual variability for all the intrinsic PK parameters. The PK parameters estimated in this study are consistent with previously reported PK parameters for oral ethanol (Holford, 1987).

2) Ethanol induced changes in measures of psychometric impairment, mainly finger-tapping, although the high variability and small sample sizes resulted in statistically significant changes only at the high doses (treatments B and D) relative to the low doses (treatments A and C) and placebo (treatment E). The card-sorting test and the DSST did not show significant changes probably due to large variability and confounding with learning effects.
3) EEG measures also showed statistically significant differences only for the peak change in relative theta power at the high doses (treatments B and D) compared to the low doses (treatments A and C) and placebo (treatment E). The EEG measures also showed considerable variability, both at baseline as well as following ethanol administration.

4) Ethanol induced significant dose-related changes in measures of subjective impairment. The SRI and ORI scales proved to be the most sensitive measures of ethanol's effect. Some of the measures also showed input-rate-related changes following oral ethanol administration.

5) There was significant acute, exposure-related tolerance to the subjective impairment induced by ethanol. The tolerance development could be characterized by a PK-PD model incorporating tolerance as a compensatory feedback mechanism to the direct impairment effect of the drug. The model allowed the estimation of ethanol sensitivity with the model parameter S. Acute tolerance development was not observed for the psychometric performance measures or the EEG measures, indicating a temporal disparity between the perceived and performance impairment induced by ethanol.

6) Two of the 6 subjects in the study were classified as "non-responders" based on their lack of subjective response to ethanol administration, even though they demonstrated consistent psychometric impairment and EEG changes.

7) The EEG changes were not correlated to the psychometric impairment or to the subjective impairment induced by ethanol.
This study had some limitations, including that it was a pilot study in a small sample of six healthy male subjects. The considerable individual variability in response to ethanol administration would require larger sample sizes in future studies to result in statistically significant conclusions. Also, the poor performance of the psychometric tests in the study indicated that a battery of simpler psychometric tests, that had been validated to be sensitive to ethanol's effects should be used in future studies in order to obtain measures that were associated with less variability and greater sensitivity to ethanol. Lastly, the 2.5 fold difference in input-rate (20 minutes vs. 50 minutes) was not large enough, relative to the large variability in the physiological processes that govern oral absorption, such as gastric emptying, to observe any clear input-rate-related differences in ethanol pharmacokinetics or pharmacodynamics. Using a larger difference in input-rate may be one method of overcoming this limitation, however, a better method would be to administer the ethanol intravenously. Intravenous administration would allow more precise control over the input-rate and the achievement of accurate and precise target concentrations.
CHAPTER 4

INTRAVENOUS ETHANOL STUDY

4.1 SPECIFIC AIMS

The specific aims of this study were:

(1) To investigate the pharmacokinetics and pharmacodynamics of different individualized doses and dose rates of IV ethanol and the development of acute tolerance to ethanol in healthy male and female subjects.

(2) To assess changes in objective measures of impairment viz., EEG and psychometric performance, as well as subjective measures of impairment after IV ethanol administration.

(3) To examine the relationship between changes in the objective measures and subjective measures of impairment, and the relationship between these measures and serum ethanol concentrations.

(4) To examine gender differences with respect to ethanol pharmacokinetics and pharmacodynamics.

4.2 STUDY DESIGN

This study was a randomized, double-blind, placebo-controlled, five-period, four-way...
crossover, concentration-controlled study in sixteen (16) healthy volunteers (8 males and 8 females). The start of each study period was separated by a washout period of at least 1 week.

The study was conducted in two phases: After passing the medical screening, subjects underwent an open-labelled Pharmacokinetic Screen and Familiarization Period (Leg 0). This period was aimed at familiarizing subjects to the study procedures, including the EEG and the psychometric test battery, as well as to estimate their individual PK parameters. During this period, subjects received a 1-hour IV infusion of ethanol. Male subjects received 0.6 g/kg and female subjects received 0.5 g/kg ethanol as a 1-hour infusion. Female subjects received a lower dose since it was anticipated that they would achieve higher levels, and possibly greater adverse effects, if given the same dose as the male subjects. Blood samples were drawn during this period to determine serum ethanol concentrations. These concentrations were used to estimate their individual PK parameters, \( V_{\text{max}} \), \( K_m \) and \( V_{\text{dss}} \). These parameter estimates were then used to design an appropriate dosing regimen to achieve a target concentration of 1000 mg/L for the crossover phase of the study. A target concentration of 1000 mg/L would be expected to achieve an adequate degree of intoxication and impairment, without many adverse effects. Also, this concentration was considered to be the legal limit for intoxication in the state at the start of the study (the current legal limit for intoxication is 800 mg/L or 0.8%). After the PK screen and familiarization period, subjects were randomized to the crossover, concentration-controlled phase (Legs 1 through 4) of the study (figure 4.1).
Medical Screening

Pharmacokinetic Screen and Familiarization Period
Males: 0.6 g/kg IV Ethanol infused over 1 hour
Females: 0.5 g/kg IV Ethanol infused over 1 hour
Leg 0

Assessment of PK parameters
$V_{\text{max}}$, $K_m$, $V_d$
Dose Individualization

RANDOMIZATION
Four-way Crossover (Legs 1 - 4)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Infusion I</th>
<th>Infusion II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1 hour)</td>
<td>(5 hours)</td>
</tr>
<tr>
<td>A</td>
<td>ethanol</td>
<td>placebo</td>
</tr>
<tr>
<td>B</td>
<td>placebo</td>
<td>ethanol</td>
</tr>
<tr>
<td>C</td>
<td>ethanol</td>
<td>ethanol</td>
</tr>
<tr>
<td>D</td>
<td>placebo</td>
<td>placebo</td>
</tr>
</tbody>
</table>

Figure 4.1 Study Design Flow Chart
During the crossover phase of the study, each treatment consisted of two infusions, Infusion I which had a duration of 1 hour, followed by Infusion II, which lasted for 5 hours. Subjects received one of the following four treatments during each study period:

Treatment A: Infusion I - ethanol infused at a rate designed to achieve the target concentration of 1000 mg/L at the end of infusion I (1 hour); Infusion II - placebo.

Treatment B: Infusion I - placebo; Infusion II - ethanol infused at a rate designed to achieve the target concentration of 1000 mg/L at the end of infusion II (6 hours).

Treatment C: Infusion I - ethanol infused at a rate designed to achieve the target concentration of 1000 mg/L at the end of infusion I (1 hour); Infusion II - ethanol infused at a rate designed to maintain the target concentration at "steady-state" for the duration of Infusion II (5 hours).

Treatment D: Infusion I - placebo; Infusion II - placebo.

Figure 4.2 shows the desired concentration-time profiles for each of the active treatments.

Each subject was assigned to one of the four randomization sequences, based on a latin-square design, listed in table 4.1, by an unblinded pharmacist, and received each treatment exactly once. Sixteen subjects were scheduled to be enrolled into the study such that two male subjects and two female subjects were assigned to each randomization sequence.

4.3 EXPERIMENTAL METHODS
Figure 4.2 Expected concentration-time profiles for treatment A (Panel 1), treatment B (Panel 2), and treatment C (Panel 3) for crossover phase of intravenous ethanol study.
Table 4.1  Randomization sequences for intravenous ethanol study

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Leg 1</th>
<th>Leg 2</th>
<th>Leg 3</th>
<th>Leg 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>II</td>
<td>B</td>
<td>D</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>III</td>
<td>C</td>
<td>A</td>
<td>D</td>
<td>B</td>
</tr>
<tr>
<td>IV</td>
<td>D</td>
<td>C</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

Trt A: Infusion I: Ethanol  Infusion II: Saline
Trt B: Infusion I: Saline  Infusion II: Ethanol
Trt C: Infusion I: Ethanol  Infusion II: Ethanol
Trt D: Infusion I: Saline  Infusion II: Saline
Infusion I: 0 - 1 hr, Infusion II: 1 - 6 hrs.
4.3.1 SUBJECTS

Sixteen healthy volunteers, 8 male and 8 female, participated in the study. Subjects were considered for inclusion if they were healthy non-smokers between the ages of 21 and 35 years. In addition, all female subjects in the study were using oral contraceptives as their method of birth control.

All subjects were determined to be healthy based on the results of medical screening consisting of: (a) medical history, (b) physical examination, (c) vital signs (supine and standing systolic and diastolic blood pressure, heart rate and body temperature) as well as an orthostatic test, (d) 12-lead EKG including a 30 second rhythm strip, (e) laboratory screen consisting of SMAC-20, CBC and urinalysis, as well as a urine drug test and breath alcohol test. In addition, female subjects had to have a negative serum β-hCG test, indicating that they were not pregnant.

Subjects were excluded from the study if (a) they were smokers, (b) they had a clinically significant history of renal, hepatic, cardiovascular, gastro-intestinal, neurological, pulmonary, or hematologic disease, (c) they had a history of alcohol abuse, drug addiction, psychological dependence on drugs, or psychiatric illness, (d) they had first degree relatives (mother, father, or siblings) with a history of mental illness or alcohol/drug abuse, (e) they took any medications chronically or had taken any prescription medication or investigational drugs for at least 4 weeks before entering the study, except for the use of oral contraceptives by female subjects, (f) had an average daily caffeine intake greater than two cups of coffee, or (g) had an average alcohol intake
greater than 6 oz. (180 ml) of ethanol (approximately twelve 12 oz. beers) per week.

During screening, subjects completed an alcohol use questionnaire based on the Khavari Alcohol Test (Khavari and Farber, 1978). This questionnaire provided information about the frequency and quantity of consumption of the three major types of alcoholic beverages (beer, wine and spirits). Based on the responses provided, the Annual Absolute Alcohol Intake (AAAI) in gms/year was calculated as a quantitative measure of previous alcohol use for each subject.

Before enrolling in the study, each subject signed an informed consent form attesting that the study procedures were explained to him/her and that his/her participation in the study was voluntary.

Within one week after each subject completed the study, the physical examination and vital signs, laboratory tests, and EKG was repeated.

4.3.2 PROCEDURES FOR PK SCREEN AND FAMILIARIZATION PERIOD

The clinical study was conducted at the General Clinical Research Center (GCRC) unit at the Medical College of Virginia Hospitals, Medical College of Virginia-Virginia Commonwealth University. The Committee on the Conduct of Human Research at MCV-VCU reviewed and approved the study protocol, and the informed consent form (December 1993) prior to the start of the study. The protocol, including revisions, as well as the consent form are in Appendix H. The study was conducted from June 1994 through June 1995.
4.3.2A Admission to Clinical Research Unit

Subjects were admitted to the GCRC unit on the evening of the day prior to the day of ethanol administration and were discharged on the morning after the day of ethanol administration. Subjects were instructed that no medications except oral contraceptives (including OTC medications and vitamins), or caffeine were to be consumed for 72 hours before the study period and during the study period. Subjects also abstained from alcohol starting 72 hours before the first treatment period through the end of the study. All subjects had a negative urine drug screen and breath alcohol test on admission for the study period. In addition, all female subjects had a negative β-hCG test for pregnancy. All subjects completed a verbal probe concerning recent medical history as well as alcohol and medication use.

4.3.2B Drug preparation and administration

On the morning of dosing, subjects received a one-hour IV infusion of ethanol. A total dose of 0.6 g ethanol/kg body weight for male subjects and 0.5 g ethanol/kg body weight for female subjects was administered as a 10% solution in normal saline over 1 hour. The infusion was administered via an indwelling catheter that was inserted into a forearm vein in the dominant arm prior to dosing. Doses were prepared by the Investigational Pharmacy at MCV, and the treatment was open-labelled.

4.3.2C Blood Sampling
Prior to dosing, a heparin containing catheter was inserted into a forearm vein of the non-dominant arm for access to blood sampling.

6 ml blood samples for determination of ethanol concentration were collected in red-top tubes with no additives at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the infusion. The blood was allowed to clot, centrifuged (within 1 hour of sampling) for 10 minutes, serum harvested and stored at \(-20^{\circ}C\) until analysis by the TDx Analyzer (Abbott Laboratories, N. Chicago, IL).

4.3.2D Electroencephalography (EEG)

Five minute segments of 28-channel EEG, using the NeuroScan EEG equipment (NeuroScan Inc., Herndon, VA), were recorded for each subject with eyes closed at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the infusion. Subjects were asked to count back from 500 by threes in an attempt to maintain vigilance during the recordings. Omni-prep (D.O. Weaver and Co., Aurora, CO) was used to prepare the scalp prior to electrode placement and Electro-gel (Electro-Cap International Inc., Dallas, TX) was used as the conducting gel. The electrodes were placed using an Electro-cap (Electro-Cap International Inc., Dallas, TX) according to the 10/20 International System with 8 additional electrodes located 50% between the standard 10/20 placement. Linked ears were used as the reference. Four additional channels were used to monitor for vertical
and lateral eye movements and electromyographic activity. All electrodes were made of tin. The electrode impedances were checked before each recording, and maintained at less than 5 kohms and similar between electrodes. The raw EEG was stored on an optical disk until later analysis. Any disturbances in the room or subject movement during the EEG recording were documented. The NeuroScan filters were set as follows: Low filter - 0.1 Hz, High filter - 60 Hz. System calibration checks were performed biweekly throughout the study to ensure stability of channel calibration and proper filter settings.

4.3.2E Psychometric Performance Tests (PPT)

A battery of four psychometric tests from the CDR Microcomputerized Assessment System (Cognitive Drug Research Ltd, Reading, U.K.) was completed by each subject at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the infusion. The psychometric test battery consisted of an immediate word recall test, a number vigilance test, a tracking test and a word recognition test. The test battery was computerized and responses were recorded using a response module fitted with two buttons, one marked "YES" and the other "NO" (Wesnes et al., 1987). For the tracking test, subjects used a joy-stick to track the target. In the evening before dosing for Leg 0, subjects practiced the psychometric test battery twice.

4.3.2F Subject-Rated Impairment (SRI) Scales
A 100 mm visual analog scale, based on the Subjective High Assessment Scale (SHAS) (Shuckit, 1984), was completed by each subject at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the infusion. The scale was similar to the one used for the oral ethanol study and had 12 items: HIGH, DRUNK, CONFUSED, DROWSY, DIZZY, CLUMSY, FLOATING, SLURRED SPEECH, UNCOMFORTABLE, FEEL GREAT, FEEL TERRIBLE and ALCOHOL EFFECTS. Subjects indicated their perceived level of intoxication response for each item by placing a mark on an unnumbered 100 mm scale that ranged from "not at all" to "extremely".

4.3.2G Observer-Rated Impairment (ORI) Scales

A 100 mm visual analog scale was completed by a blinded investigator (VAR) for each subject at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the infusion. The scale was similar to the one used in the oral ethanol study and had 4 items: HIGH, DRUNK, CONFUSED and DROWSY. The blinded investigator indicated his perception of the subject's level of intoxication by placing a mark on an unnumbered 100 mm scale that ranged from "not at all" to "extremely".

4.3.2H Safety Measurements

Blood pressure (sitting) and heart rate were measured, using a Dynamap (Critikon Inc.,
Tampa, FL), at the following times: pre-dose and 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the infusion.

All subjects were observed for symptoms and signs of clinical intolerance to the drug or procedures and asked to report any adverse effects. These were evaluated by the Medical Monitor (IG) for their clinical significance and potential need for treatment.

4.3.2.1 Diet

On the evening prior to dosing, subjects received a light snack. Subjects fasted from midnight on the evening before ethanol administration until 4 hours after the start of the infusion. Water was permitted *ad libitum* throughout the study period. Dinner and a snack were served 9 and 14 hours after the start of the infusion respectively. Caffeine-free beverages were served with meals.

4.3.2.2 Discharge from Clinical Research Unit

Subjects were discharged on the morning of the day after ethanol administration. A breath alcohol (Alcosenser) test was done prior to discharge at the end of each treatment period to ensure that the subjects did not have detectable ethanol levels.

A study flow sheet is included (Table 4.2). When the study measurements were scheduled at the same time, they were conducted in the following sequence: 1) blood samples 2) EEG 3) PPT 4) SRI and ORI scales and 5) safety measurements, with the
Table 4.2  Study Period Flow Sheet for Leg 0 of intravenous ethanol study

<table>
<thead>
<tr>
<th>Time</th>
<th>SAC</th>
<th>EEG</th>
<th>PP</th>
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SAC: Serum Samples for Alcohol Determination, EEG: Electroencephalography, PP: Psychometric Performance Battery, SRI/ORI: Subject Rated Impairment & Observer Rated Impairment Scale, VS: Vital Signs (blood pressure, heart rate, temperature)
blood sample being collected at exactly the scheduled time.

4.3.3 DETERMINATION OF DOSING REGIMENS FOR ACHIEVING CONCENTRATION-CONTROL

I. Estimation of PK Parameters from PK Screen and Familiarization period.

The following subject-specific parameters were estimated from the individual serum concentration-time data from the PK screen and familiarization period (Leg 0):

- $V_{max}$: Maximum elimination rate
- $K_m$: Michaelis-Menten constant
- $V_{dss}$: Volume of distribution.

Initial estimates for the pharmacokinetic parameters were obtained from the slopes of the linear and semi-log concentration-time plots as follows:

$V_{max}$ was estimated from the slope (slopel) of the linear regression performed on the initial apparent linear declining phase of the concentration-time profiles as:

$$V_{max} = -slope1$$

$K_m$ was estimated from the slope of the linear regression (slope2) performed on the terminal apparent linear declining phase of the log concentration-time profiles as:

$$K_m = - \frac{V_{max}}{2.303 \cdot slope2}$$

$V_{dss}$ was calculated as:

$$V_{dss} = CL_{tot} \cdot MRT$$
where CL is the total clearance and MRT is the mean residence time calculated by non-compartmental methods (see section 4.3.5B for equations for calculation of CL and MRT).

A one-compartment model with zero-order input and capacity-limited elimination (figure 4.3) was used to fit the concentration-time data for each subject using Scientist (version 2.0 for Windows, MicroMath Inc., Salt Lake City, UT). The model equations were as follows:

\[
\frac{dC}{dt} = \frac{k_0}{V_{dss}} - \frac{(V_{max} \times C)}{(K_m + C)}
\]

during infusion:

\[
\frac{dC}{dt} = -\frac{(V_{max} \times C)}{(K_m + C)}
\]

where dC/dt is the rate of change of concentration (C) and k0 is the infusion rate in mg/hr.

Goodness of fit criteria included maximization of the coefficient of determination and Model Selection Criteria, minimization of the standard deviation of the parameter estimates, random scatter in the plots of residuals vs. independent variable, normal distribution of the residuals as well as visual inspection of observed and fitted curves (Scientist Manual, 1994).

The final estimates of the parameters, V_{max}, K_m, and V_{dss}, were used in the determination
Figure 4.3 One compartment body model for leg 0 for intravenous ethanol study
of an appropriate dosing regimen for that subject for the remaining four legs of the study.

II. Calculation of Doses for Legs 1 - 4.

During the crossover phase of the study (Legs 1 - 4), subjects received the following treatments according to the randomization sequences. Each treatment consisted of two infusions. Infusion I had a duration of 1 hour. Infusion II, which immediately followed Infusion I, had a duration of 5 hours:

<table>
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<tr>
<th>Treatment</th>
<th>Infusion I</th>
<th>Infusion II</th>
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<tbody>
<tr>
<td>A</td>
<td>Dose $I_A$</td>
<td>placebo</td>
</tr>
<tr>
<td>B</td>
<td>placebo</td>
<td>Dose $I_B$</td>
</tr>
<tr>
<td>C</td>
<td>Dose $I_C$</td>
<td>Dose $I_C$</td>
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<tr>
<td>D</td>
<td>placebo</td>
<td>placebo</td>
</tr>
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</table>

For treatment A, the dose for Infusion I (Dose $I_A$) was calculated from the subject’s individual parameters to achieve a target concentration ($C_{\text{target}}$) of 1000 mg/L ($\pm$ 10%) at the end of the infusion ($T_{\text{inft}}$ = 1 hour) as follows:

$$Dose_{I_A} = C_{\text{target}} \times Vd_{SS} + \frac{V_{\text{max}} \times C_{\text{target}}}{K_m + C_{\text{target}}} \times Vd_{SS} \times T_{\text{inft}}$$

For treatment B, the dose for Infusion II (Dose $I_B$) was calculated from the subject’s individual parameters to achieve a target concentration ($C_{\text{target}}$) of 1000 mg/L ($\pm$ 10%)
For treatment C, the dose for Infusion I (Dose \( I_C \), identical to Dose \( I_A \)) was calculated from the subject's individual parameters to achieve a target concentration \( (C_{\text{target}}) \) of 1000 mg/L (± 10%) at the end of the infusion \( (T_{\text{inf}}=1 \text{ hour}) \) as follows:

\[
Dose_{I_C} = C_{\text{target}} \times V_{d_{ss}} + \frac{V_{\text{max}} \times C_{\text{target}}}{K_m + C_{\text{target}}} \times V_{d_{ss}} \times T_{brfII}
\]

The dose for Infusion II (Dose \( II_C \)) was calculated to maintain concentrations at the target level (1000 mg/L ± 10%) over the next 5 hours \( (T_{\text{inf}}=5 \text{ hrs}) \) as follows:

\[
Dose_{II_C} = \frac{V_{\text{max}} \times C_{\text{target}}}{K_m + C_{\text{target}}} \times V_{d_{ss}} \times T_{brfII}
\]

The doses calculated using the above equations were adjusted based on simulated concentration vs. time profiles using calculated doses and estimated PK parameters. All parameter estimations and dose calculations were performed by the author and the final doses to be administered were provided to the Investigational Pharmacy, MCV-VCU. The pharmacist prepared and dispensed the appropriate solutions according to the randomization sequences.

4.3.4 PROCEDURES FOR RANDOMIZED, CROSSOVER STUDY
4.3.4A Admission to Clinical Research Unit

Subjects were admitted to the GCRC unit on the evening of the day prior to the day of ethanol or placebo administration and were discharged on the morning after the day of ethanol or placebo administration. Subjects were instructed that no medications except oral contraceptives (including OTC medications and vitamins), or caffeine were to be consumed for 72 hours before each study period and during each study period. Subjects also abstained from alcohol starting 72 hours before the first study period through the end of the study. All subjects had a negative urine drug screen and breath alcohol test on admission for each study period. In addition, all female subjects had a negative β-hCG test for pregnancy. All subjects completed a verbal probe concerning recent medical history as well as alcohol and medication use.

4.3.4B Drug preparation and administration

During each study period, subjects received one of the following treatments according to the sequence he/she was randomized to. Dosing consisted of two infusions: Infusion I was administered for 1 hour, followed by Infusion II which will be administered over the next 5 hours. The total dose of ethanol, which was individualized for each subject based on his/her pharmacokinetic parameters, was administered as a 10% solution in normal saline. Placebo doses consisted of normal saline. The infusions were administered via an indwelling catheter that was inserted into a forearm vein in the dominant arm prior to dosing.
Doses were prepared by an unblinded pharmacist at the Investigational Pharmacy, MCV-VCU, who assigned subjects to one of the four randomization sequences such that 2 male and 2 female subjects were randomized to each sequence. Each treatment was given exactly once and in random order according to the randomization sequence. Both the subjects and the investigators were blinded to treatment. A sealed copy of the randomization schedule was available at the research unit in case of an emergency.

4.3.4C Blood Sampling

Prior to dosing, a heparin containing catheter was inserted into a forearm vein in the non-dominant arm for access to blood sampling.

6 ml samples for determination of ethanol concentration were collected in red-top tubes with no additives at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The blood was allowed to clot, centrifuged (within 1 hour of sampling) for 10 minutes, serum harvested and stored at -20°C until analysis by the TDx Analyzer (Abbott Diagnostics, N. Chicago, IL).

4.3.4D Electroencephalography (EEG)

Five minute segments of 28-channel EEG, using the NeuroScan EEG equipment (NeuroScan Inc., Herndon, VA), were recorded for each subject with eyes closed at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3
hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The materials, equipment and methods used were the same as for Leg 0 (section 4.3.2D). The raw EEG was stored on an optical disk until later analysis.

4.3.4E Psychometric Performance Tests (PPT)

A battery of four psychometric tests from the CDR Microcomputerized Assessment System (Cognitive Drug Research Ltd, Reading, U.K.) was completed by each subject at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The psychometric test battery consisted of an immediate word recall test, a number vigilance test, a tracking test and a word recognition test, and was identical to the battery used in Leg 0. The equipment and methods used were the same as for Leg 0 (see section 4.3.2E).

4.3.4F Subject-Rated Impairment (SRI) Scales

A 100 mm visual analog scale, based on the Subjective High Assessment Scale (SHAS), was completed by each subject at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The SRI scale was identical to the scale used for Leg 0 (see section 4.3.2F), and subjects indicated their perceived level of intoxication response for each item by placing a mark on an unnumbered 100 mm
scale that ranged from "not at all" to "extremely".

4.3.4G Observer-Rated Impairment (ORI) Scales

A 100 mm visual analog scale was completed by a blinded investigator (VAR) for each subject at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The ORI scale was identical to the scale used for Leg 0 (see section 4.3.2G), and the blinded investigator indicated his perception of the subject's level of intoxication by placing a mark on an unnumbered 100 mm scale that ranged from "not at all" to "extremely".

4.3.4H Safety Measurements

Blood pressure (sitting) and heart rate were measured, using a Dynamap (Critikon Inc., Tampa, FL), at the following times: pre-dose and 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I.

All subjects were observed for symptoms and signs of clinical intolerance to the drug or procedures and asked to report any adverse effects. These were evaluated by the Medical Monitor (IG) for their clinical significance and potential need for treatment.

4.3.4I Diet

On the evening prior to dosing, subjects received a light snack. Subjects fasted from
midnight on the evening before ethanol administration until 4 hours after the start of Infusion I. Water was permitted *ad libitum* throughout the study period. Dinner and a snack were served 9 and 14 hours after the start of Infusion I respectively. Caffeine-free beverages were served with meals.

4.3.4J Discharge from Clinical Research Unit

Subjects were discharged on the morning of the day after ethanol or placebo administration. A breath alcohol (Alcosenser) test was done prior to discharge at the end of each treatment period to ensure that the subjects did not have detectable ethanol levels.

A study flow sheet is included (table 4.3). When the study measurements were scheduled at the same time, they were conducted in the following sequence: 1) blood samples 2) EEG 3) PPT 4) SRI and ORI scales and 5) safety measurements, with the blood sample being collected at exactly the scheduled time.

After each subject had completed the study, they were asked to assess which treatment they believed they had received during each period of the study.

4.3.5 SAMPLE ANALYSIS

4.3.5A Analytical Method for Ethanol in Serum

Analysis of serum samples for ethanol concentrations was performed in the Biopharmaceutical Analysis Laboratory at the Department of Pharmacy and
Table 4.3 Study Period Flow Sheet for Legs 1-4 of intravenous ethanol study

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SAC: Serum Samples for Alcohol Determination, EEG: Electroencephalography, PP: Psychometric Performance Battery, SRI/ORI: Subject Rated Impairment & Observer Rated Impairment Scale, VS: Vital Signs (blood pressure, heart rate, temperature), *: Skin temperature measured every 15 minutes during this period.
Pharmaceutics at MCV-VCU. Performance validation and sample analysis were conducted with the guidance of Clark March in the Biopharmaceutical Analysis Laboratory at the Department of Pharmacy and Pharmaceutics at MCV-VCU.

4.3.5B Assay Procedure

The analytical method used to measure ethanol concentrations in serum was fluorescence polarization immunoassay using the TDx Analyzer (Abbott Laboratories, Inc. North Chicago, IL). The assay method used was identical to the method used for the measurement of ethanol concentrations for the oral ethanol study. The assay principles and procedures, including materials and methods are described in section 3.3.3B.

4.3.5C Performance Characteristics and Validation for Ethanol assay

Performance characteristics and performance validation methods and results are described in section 3.3.3C and section 3.3.3D. Table 4.4 lists the figures of merit for the analytical method.

4.3.5D Analysis of subject samples

The TDx assay was used to determine ethanol concentrations in serum from sixteen subjects that completed the clinical study. There were a total of 20 samples per subject per period and four active treatment periods per subject (Leg 0 and treatments A, B and C). The total number of samples was about 1000. Calibration was performed prior to
Table 4.4  Figures of merit for TDx assay method for determination of serum ethanol concentrations

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<tbody>
<tr>
<td><strong>Experimental Limit of Quantitation (ELOQ)</strong></td>
<td>100 mg/L</td>
</tr>
<tr>
<td><strong>Valid Concentration Range</strong></td>
<td>100 to 3000 mg/L</td>
</tr>
<tr>
<td><strong>Precision (%RSD)</strong></td>
<td>Control X (100 mg/L): 19%</td>
</tr>
<tr>
<td></td>
<td>Control L (500 mg/L): 9%</td>
</tr>
<tr>
<td></td>
<td>Control M (1000 mg/L): 7%</td>
</tr>
<tr>
<td></td>
<td>Control H (2500 mg/L): 4%</td>
</tr>
<tr>
<td><strong>Accuracy (%DFN)</strong></td>
<td>Control X (10 mg/dL): 15%</td>
</tr>
<tr>
<td></td>
<td>Control L (50 mg/dL): 11%</td>
</tr>
<tr>
<td></td>
<td>Control M (100 mg/dL): 1%</td>
</tr>
<tr>
<td></td>
<td>Control H (250 mg/dL): 3%</td>
</tr>
</tbody>
</table>
performance validation. All four controls (X, L, M and H, where X = 100 mg/L, L = 500 mg/L, M = 1000 mg/L, and H = 2500 mg/L) were run at the start of subject sample analysis to ensure that the calibration curve was stable and valid. The samples for a single study period for each subject were split and ten samples were run on each carousel along with 2 of the controls (X, L, M and H). This analytical method for the determination of ethanol concentrations in serum was simple, specific, adequately sensitive, precise and accurate within acceptable limits for the purposes of this study.

4.3.6 PHARMACOKINETIC ANALYSIS

4.3.6A Evaluation of concentration-control

In order to evaluate the ability of the dose calculation algorithm used for achieving the desired concentrations for the crossover phase of the study and to assess whether adequate concentration-control had been achieved, the maximum concentrations (C_{max}) achieved were determined for each treatment and compared to the target maximum concentration, C_{target}.

For treatment C, the average "steady-state" concentration (C_{avg,ss}) was calculated as the average of all concentrations measured during Infusion II (1 hr through 6 hr time-points) for each subject (C_{ss(1-6)}).

The percent coefficient of variation (%COV) of these steady-state concentrations (COV_{C_{avg}}) was calculated to assess the degree of fluctuation of the "steady-state"
concentrations about the $C_{avg}$ as:

$$COV_{avg} = \frac{S.D. \ of \ C_{avg}}{C_{avg}} \times 100$$

Also, the percent difference from target (%DFT) was calculated to assess the magnitude of the error in achieving the average target concentration as:

$$%DFT = \frac{C_{avg} - C_{target}}{C_{target}} \times 100$$

The COV$_{avg}$ is a measure of the precision of the achieved concentrations, while the %DFT is a measure of the accuracy of the achieved concentrations relative to the target concentration.

4.3.6B Noncompartmental Methods

Serum ethanol concentration vs. time profiles were constructed for each subject and treatment on both linear and semi-logarithmic scales. The following PK parameters were estimated from the concentration-time data for each subject and treatment by non-compartmental methods: maximum concentration ($C_{max}$), time to achieve maximum concentration ($T_{max}$), area under the concentration-time curve extrapolated to infinity ($AUC_{\infty}$), total body clearance ($CL_{tot}$), volume of distribution ($V_{ss}$), maximum elimination rate ($V_{max}$) and Michaelis-Menten constant ($K_m$). $C_{max}$ was estimated as the maximum observed serum concentration and $T_{max}$ as the time (relative to dosing) that $C_{max}$ occurred.
AUC∞ was calculated as:

\[ AUC_\infty = AUC_{\text{trp}} + \frac{C_n}{\lambda} \]

where \( AUC_{\text{trp}} \) is the AUC from 0 to the time \( t_n \) of the last measured concentration \( (C_n) \) calculated by the trapezoidal rule and \( C_n/\lambda \) is the AUC extrapolated from \( t_n \) to infinity \( (AUC_{\text{extrp}}) \) (Gibaldi and Perrier, 1982). \( \lambda \) was estimated as \( V_{\text{max}}/K_m \).

\( CL_{\text{tot}} \) was calculated as:

\[ CL_{\text{tot}} = \frac{D}{AUC_\infty} \]

where \( D \) is the total administered dose.

\( Vd_{ss} \) was calculated as:

\[ Vd_{ss} = CL_{\text{tot}} \times MRT \]

where MRT is the mean residence time calculated as:

\[ MRT = \frac{AUMC_\infty}{AUC_\infty} - \frac{T}{2} \]

where \( T \) is the duration of the infusion (1 hr for treatment A, 5 hours for treatment B and 6 hours for treatment C) and \( AUMC_\infty \) is the area under the moment curve extrapolated to infinity, calculated by determining the area under the moment curve \( (AUMC) \) from 0 to the time \( t_n \) of the last measured concentration \( (C_n) \) by the trapezoidal rule by summing individual areas calculated by
\[
AUMC = \frac{(C_1 \cdot t_1 + C_2 \cdot t_2) \cdot (t_2 - t_1)}{2}
\]

and then extrapolating to infinity as follows:

\[
AUMC_\infty = AUMC_{\text{imp}} + \frac{C_{\text{a}} \cdot t_{\text{a}}}{\lambda} + \frac{C_{\text{d}}}{\lambda^2}
\]

(Gibaldi and Perrier, 1982). The infusion duration for treatment C was taken to be 6 hours, although treatment C consisted of two infusions administered at different rates for different durations (1 hour and 6 hours).

\( V_{\text{max}} \) was estimated from the slope (slope1) of the linear regression performed on the initial apparent linear declining phase of the concentration-time profiles as:

\[
V_{\text{max}} = - \text{slope1}
\]

\( K_{\text{m}} \) was estimated from the slope of the linear regression performed on the terminal apparent linear declining phase of the log concentration-time profiles as:

\[
K_{\text{m}} = - \frac{V_{\text{max}}}{2.303 \cdot \text{slope2}}
\]

Descriptive statistics, including mean, standard deviation, coefficient of variation (\%COV), median and range were calculated for each parameter by treatment and subject as well as across treatments.

4.3.6C Compartmental Methods

Compartmental analysis was performed for individual serum concentration-time data to
estimate the intrinsic pharmacokinetic parameters, maximum elimination rate \( (V_{\text{max}}) \), Michaelis-Menten constant \( (K_m) \) and volume of distribution \( (V_{\text{dss}}) \). Model fitting was performed using Scientist (version 2.0 for Windows, MicroMath Inc., Salt Lake City, UT). Several models were evaluated, such as one and two-compartment body models with multiple zero-order inputs, and incorporating capacity-limited elimination with and without a parallel first-order elimination pathway. Weighing schemes of 1 and \( 1/y \) were evaluated. Non-compartmental PK parameter estimates were used as initial estimates for \( V_{\text{max}}, K_m \) and \( V_{\text{dss}} \). The best model was selected based on several goodness of fit criteria: maximization of the coefficient of determination and Model Selection Criteria, minimization of the standard deviation of the parameter estimates, random scatter in the plots of residuals vs. independent variable, normal distribution of the residuals as well as visual inspection of observed and fitted curves (Scientist Manual, 1994).

Initial attempts at model fitting were aimed at fitting a one-compartment model to the individual concentration-time data using the same model as that used for the Leg 0 data. However, most of the profiles showed a significant distribution phase at the end of the infusion that was better fit using a two-compartment model. Thus, the final model selected was a two-compartmental body model with zero-order input into the central compartment, first-order distribution to and re-distribution from the peripheral compartment, with capacity-limited elimination (figure 4.4). The best fits were obtained with a weight of 1. Descriptive statistics, including mean, standard deviation, %COV, median and range were calculated for each parameter by treatment and subject as well
Figure 4.4 Two compartment body model for crossover phase of intravenous ethanol study
4.3.7 PHARMACODYNAMIC ANALYSIS

4.3.7A EEG Analysis

EEG recordings were stored on optical disks and analyzed off-line. Each of the 5-minute recordings was reviewed and edited to remove each 2.5 second epoch that was contaminated with artifacts (eye movement, muscle movement, electrode artifacts, or other disturbances noted during the recording). The remaining artifact-free epochs were averaged to form an average file for each recording using the statistics program of the NeuroScan software (version 3.0, Neuroscan Inc., Herndon, VA). The file containing the average power and relative power in each of the five classical frequency bands (delta: 0.39 - 3.0 Hz; theta: 4.3 - 7.8 Hz; alpha: 8.2 - 11.7 Hz; beta I: 12.1 - 16.0 Hz; and beta II: 16.4 - 30 Hz) at each of the 28 electrodes was imported into a spreadsheet program (Microsoft Excel version 5.0, Microsoft Inc., Seattle WA) for further processing.

From each average recording, the following PD measures were obtained: total power across all electrodes and across all frequency bands, total power across all electrodes within each frequency band and relative power across all electrodes within each frequency band.

Power was determined for each average recording by squaring the amplitude of the EEG signal at each electrode in each frequency band. Total power in each frequency band was
calculated by summing the power across all electrodes for the given frequency band. Total power across all frequency bands was calculated by summing the total power across all five frequency bands. Relative power in each frequency band was calculated by dividing the total power of the frequency band by the total power across all 5 frequency bands.

4.3.7B Psychometric Performance Tests Analysis

For each of the psychometric tests, the following measures were obtained:

1. Immediate word recall: Accuracy (% words correctly recalled)
2. Number vigilance: Accuracy (% correct) and Reaction time (msec)
3. Tracking: Mean tracking error or mean distance between cursor and target during the test (cm)
4. Word recognition: Sensitivity (a measure of accuracy of word recognition) and reaction time (msec).

4.3.7C Impairment Scales Analysis

For the SRI and ORI scales, a score between 0 and 100 was obtained for each item, by measuring the number of millimeters between the left end of the scale and the mark placed by the subject at each time point. Since two of the eight male subjects and four of the female subjects in the study were "non-responders" and did not show consistent responses on the SRI scales (maximal observed response less than 20 mm) even though
they showed consistent psychometric impairment and EEG changes, subjects were given a "non-responder" score (NR) of 0 if they were non-responders or 1 if they were responders.

4.3.7D Pharmacodynamic Analysis

Response-time profiles, i.e., plots of change in response measure from pre-dose baseline vs. time plots, for each subject during each treatment period were plotted for each response measure. The PD response measures evaluated were:

**EEG measures:** total power across all bands, total power in each of the 5 frequency bands (delta, theta, alpha, beta I, beta II), relative power in each of the 5 frequency bands (delta, theta, alpha, beta I, beta II);

**PP measures:** accuracy for immediate word recall, accuracy and reaction time for number vigilance, mean tracking error for tracking and sensitivity and reaction time for word recognition;

**Impairment Scales:** scores for each of the 12 items on the SRI scales and 4 items of the ORI scales.

Pharmacodynamic parameters including baseline response ($E_o$), maximal or minimal observed response ($E_{max}^{obs}$ or $E_{min}^{obs}$) and time of maximal or minimal observed response ($t_{max}$ or $t_{min}$) were determined for each PD measure. The baseline response ($E_o$) was defined as the response prior to drug administration at 0 hour. $E_{max}^{obs}$ was determined as the highest response observed during the first 12 hours after the start of Infusion I (first
6 hours for treatment A) and $E_{\text{min}}$ was determined as the lowest response observed during the first 12 hours after the start of Infusion I (first 6 hours for treatment A). The $E_{\text{max}}$ and $E_{\text{min}}$ were determined from data obtained only during the first 12 hours after the start of Infusion I (first 6 hours for treatment A) because the responses were expected to be the greatest during this period.

Descriptive statistics, including mean, standard deviation, %COV, median and range were calculated for each parameter by treatment and subject as well as across treatments. In addition, response vs. concentration profiles were plotted for each response measure for each subject at each treatment, to evaluate the effect-concentration relationship as well as the development of acute tolerance to the effects. The presence of a clockwise hysteresis loop in the response-time profiles would be consistent with development of acute tolerance for that response.

4.3.8 STATISTICAL ANALYSIS

Statistical analysis was performed 1) to evaluate the input-rate related changes in the pharmacokinetic and pharmacodynamic end-points, EEG, psychometric performance and subjective impairment following administration of fast, slow and "steady-state" infusions of ethanol in healthy male and female subjects, as well as to evaluate the development of tolerance to these objective and subjective measures; 2) to evaluate gender differences in ethanol pharmacokinetics and pharmacodynamics and 3) to determine the relationship between the EEG changes after IV ethanol administration and changes in psychometric
performance and subjective measures of impairment

Because there are many variables of interest in this statistical analysis, the multiplicity of desired inferential statements about the data become problematic. Adjusting the level of significance ($\alpha$) for the multiple statistical comparisons, as made in traditional confirmatory analysis, would result in extremely small $\alpha$ values and virtually no likelihood of detecting any statistically significant differences. Therefore, using the concept of descriptive data analysis, as described in section 3.3.6 for the oral ethanol study, expected differences between treatments based on previously reported studies and patterns apparent from examining the data were evaluated statistically without adjusting the level of significance (Abt, 1987; Abt, 1990). The results of these analyses were used to make descriptive inferential statements about the data, but not to reject the null hypothesis. Hypotheses generated by this study would have to be confirmed by prospective studies involving a larger number of subjects.

Primary pharmacokinetic parameters that were evaluated using descriptive data analysis included volume of distribution ($V_{\text{dss}}$), maximum elimination rate ($V_{\text{m,u}}$) and Michaelis-Menten constant ($K_m$). Primary pharmacodynamic measures that were evaluated included peak changes in relative EEG power in the theta and alpha bands, peak changes in reaction time for the number vigilance test, peak changes in the sensitivity measure of the word recognition test, peak changes in the items, "DRUNK", and "ALCOHOL EFFECTS" on the SRI scales, and peak changes in the item "DRUNK" on the ORI scales. Statistical comparisons for the other PD end-points (including changes in total
power, changes in relative EEG power in the delta, and beta bands, changes in accuracy measures of the immediate word recall and number vigilance tests, changes in mean tracking error of the tracking test, changes in reaction time for the word recognition test, changes in the item "HIGH" on the SRI as well as ORI scales) were treated as exploratory data analysis. These were used to generate hypothesis rather than to make formal conclusions based on the data.

The significance of the baseline (EJ as a covariate was examined to evaluate the relationship between the baseline of the response and the PD response. The NR score was used as a covariate in the statistical comparison of PD measures to evaluate its effect on the PD response. The AAAI measure of previous alcohol use was also used as a covariate to evaluate the effect of previous alcohol history on the PD responses measured in this study.

To evaluate the treatment effects on the PK and PD measures, the PK parameters and summary PD parameters (E_{max}^{obs} or E_{min}^{obs}, T_{max} or T_{min}) for the primary PD measures for each treatment were compared across treatments and across gender using statistical techniques appropriate for a 4-way crossover design. The model used to fit the data was of the form:

\[ Y_{ijklm} = \mu + \delta_i + \tau_j + \delta_{k(0)} + \alpha_l + \beta_m + \epsilon_{ijklm} \]

\[ i = 1,II,III,IV \text{ (sequences)}; \]
\[ j = 1,2,3,4 \text{ (periods)}; \]
\[ k = 1,2,\ldots,16 \text{ (subjects)}; \]
\[ l = A, B, C, D \text{ (treatments)} \text{ (only active treatments A, B, C for PK parameters)}; \]
\[ m = \text{male, female (gender)}; \]

where \( Y_{ijklm} \) is the response for the \( k \)th subject of the \( m \)th gender in the \( i \)th sequence in the \( j \)th period after the \( l \)th treatment, \( \mu \) is the overall mean, \( \delta_i \) is the effect of the \( i \)th sequence, \( \pi_j \) is the effect of the \( j \)th period, \( \xi_{ikj} \) is the effect of the \( k \)th subject within the \( i \)th sequence, \( \alpha_l \) is the effect of the \( l \)th treatment, \( \beta_m \) is the effect of the \( m \)th gender and \( \epsilon_{ijklm} \) is the random error associated with \( Y_{ijkl} \). The \( \epsilon_{ijklm} \) are assumed to be normally distributed random variables with mean of 0 and variance \( \sigma^2 \). It is also assumed that the nested effects for subject are randomly and independently distributed with a mean of 0 and common variance of \( \sigma^2 \), and independent of \( \epsilon_{ijklm} \).

Model fitting was performed using PROC MIXED in SAS (SAS Institute, Cary, NC). This procedure allows the modelling of the mean of the dependent variable, \( y \), as well as the variance of \( y \). The estimation method used for the covariance parameters was restricted maximum likelihood (REML). The variance of \( y \) was modelled by evaluating two variance structure matrices, simple (random effect) and autoregressive. For most variables, the simple structure resulted in better model fits based on maximization of the Akaike's Information Criterion (SAS/STAT User’s Guide, 1990, SAS Technical Report, 1992). The level of significance (\( \alpha \)) was set at 0.05. In case of significant differences (\( p < 0.05 \)), multiple comparisons were performed using the ESTIMATE procedure in SAS (SAS/STAT User’s Guide, 1990).
Residuals were tested for normality using PROC UNIVARIATE in SAS (SAS/STAT User's Guide, 1990). This procedure generates box plots and normal probability plots, which were examined to test for normality of the residuals. This procedure also computes the Shapiro-Wilk statistic, W, for the null hypothesis that the residuals are normally distributed. The null hypothesis of normality was rejected if the probability of a smaller value of W was less than 0.05.

One of the aims of this study was to assess the relationship between the EEG changes and changes in PP as well as the relationship between the EEG changes and SRI. In order to achieve this, linear regression of the EEG parameters (E_{max}^{obs} for relative theta power) on the PP parameters (E_{max}^{obs} for number vigilance reaction time), and on the SRI parameters (E_{max}^{obs} for SRI-ALCOHOL EFFECTS score) were performed individually to assess the significance of the relationship between the EEG changes and changes in PP and SRI. Since this was a crossover study, the regression was only performed for observations for treatment A. The level of significance (\( \alpha \)) was set at 0.05. This test allowed us to determine if the EEG changes were more closely associated with PP changes or with the changes in subject-rated impairment.

4.4 RESULTS AND DISCUSSION

4.4.1 CLINICAL RESULTS
4.4.1A  Subject Demographics

Sixteen subjects, eight males and eight females, were entered into the study after successfully passing the medical screening, and all sixteen subjects completed all five periods of the study. Demographic and physical characteristics of the subjects are shown in table 4.5. The subjects were between 22 and 33 years of age. The weights of male subjects ranged from 60 to 84 kg with an mean of 74 kg. The weight of female subjects ranged from 50 to 85 kg with an mean of 64 kg.

Table 4.5 also lists the Annual Absolute Alcohol Intake (AAAI) in gms/year for each subject. The median AAAI for male subjects was 236 gms/year and for female subjects was 232 gms/year. There was, however, considerable variability with AAAI values ranging from 32 gms/year to 1288 gms/year across subjects.

4.4.1B  Adverse Events

In general, all subjects tolerated the study drug and procedures reasonably well. Table 4.6 lists the adverse events experienced by the subjects by treatment. The most common adverse event that was associated with ethanol was the intermittent local stinging and pain at the site of the infusion, which was generally transient and usually resolved by the end of the first hour of the infusion. Other adverse events associated with ethanol administration were nausea, vomiting, dizziness and headache. The dizziness and nausea generally occurred at about the same time as the occurrence of the peak concentrations, while the headache generally had a later onset. All adverse events were resolved by the
Table 4.5  Demographic and physical characteristics of subjects in intravenous ethanol study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age [yrs]</th>
<th>Weight [kg]</th>
<th>Height [cm]</th>
<th>Race</th>
<th>Alcohol consumption AAAI [gms/year]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>27</td>
<td>77.8</td>
<td>181</td>
<td>Caucasian</td>
<td>496</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>25</td>
<td>74.4</td>
<td>188</td>
<td>Caucasian</td>
<td>206</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>24</td>
<td>68.4</td>
<td>185</td>
<td>Caucasian</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>32</td>
<td>70.5</td>
<td>178</td>
<td>Caucasian</td>
<td>343</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>27</td>
<td>60.2</td>
<td>177</td>
<td>Caucasian</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>30</td>
<td>74.5</td>
<td>169</td>
<td>Asian</td>
<td>125</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>33</td>
<td>81.2</td>
<td>174</td>
<td>Caucasian</td>
<td>266</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>22</td>
<td>83.7</td>
<td>183</td>
<td>Caucasian</td>
<td>1288</td>
</tr>
</tbody>
</table>

Mean COV % | 14% | 10% | 3% | 113% | 36-1288 |

Range       | 22-32 | 60.2-83.7 | 169-188 | 36-1288 |

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age [yrs]</th>
<th>Weight [kg]</th>
<th>Height [cm]</th>
<th>Race</th>
<th>Alcohol consumption AAAI [gms/year]</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Female</td>
<td>26</td>
<td>60.9</td>
<td>158</td>
<td>Caucasian</td>
<td>339</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>22</td>
<td>61.5</td>
<td>170</td>
<td>Indian-American</td>
<td>330</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>31</td>
<td>49.4</td>
<td>165</td>
<td>Caucasian</td>
<td>239</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>32</td>
<td>84.6</td>
<td>172</td>
<td>Caucasian</td>
<td>179</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>23</td>
<td>69.3</td>
<td>170</td>
<td>Caucasian</td>
<td>516</td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>23</td>
<td>58.2</td>
<td>160</td>
<td>Caucasian</td>
<td>53</td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>23</td>
<td>54.3</td>
<td>159</td>
<td>Hispanic</td>
<td>224</td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>30</td>
<td>70.9</td>
<td>175</td>
<td>African-American</td>
<td>32</td>
</tr>
</tbody>
</table>

Mean COV % | 16% | 17% | 4% | 66% | 32-516 |

Range       | 22-31 | 54.3-84.6 | 159-175 | 32-516 |
Table 4.5a. Responder/Non-Responder Score for subjects in IV ethanol study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Responder (R)/Non-Responder (NR) Status</th>
<th>NR Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>R</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>R</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 4.6  Adverse events by treatment for intravenous ethanol study

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of subjects (out of 16) reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Leg 0</td>
</tr>
<tr>
<td>intermittent stinging at infusion site</td>
<td>10</td>
</tr>
<tr>
<td>Ethanol-like taste on tongue</td>
<td>8</td>
</tr>
<tr>
<td>nausea (with vomiting)</td>
<td>2</td>
</tr>
<tr>
<td>dizziness/ lightheadedness</td>
<td>1</td>
</tr>
<tr>
<td>headache</td>
<td>3</td>
</tr>
<tr>
<td>sedation</td>
<td>0</td>
</tr>
</tbody>
</table>
4.4.2 PHARMACOKINETICS

4.4.2A Evaluation of concentration-control

Serum ethanol concentration vs. time profiles for Leg 0 for each treatment and subject are shown in Appendix I1. Figure 4.5 shows the serum ethanol concentration vs. time for all subjects by gender for Leg 0. Table 4.7 lists the PK parameters obtained from the data from Leg 0. The mean ± S.D. C\textsubscript{max} for male subjects was 924 ± 175 mg/L and for female subjects was 821 ± 166 mg/L. Dose-corrected C\textsubscript{max} values were higher for female subjects than for male subjects (1641 ± 331 mg/L/(mg/kg) for female subjects and 1539 ± 291 mg/L/(mg/kg) for male subjects).

Intrinsic PK parameters V\textsubscript{max}, K\textsubscript{m} and V\textsubscript{dss} were estimated by fitting a one-compartment model with zero-order input and capacity-limited elimination to the individual concentration-time profiles. The fits were considered to be adequate based on the coefficient of determinations and Model Selection Criteria; random scatter in the plots of residuals vs. independent variable; normal distribution of the residuals as well as visual inspection of observed and fitted curves.

As table 4.7 indicates, the intrinsic PK elimination parameters, V\textsubscript{max} and K\textsubscript{m}, did not appear to be different between male and female subjects. The mean ± S.D. V\textsubscript{max} across all sixteen subjects was 245 ± 49 mg/L/hr and the mean ± S.D. K\textsubscript{m} across all sixteen
Figure 4.5a  Serum Ethanol Concentration-time profiles for Leg 0 for male subjects

Figure 4.5b  Serum Ethanol Concentration-time profiles for Leg 0 for female subjects
Table 4.7  Mean (%COV) Pharmacokinetic parameters by gender for Leg 0 for intravenous ethanol study

<table>
<thead>
<tr>
<th></th>
<th>Dose [g/kg]</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; [mg/L]</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; [mg/L/(g/kg)]&lt;sup&gt;1&lt;/sup&gt;</th>
<th>V&lt;sub&gt;max&lt;/sub&gt; [mg/L/hr]</th>
<th>K&lt;sub&gt;m&lt;/sub&gt; [mg/L]</th>
<th>V&lt;sub&gt;d&lt;/sub&gt; [L/kg]&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0.6</td>
<td>924 (19%)</td>
<td>1539 (19%)</td>
<td>241 (27%)</td>
<td>163 (41%)</td>
<td>47 (16%)</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>0.5</td>
<td>821 (20%)</td>
<td>1641 (20%)</td>
<td>250 (13%)</td>
<td>164 (37%)</td>
<td>35 (18%)</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1: Dose-corrected C<sub>max</sub>  
2: body-weight corrected V<sub>d</sub>
subjects was 164 ± 62 mg/L. The mean ± S.D. Vdss for male subjects was 47 ± 8 L and for female subjects was 35 ± 6 L. However, when the Vdss was corrected for weight, the mean estimates for male and female subjects did not appear to be different. This indicates that the apparent gender difference in volumes of distribution is due to the differences in weight between males and females. The differences in Vdss also explains the significant difference in dose-corrected Cmax between male and female subjects.

Table 4.8 lists the mean ± SD of the doses calculated from the estimated PK parameters for the crossover phase of the study by treatment. There were no differences between the calculated doses (in g/kg) between male and female subjects. The mean (± S.D.) calculated doses were 0.71 (± 0.10) g/kg for treatment A, 1.13 (± 0.13) g/kg for treatment B and 1.31 (± 0.14) g/kg for treatment C. The variability in the calculated doses was also fairly low, with %COV ranging from 11% to 14% across treatments. This indicates that the subjects in this study were fairly similar with respect to their ethanol pharmacokinetics, and that differences in body weight accounted for most of the differences in PK parameters observed in these subjects.

Table 4.8 also lists the doses that would have been predicted for treatments A, B and C using previously published PK parameter estimates for ethanol (Holford, 1987). Comparison of the calculated doses for the subjects in this study with these population-predicted doses indicated that on average, the doses in g/kg were similar, within 10% of each other. This was observed across treatments and indicates that the subjects in this study had pharmacokinetic characteristics for ethanol that were fairly representative of
Table 4.8  

Doses calculated from Leg 0 PK parameters for crossover phase of intravenous ethanol study.

<table>
<thead>
<tr>
<th></th>
<th>Trt A [g/kg]</th>
<th>Trt B [g/kg]</th>
<th>Trt C [g/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n=8)</td>
<td>0.75 (12%)</td>
<td>1.20 (8%)</td>
<td>1.38 (8%)</td>
</tr>
<tr>
<td>Females (n=8)</td>
<td>0.66 (13%)</td>
<td>1.06 (12%)</td>
<td>1.25 (11%)</td>
</tr>
<tr>
<td>All (n=16)</td>
<td>0.71 (14%)</td>
<td>1.13 (11%)</td>
<td>1.31 (11%)</td>
</tr>
<tr>
<td>Population¹</td>
<td>0.65</td>
<td>1.10</td>
<td>1.22</td>
</tr>
</tbody>
</table>

¹: Doses predicted for treatments A, B and C based on previously published parameter estimates ($V_{max}=232$ mg/L/hr, $K_m=82.1$ mg/L, $V_d=0.53$ L/kg)
the population (Holford, 1987). However, the PK screen and familiarization period was necessary to incorporate the considerable inter-individual variability in the PK parameters in the calculation of doses. If all the subjects had been given fixed doses, and even if they had been dosed on the basis of their body weight, the resulting variability in achieved concentrations could have been as high as 20%, as seen for the C_{max} values for Leg 0. Thus, the PK screen and familiarization period was essential to the study design, which was to achieve concentration-control, i.e., to achieve and maintain concentrations within about 10% of the target concentrations.

Serum ethanol concentration vs. time profiles for each subject, by treatment, for the crossover phase of the study are shown in Appendix 12. Figure 4.6 shows the serum ethanol concentration vs. time for all subjects by treatment.

Table 4.9 lists the actual C_{max} values achieved for treatments A and B, by gender. As Table 4.9 indicates, the mean ± S.D. C_{max} for treatment A was 1119 ± 175 mg/L and for treatment B was 1029 ± 168 mg/L. The achieved peak concentrations were, on average about 12% higher than the target concentration of 1000 mg/L for treatment A and about 3% higher than the target concentration for treatment B.

There were no significant differences in C_{max} values between male and female subjects, even though the mean C_{max} values for male subjects for treatment A was higher than for female subjects (1182 mg/L for male subjects vs. 1056 mg/L for female subjects). This apparent difference may be due to subject 8, who was identified as a pharmacokinetic outlier, showing the highest achieved concentrations across treatments. He also appeared
Figure 4.6a  Serum Ethanol Concentration-time profiles for treatment A for male subjects

Figure 4.6b  Serum Ethanol Concentration-time profiles for treatment A for female subjects
Figure 4.6c  Serum Ethanol Concentration-time profiles for treatment B for male subjects

Figure 4.6d  Serum Ethanol Concentration-time profiles for treatment B for female subjects
Figure 4.6e  Serum Ethanol Concentration-time profiles for treatment C for male subjects

Figure 4.6f  Serum Ethanol Concentration-time profiles for treatment C for female subjects
Table 4.9  Mean (COV%) $C_{\text{max}}$ achieved for crossover phase of intravenous ethanol study.

<table>
<thead>
<tr>
<th></th>
<th>Trt A [mg/L]</th>
<th>Trt B [mg/L]</th>
<th>Trt C [mg/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n=8)</td>
<td>1182 (16%)</td>
<td>1048 (16%)</td>
<td>1286 (16%)</td>
</tr>
<tr>
<td>Females (n=8)</td>
<td>1056 (14%)</td>
<td>1011 (18%)</td>
<td>1253 (12%)</td>
</tr>
<tr>
<td>All (n=16)</td>
<td>1119 (16%)</td>
<td>1029 (16%)</td>
<td>1269 (14%)</td>
</tr>
</tbody>
</table>
to have a much slower elimination rate for ethanol than the other subjects. PK analysis indicated that his $V_{\text{max}}$ estimated from Leg 0 data was quite different from the estimate obtained from compartmental analysis of concentration-time data from the crossover phase of the study. It appears that his PK parameters may not have been accurately estimated during Leg 0, resulting in peak concentrations that were as much as 40% higher than the target concentration.

Table 4.10 lists the measures of precision and accuracy for achieved concentrations for treatment C. The mean $\pm$ S.D. $C_{\text{avg}}$ achieved was $1070 \pm 144$ mg/L, which was almost identical for male and female subjects. The mean %DFT was 7% indicating that, on average, the steady-state concentrations were 7% higher than the target steady-state concentration of 1000 mg/L. However, the range for the %DFT was quite high, with values ranging from -14% to 38%, indicating that there were some subjects whose $C_{\text{avg}}$ was not within the desired range of target steady-state concentrations (1000 mg/L $\pm$ 10%). The mean $\text{COV}_{\text{avg}}$ was 9% across subjects, indicating that, on average, the concentrations at steady-state fluctuated by 9% about the mean. The $\text{COV}_{\text{avg}}$ values ranged from 5% to 14%.

In summary, it appears that the PK screen followed by dose individualization allowed the incorporation of the inter-individual variability in PK parameters in the calculation of the doses administered in the study. Also, the peak concentrations as well as the "steady-state" concentrations achieved in this study were within acceptable limits of accuracy and precision.
Table 4.10  Measures of precision and accuracy for concentrations achieved for treatment C for intravenous ethanol study.

<table>
<thead>
<tr>
<th></th>
<th>$C_{avg}^1$ [mg/L]</th>
<th>COV$_{avg}^2$ [%]</th>
<th>%DFT$^3$ [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n=8)</td>
<td>1070 (15%)</td>
<td>9% (5%-14%)</td>
<td>7% (-14% - 38%)</td>
</tr>
<tr>
<td>Females (n=8)</td>
<td>1071 (13%)</td>
<td>8% (5%-10%)</td>
<td>7% (-20% - 21%)</td>
</tr>
<tr>
<td>All (n=16)</td>
<td>1070 (13%)</td>
<td>9% (5%-14%)</td>
<td>7% (-14% - 38%)</td>
</tr>
</tbody>
</table>

1: $C_{avg}$ expressed as Mean (%COV)
2: COV$_{avg}$ expressed as Mean (Range)
3: %DFT expressed as Mean (Range)
Non-compartmental analysis was performed on the individual concentration-time profiles by subject and treatment. Figure 4.6 shows the concentration vs. time profiles for all subjects by treatment. As figure 4.6 illustrates, peak concentrations were achieved at the end of the infusion for treatments A and B. For treatment C, peak concentrations were generally achieved at the end of Infusion 1 (1 hour), followed by a rapid distribution loss with concentrations subsequently levelling off to steady-state concentrations. This rapid distribution phase was also apparent for most subjects after treatment A. Terminal elimination profiles are consistent with capacity-limited elimination, showing an initial linear (apparent zero-order) decline, and a later exponential (apparent first-order) decline. Mean pharmacokinetic parameters determined by non-compartmental analysis are presented in table 4.11. Dose-corrected $C_{\text{max}}$ values were not significantly different across treatments, but showed differences between male and female subjects across treatments. $T_{\text{max}}$ was observed at the end of the infusion for treatments A and B. The $T_{\text{max}}$ values for treatment C ranged from 1 to 6 hours, with a median of 1.0 hours. Mean ± S.D. $AUC_{\infty}$ values were $4292 \pm 2289 \text{ mg/L*hr}$ for treatment A, $5678 \pm 1296 \text{ mg/L*hr}$ for treatment B and $10044 \pm 2487 \text{ mg/L*hr}$ for treatment C. The precision of the $AUC_{\infty}$ estimates was assessed by calculating the percent AUC extrapolated (%$AUC_{\text{extrap}}$) by dividing the $AUC_{\text{extrap}}$ by the $AUC_{\infty}$. The $%AUC_{\text{extrap}}$ was ranged from 2% to 29% across individual $AUC_{\infty}$ calculations. $\text{CL}_{\text{tot}}$ (mean ± SD) estimates were $211 \pm 62 \text{ ml/min}$, $235 \pm 47 \text{ ml/min}$ and $156 \pm 37 \text{ ml/min}$. \[\text{CL}_{\text{tot}}\]
Table 4.11  Mean (%COV) Non-compartmental Pharmacokinetic parameters by gender for crossover phase of intravenous ethanol study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$</th>
<th>$T_{\text{max}}$</th>
<th>$AUC_{\infty}$</th>
<th>$V_{\text{max}}$</th>
<th>$K_m$</th>
<th>$V_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[mg/L]</td>
<td>[mg/L/(g/kg)]²</td>
<td>[hr]</td>
<td>[mg/L/hr]</td>
<td>[mg/L]</td>
<td>[L]</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1182</td>
<td>22</td>
<td>1.0</td>
<td>4854</td>
<td>147</td>
<td>307</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(16%)</td>
<td>(16%)</td>
<td>(0.8-1.0)</td>
<td>(64%)</td>
<td>(27%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>Females</td>
<td>1056</td>
<td>26</td>
<td>1.0</td>
<td>3731</td>
<td>157</td>
<td>275</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(14%)</td>
<td>(17%)</td>
<td>(1.0-1.3)</td>
<td>(24%)</td>
<td>(18%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>All</td>
<td>1119</td>
<td>24</td>
<td>1.0</td>
<td>4292</td>
<td>152</td>
<td>291</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(16%)</td>
<td>(18%)</td>
<td>(0.8-1.3)</td>
<td>(53%)</td>
<td>(22%)</td>
<td>(37%)</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1048</td>
<td>12</td>
<td>6.0</td>
<td>5960</td>
<td>195</td>
<td>503</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(16%)</td>
<td>(8%)</td>
<td>(5.0-6.3)</td>
<td>(22%)</td>
<td>(15%)</td>
<td>(9%)</td>
</tr>
<tr>
<td>Females</td>
<td>1011</td>
<td>15</td>
<td>6.0</td>
<td>5396</td>
<td>176</td>
<td>408</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(18%)</td>
<td>(15%)</td>
<td>(6.0-6.3)</td>
<td>(24%)</td>
<td>(15%)</td>
<td>(14%)</td>
</tr>
<tr>
<td>All</td>
<td>1029</td>
<td>13</td>
<td>6.0</td>
<td>5678</td>
<td>185</td>
<td>456</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(16%)</td>
<td>(18%)</td>
<td>(5.0-6.3)</td>
<td>(23%)</td>
<td>(15%)</td>
<td>(16%)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1286</td>
<td>13</td>
<td>1.0</td>
<td>9835</td>
<td>203</td>
<td>400</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(16%)</td>
<td>(11%)</td>
<td>(1.0-6.0)</td>
<td>(25%)</td>
<td>(29%)</td>
<td>(24%)</td>
</tr>
<tr>
<td>Females</td>
<td>1253</td>
<td>16</td>
<td>1.0</td>
<td>10253</td>
<td>197</td>
<td>512</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(12%)</td>
<td>(11%)</td>
<td>(0.8-6.0)</td>
<td>(26%)</td>
<td>(34%)</td>
<td>(37%)</td>
</tr>
<tr>
<td>All</td>
<td>1269</td>
<td>14</td>
<td>1.0</td>
<td>10044</td>
<td>200</td>
<td>456</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(14%)</td>
<td>(16%)</td>
<td>(0.8-6.0)</td>
<td>(25%)</td>
<td>(30%)</td>
<td>(30%)</td>
</tr>
</tbody>
</table>

1: $T_{\text{max}}$ expressed as Median (Range)  2: Dose-corrected $C_{\text{max}}$  3: Dose-corrected $AUC_{\infty}$
ml/min for treatments A, B and C respectively.

As table 4.11 indicates, the intrinsic PK parameters, \( V_{\text{max}} \), \( K_m \) and \( V_{\text{dss}} \) did not appear to be different across treatments. However, the \( V_{\text{dss}} \) was different between male and female subjects. Table 4.12 lists the mean intrinsic PK parameters, estimated by non-compartmental methods across treatments, by gender, along with the inter-individual and intra-individual variability measures (%COV). The mean (± SD) \( V_{\text{max}} \) was 179 (± 47) mg/L/hr across subjects and treatments. The mean (± SD) \( K_m \) was 401 (± 207) mg/L across subjects and treatments. The mean (± SD) \( V_{\text{dss}} \) was 36 (± 16) L across treatments. As table 4.12 indicates, the inter-individual variability, as measured by the %COV, was considerable for the PK parameters, especially for the \( K_m \). This may be a consequence of the sampling schedule and the relatively poor precision in the analytical methods, particularly at low concentrations. For all parameters, the intra-individual variability was lower than the inter-individual variability.

4.4.2C Compartmental Analysis

A two-compartmental body model with multiple zero-order inputs into the central compartment, first-order distribution to and re-distribution from the peripheral compartment, with capacity-limited elimination was fit to the individual ethanol concentration vs. time profiles. Initial attempts to fit a one-compartment model, similar to the model used for Leg 0 data did not result in adequate fits due to the presence of a distributional component in the declining phase of the ethanol concentration-time profiles.
Table 4.12  Mean Non-compartmental PK parameter estimates across treatments, by gender, for intravenous ethanol study

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{max}}$ [mg/L/(\text{hr})]</th>
<th>$K_{\text{m}}$ [mg/L]</th>
<th>$V_{d_{\text{ss}}}$ [L]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n=24)</td>
<td>Females (n=24)</td>
<td>All (n=48)</td>
</tr>
<tr>
<td>Overall Mean</td>
<td>181</td>
<td>177</td>
<td>179</td>
</tr>
<tr>
<td>Inter-Individual variability (%COV)</td>
<td>27%</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Intra-Individual variability (Mean %COV)</td>
<td>21%</td>
<td>17%</td>
<td>19%</td>
</tr>
</tbody>
</table>
for treatments A, B and C, which was not very evident for data from Leg 0.

The final fits were considered to be adequate based on the coefficients of determination, which ranged from 0.873 to 0.996 and Model Selection Criteria, which ranged from 0.931 to 4.380; random scatter in the plots of residuals vs. independent variable; normal distribution of the residuals as well as visual inspection of observed and fitted curves.

The standard deviations and calculated %COVs of the parameter estimates were considerably high, especially for $V_{\text{mu}}$ with %COVs ranging from 41% to 689%, and for $K_{\text{m}}$ with %COVs ranging from 77% to 1519%.

Individual concentration vs. time profiles illustrating the observed values and fitted curves are shown in Appendix 13. Figure 4.7 shows the observed values and fitted curves by treatment for a representative subject (subject 7).

Table 4.13 lists the compartmental PK parameter estimates by treatment and gender. The estimates for $V_{\text{max}}$ showed a statistically significant difference between treatments ($p=0.0023$). Multiple comparisons revealed that treatment A was different from treatments B and C, which were not different from each other. This statistically significant difference may be due to differences in sample schedule, i.e., treatment A consisted of a 1-hour infusion, and samples were collected for up to 13 hours after the end of the infusion whereas samples were collected only up to 8 hours after the end of the infusion for treatments B and C, thus allowing for a better estimate of $V_{\text{max}}$ for treatment A. The estimates for $K_{\text{m}}$ were not significantly different across treatments or subjects when compared statistically. The $V_{\text{dss}}$ estimates were not different between treatments,
Figure 4.7 Serum ethanol concentration vs time profiles (observed values and fitted curves) by treatment for a representative subject (subject 7) for crossover phase of IV ethanol study.
Table 4.13  Mean (%COV) Compartmental Pharmacokinetic parameters by gender for crossover phase of intravenous ethanol study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$V_{\text{max}}$</th>
<th>$K_m$</th>
<th>$V_{dc}$</th>
<th>$k_{12}$</th>
<th>$k_{21}$</th>
<th>$V_{dss}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[mg/L/hr]</td>
<td>[mg/L]</td>
<td>[L]</td>
<td>[hr$^{-1}$]</td>
<td>[hr$^{-1}$]</td>
<td>[L]</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>320</td>
<td>279</td>
<td>32</td>
<td>0.93</td>
<td>1.41</td>
<td>55</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(26%)</td>
<td>(39%)</td>
<td>(25%)</td>
<td>(28%)</td>
<td>(54%)</td>
<td>(18%)</td>
</tr>
<tr>
<td>Females</td>
<td>318</td>
<td>216</td>
<td>26</td>
<td>0.91</td>
<td>2.11</td>
<td>41</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(17%)</td>
<td>(30%)</td>
<td>(21%)</td>
<td>(45%)</td>
<td>(60%)</td>
<td>(26%)</td>
</tr>
<tr>
<td>All</td>
<td>319</td>
<td>247</td>
<td>29</td>
<td>0.92</td>
<td>1.76</td>
<td>48</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(21%)</td>
<td>(37%)</td>
<td>(25%)</td>
<td>(36%)</td>
<td>(61%)</td>
<td>(26%)</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>357</td>
<td>278</td>
<td>36</td>
<td>0.67</td>
<td>2.10</td>
<td>50</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(24%)</td>
<td>(39%)</td>
<td>(8%)</td>
<td>(54%)</td>
<td>(57%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>Females</td>
<td>360</td>
<td>231</td>
<td>28</td>
<td>1.08</td>
<td>3.58</td>
<td>38</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(22%)</td>
<td>(31%)</td>
<td>(28%)</td>
<td>(67%)</td>
<td>(57%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>All</td>
<td>359</td>
<td>255</td>
<td>32</td>
<td>0.88</td>
<td>2.84</td>
<td>44</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(22%)</td>
<td>(37%)</td>
<td>(22%)</td>
<td>(68%)</td>
<td>(63%)</td>
<td>(21%)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>359</td>
<td>277</td>
<td>31</td>
<td>0.79</td>
<td>1.63</td>
<td>48</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(23%)</td>
<td>(25%)</td>
<td>(13%)</td>
<td>(27%)</td>
<td>(53%)</td>
<td>(17%)</td>
</tr>
<tr>
<td>Females</td>
<td>379</td>
<td>233</td>
<td>23</td>
<td>1.15</td>
<td>2.09</td>
<td>36</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(17%)</td>
<td>(25%)</td>
<td>(24%)</td>
<td>(42%)</td>
<td>(49%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>All</td>
<td>369</td>
<td>255</td>
<td>27</td>
<td>0.97</td>
<td>1.86</td>
<td>42</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(20%)</td>
<td>(26%)</td>
<td>(24%)</td>
<td>(42%)</td>
<td>(51%)</td>
<td>(22%)</td>
</tr>
</tbody>
</table>

1: body weight-corrected $V_{dss}$
but showed a significant gender difference (mean (± S.D.) $V_{dss}$ of 51 (± 9) L for male subjects and 38 (± 8) L for female subjects across treatments). The estimates for $k_{12}$ did not show any significant differences between treatments, however a significant difference was observed for the estimates of $k_{21}$ ($p=0.0209$). Multiple comparisons revealed that treatment B was different from treatments A and C, which were not different from each other. This may be due to the difficulty in estimating distribution and re-distribution rate constants for drugs following multi-compartment characteristics when given as long duration infusions, since the drug undergoes distribution during the infusion and the distribution phase may not be as readily observed as for a drug with two-compartment characteristics given as a short infusion (as in treatment A). This phenomenon has been observed for other drugs as well, which show a rapid distribution phase when given as a short infusion, but the distribution phase is not as apparent when given as a slow prolonged infusion, and is called the "vanishing exponential" for drugs following first-order pharmacokinetics (Gibaldi and Perrier, 1982).

The mean intrinsic PK parameters, estimated by compartmental methods across subjects and treatments, along with the inter-individual and intra-individual variability measures (%COV) are presented in table 4.14, by gender. The mean (± S.D.) $V_{max}$ was 349 (± 75) mg/L/hr across subjects and treatments. The mean (± S.D.) $K_{m}$ was 252 (± 83) mg/L across subjects and treatments. The mean ± SD $V_{dss}$ was 51 (± 9) L across treatments for male subjects, and 38 (± 8) L across treatments for female subjects. The mean (± S.D.) $k_{12}$ was 0.92 (± 0.40) hr$^{-1}$ across subjects and treatments. The mean (±
Table 4.14  Mean Compartmental PK parameter estimates across treatments for males (M) and Females (F) for intravenous ethanol study

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{max}}$ [mg/L/hr]</th>
<th>$K_m$ [mg/L]</th>
<th>$k_{12}$ [hr⁻¹]</th>
<th>$k_{21}$ [hr⁻¹]</th>
<th>$V_{\text{d, ext}}$ [L]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>All</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Overall Mean</td>
<td>346</td>
<td>352</td>
<td>349</td>
<td>278</td>
<td>227</td>
</tr>
<tr>
<td>Inter-Individual variability (%COV)</td>
<td>24%</td>
<td>19%</td>
<td>22%</td>
<td>34%</td>
<td>28%</td>
</tr>
<tr>
<td>Intra-Individual variability (Mean%COV)</td>
<td>11%</td>
<td>12%</td>
<td>12%</td>
<td>14%</td>
<td>14%</td>
</tr>
</tbody>
</table>


S.D.) $k_{21}$ was $2.15 \pm 1.4$ hr$^{-1}$ across subjects and treatments. This corresponds to a distribution half-life of around 0.23 hours (or around 14 minutes), indicating that the distribution phase for ethanol is quite rapid.

As table 4.14 indicates, the inter-individual variability, as measured by the %COV, was considerable for the PK parameters, especially for $k_{12}$, $k_{21}$ and $K_m$. This may be a consequence of the sampling schedule and the relatively poor precision in the analytical methods, particularly at low concentrations. For all parameters, intra-individual variability was lower than the inter-individual variability. The mean and inter-individual variability estimates of the intrinsic PK parameters are consistent with values reported in other studies evaluating the PK of IV ethanol (Wagner et al., 1976; Wilkinson et al., 1976; Holford, 1987; Rangno et al., 1981). The mean estimate of $K_m$ of 252 mg/L obtained in this study is higher than the population estimate of 80 mg/L reported in other studies (Wilkinson, 1980; Holford, 1987). However, these studies have emphasized the large variability in $K_m$ (upto 10-fold) due to differences in sampling schedules, assay precision and sensitivity at concentrations around the $K_m$, as well as inter-individual differences in PK of ethanol. The estimates of $V_{ds}$ are consistent with values obtained in other studies and demonstrate gender differences consistent with differences in body water content between males and females (Marshall et al., 1983; Holford, 1987).

4.4.3 PHARMACODYNAMICS
Baseline-corrected response vs. time profiles for the EEG measures evaluated, including total power across all frequency bands, total and relative power within each of the five frequency bands (delta, theta, alpha, beta I and beta II) are shown in Appendix J. A review of these plots reveal the following:

1) total power showed a transient increase across all treatments, including placebo.

2) relative delta power showed a transient increase for active treatments A, B and C relative to placebo, that was observed only for male subjects.

3) relative theta power showed an initial increase across all treatments followed by a transient decrease that was observed for the active treatments only in male subjects. Female subjects did not show a consistent decrease in relative theta power following ethanol administration.

4) relative alpha power showed a transient decrease that was treatment-related, however, this was seen only for male subjects.

5) relative beta (I and II) power showed consistent decreases following ethanol administration relative to placebo. This was observed for all subjects.

These observations are consistent with an increase in EEG power in the slow bands and a corresponding decrease in EEG power in the fast bands. This results in a generalized slowing of the EEG power following ethanol administration.

The means and %COV of the baseline EEG measures are presented in table 4.15. The baseline measures were not different across subjects and treatments, and showed fairly
Table 4.15 Pharmacodynamic parameters (Means and %COV) for EEG measures across treatments and subjects

Table 4.15a Total Power

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [$\mu V^2$]</th>
<th>$E_{\text{max}}$ [$\mu V^2$]</th>
<th>$E_{\text{max}} - E_0$ [$\mu V^2$]</th>
<th>$T_{\text{max}}$ [hr] $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Males</td>
<td>390 (22%)</td>
<td>469 (22%)</td>
<td>79 (67%)</td>
<td>2.5 (0.8-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>417 (22%)</td>
<td>492 (16%)</td>
<td>76 (58%)</td>
<td>1.8 (0.3-5.0)</td>
</tr>
<tr>
<td>All</td>
<td>403 (22%)</td>
<td>481 (18%)</td>
<td>77 (61%)</td>
<td>2.0 (0.3-6.0)</td>
</tr>
<tr>
<td>B Males</td>
<td>406 (25%)</td>
<td>487 (20%)</td>
<td>82 (71%)</td>
<td>6.8 (0.5-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>409 (26%)</td>
<td>505 (24%)</td>
<td>96 (73%)</td>
<td>6.2 (1.3-9.0)</td>
</tr>
<tr>
<td>All</td>
<td>407 (25%)</td>
<td>496 (22%)</td>
<td>89 (71%)</td>
<td>6.5 (0.5-12.0)</td>
</tr>
<tr>
<td>C Males</td>
<td>407 (21%)</td>
<td>512 (26%)</td>
<td>105 (84%)</td>
<td>6.8 (0.5-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>407 (25%)</td>
<td>523 (17%)</td>
<td>115 (50%)</td>
<td>1.7 (0.3-5.0)</td>
</tr>
<tr>
<td>All</td>
<td>407 (22%)</td>
<td>517 (22%)</td>
<td>110 (66%)</td>
<td>3.0 (0.3-11.0)</td>
</tr>
<tr>
<td>D Males</td>
<td>368 (24%)</td>
<td>463 (23%)</td>
<td>95 (88%)</td>
<td>6.5 (1.3-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>405 (27%)</td>
<td>481 (23%)</td>
<td>77 (36%)</td>
<td>4.0 (0.5-6.7)</td>
</tr>
<tr>
<td>All</td>
<td>386 (25%)</td>
<td>472 (22%)</td>
<td>86 (71%)</td>
<td>6.0 (0.5-12.0)</td>
</tr>
</tbody>
</table>

1: $T_{\text{max}}$ expressed as Median (range)
Table 4.15b  Relative Delta Power

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( E_0 ) [-]</th>
<th>( E_{\text{max}} ) [-]</th>
<th>( E_{\text{max}} - E_0 ) [-]</th>
<th>( T_{\text{max}} ) [hr](^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.396 (18%)</td>
<td>0.514 (12%)</td>
<td>0.117 (60%)</td>
<td>3.5 (0.8-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.448 (19%)</td>
<td>0.499 (16%)</td>
<td>0.059 (118%)</td>
<td>4.0 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.422 (19%)</td>
<td>0.506 (14%)</td>
<td>0.088 (84%)</td>
<td>4.0 (0.3-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.416 (24%)</td>
<td>0.517 (9%)</td>
<td>0.104 (87%)</td>
<td>5.0 (0.3-9.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.442 (15%)</td>
<td>0.497 (18%)</td>
<td>0.065 (93%)</td>
<td>4.8 (1.0-9.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.429 (19%)</td>
<td>0.507 (14%)</td>
<td>0.085 (91%)</td>
<td>5.0 (0.3-9.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.390 (23%)</td>
<td>0.548 (9%)</td>
<td>0.158 (52%)</td>
<td>4.5 (1.0-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.450 (16%)</td>
<td>0.528 (10%)</td>
<td>0.078 (58%)</td>
<td>2.5 (0.8-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.420 (20%)</td>
<td>0.538 (9%)</td>
<td>0.118 (64%)</td>
<td>4.0 (0.8-11.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.451 (17%)</td>
<td>0.509 (15%)</td>
<td>0.058 (75%)</td>
<td>4.0 (0.3-6.3)</td>
</tr>
<tr>
<td>Females</td>
<td>0.447 (17%)</td>
<td>0.511 (14%)</td>
<td>0.064 (96%)</td>
<td>5.3 (0.3-12.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.449 (16%)</td>
<td>0.510 (14%)</td>
<td>0.061 (85%)</td>
<td>4.0 (0.3-12.0)</td>
</tr>
</tbody>
</table>

\(^1\): \( T_{\text{max}} \) expressed as Median (range)
Table 4.15c  Relative Theta Power

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [-]</th>
<th>$E_{min}$ [-]</th>
<th>$E_0-E_{min}$ [-]</th>
<th>$T_{min}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.294 (21%)</td>
<td>0.225 (14%)</td>
<td>0.069 (67%)</td>
<td>3.5 (0.8-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.255 (25%)</td>
<td>0.222 (21%)</td>
<td>0.035 (144%)</td>
<td>2.0 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.275 (23%)</td>
<td>0.224 (17%)</td>
<td>0.052 (96%)</td>
<td>2.5 (0.3-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.293 (27%)</td>
<td>0.223 (12%)</td>
<td>0.070 (91%)</td>
<td>4.0 (0.3-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.249 (28%)</td>
<td>0.223 (29%)</td>
<td>0.030 (109%)</td>
<td>6.8 (1.3-11.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.271 (28%)</td>
<td>0.223 (21%)</td>
<td>0.050 (106%)</td>
<td>6.3 (0.3-11.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.301 (25%)</td>
<td>0.216 (15%)</td>
<td>0.085 (75%)</td>
<td>7.3 (2.0-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.245 (28%)</td>
<td>0.216 (33%)</td>
<td>0.031 (109%)</td>
<td>4.0 (1.7-12.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.273 (28%)</td>
<td>0.216 (25%)</td>
<td>0.058 (98%)</td>
<td>6.2 (1.7-12.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.264 (23%)</td>
<td>0.227 (19%)</td>
<td>0.037 (87%)</td>
<td>3.5 (0.5-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.247 (28%)</td>
<td>0.227 (29%)</td>
<td>0.021 (109%)</td>
<td>1.0 (0.3-12.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.256 (25%)</td>
<td>0.227 (27%)</td>
<td>0.029 (97%)</td>
<td>2.5 (0.3-12.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{max}$ expressed as Median (range)
Table 4.15d Relative Alpha Power

<table>
<thead>
<tr>
<th>Treatment</th>
<th>E_o [-]</th>
<th>E_min [-]</th>
<th>E_o - E_min [-]</th>
<th>T_min [hr]^1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.181 (18%)</td>
<td>0.132 (18%)</td>
<td>0.050 (53%)</td>
<td>3.5 (0.8-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.172 (35%)</td>
<td>0.142 (31%)</td>
<td>0.030 (144%)</td>
<td>3.0 (0.8-5.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.176 (26%)</td>
<td>0.137 (25%)</td>
<td>0.040 (90%)</td>
<td>3.5 (0.8-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.167 (19%)</td>
<td>0.127 (15%)</td>
<td>0.042 (71%)</td>
<td>5.0 (1.3-9.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.173 (33%)</td>
<td>0.137 (36%)</td>
<td>0.037 (87%)</td>
<td>6.3 (2.0-7.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.170 (27%)</td>
<td>0.132 (21%)</td>
<td>0.039 (76%)</td>
<td>6.2 (1.3-9.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.179 (20%)</td>
<td>0.122 (15%)</td>
<td>0.057 (49%)</td>
<td>4.0 (1.7-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.169 (33%)</td>
<td>0.124 (25%)</td>
<td>0.045 (67%)</td>
<td>5.0 (0.5-6.3)</td>
</tr>
<tr>
<td>All</td>
<td>0.174 (26%)</td>
<td>0.123 (20%)</td>
<td>0.051 (57%)</td>
<td>4.5 (0.5-11.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.160 (16%)</td>
<td>0.141 (18%)</td>
<td>0.019 (87%)</td>
<td>3.5 (0.3-6.3)</td>
</tr>
<tr>
<td>Females</td>
<td>0.174 (32%)</td>
<td>0.131 (17%)</td>
<td>0.045 (92%)</td>
<td>4.5 (0.5-9.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.167 (25%)</td>
<td>0.136 (17%)</td>
<td>0.032 (105%)</td>
<td>4.0 (0.3-9.0)</td>
</tr>
</tbody>
</table>

^1: T_{min} expressed as Median (range)
Table 4.15e  Relative Beta I Power

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_o$ [-]</th>
<th>$E_{max}$ [-]</th>
<th>$E_{max}-E_o$ [-]</th>
<th>$T_{max}$ [hr] $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.095 (8%)</td>
<td>0.083 (16%)</td>
<td>0.012 (93%)</td>
<td>3.5 (0.8-5.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.089 (21%)</td>
<td>0.086 (15%)</td>
<td>0.006 (108%)</td>
<td>2.8 (1.0-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.092 (15%)</td>
<td>0.084 (15%)</td>
<td>0.009 (106%)</td>
<td>3.5 (0.8-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.091 (12%)</td>
<td>0.080 (14%)</td>
<td>0.012 (60%)</td>
<td>7.5 (1.3-9.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.097 (29%)</td>
<td>0.087 (18%)</td>
<td>0.012 (145%)</td>
<td>1.8 (0.3-8.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.094 (22%)</td>
<td>0.083 (16%)</td>
<td>0.012 (108%)</td>
<td>6.3 (0.3-9.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.097 (6%)</td>
<td>0.074 (11%)</td>
<td>0.023 (37%)</td>
<td>4.5 (1.7-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.097 (28%)</td>
<td>0.083 (17%)</td>
<td>0.014 (107%)</td>
<td>3.5 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.097 (20%)</td>
<td>0.079 (16%)</td>
<td>0.018 (68%)</td>
<td>4.5 (0.3-11.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.090 (8%)</td>
<td>0.081 (11%)</td>
<td>0.009 (65%)</td>
<td>4.0 (0.3-6.3)</td>
</tr>
<tr>
<td>Females</td>
<td>0.095 (22%)</td>
<td>0.085 (18%)</td>
<td>0.010 (68%)</td>
<td>2.0 (0.3-8.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.093 (17%)</td>
<td>0.083 (15%)</td>
<td>0.010 (65%)</td>
<td>3.5 (0.3-8.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{max}$ expressed as Median (range)
Table 4.15f Relative Beta II Power

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( E_o ) [-]</th>
<th>( E_{\text{min}} ) [-]</th>
<th>( E_o - E_{\text{min}} ) [-]</th>
<th>( T_{\text{min}} ) [hr] (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.033 (10%)</td>
<td>0.028 (21%)</td>
<td>0.006 (99%)</td>
<td>3.0 (0.5-5.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.035 (18%)</td>
<td>0.030 (19%)</td>
<td>0.005 (68%)</td>
<td>1.7 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.034 (15%)</td>
<td>0.029 (20%)</td>
<td>0.005 (84%)</td>
<td>1.8 (0.3-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.033 (17%)</td>
<td>0.028 (20%)</td>
<td>0.005 (116%)</td>
<td>6.7 (2.0-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.038 (27%)</td>
<td>0.031 (12%)</td>
<td>0.008 (132%)</td>
<td>5.5 (0.3-8.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.035 (24%)</td>
<td>0.029 (17%)</td>
<td>0.007 (125%)</td>
<td>6.3 (0.3-12.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.034 (17%)</td>
<td>0.024 (16%)</td>
<td>0.010 (44%)</td>
<td>5.7 (2.0-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.039 (29%)</td>
<td>0.029 (18%)</td>
<td>0.010 (94%)</td>
<td>4.5 (0.8-8.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.037 (25%)</td>
<td>0.026 (19%)</td>
<td>0.010 (72%)</td>
<td>5.0 (0.8-11.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.034 (18%)</td>
<td>0.028 (5%)</td>
<td>0.006 (85%)</td>
<td>2.8 (0.3-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.037 (20%)</td>
<td>0.032 (19%)</td>
<td>0.005 (49%)</td>
<td>6.7 (0.8-9.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.036 (19%)</td>
<td>0.030 (15%)</td>
<td>0.006 (73%)</td>
<td>5.0 (0.3-12.0)</td>
</tr>
</tbody>
</table>

\(^1\): \( T_{\text{min}} \) expressed as Median (range)
low variability ranging from 15% to 28% between subjects across measures.

Figures 4.8 - 4.13 show the peak changes in the EEG measures, including total power, relative power in each of the five frequency bands, delta, theta, alpha, beta I and beta II), by treatment for male and female subjects.

Statistical comparison of the $E_{\text{max}}$ or $E_{\text{min}}$ for the EEG measures revealed significant treatment differences for relative alpha power ($p=0.0337$), relative beta I power ($p=0.0093$) and for relative beta II power ($p=0.0226$). Multiple comparisons indicated that treatment C was significantly different from treatments A, B and D, while A and B could not be distinguished from placebo. Residuals were found to be normally distributed for these variables. There was a significant treatment-by-gender interaction for the $E_{\text{min}}$ for relative alpha power. Further comparison of treatment means by gender revealed that the significant differences between active treatments A, B and C and placebo (treatment D) was observed only for male subjects ($p=0.0055$), while female subjects did not show significant differences in relative alpha power across treatments. There were no significant sequence or period effect on any of the EEG variables evaluated. The p values for the significance of the baseline response as a covariate was less than 0.05 for all the EEG variables evaluated except for relative beta I power. This indicates that the baseline response contributed significantly to the overall variability in the EEG response to ethanol. The NR score and AAAI were not significant as covariates in the analysis, indicating that these variables did not contribute significantly to the overall variability in the magnitude of the EEG response to ethanol.
Figure 4.8  Baseline-corrected peak change in total power by treatment for IV ethanol study.

Figure 4.9  Baseline-corrected peak change in relative delta power by treatment for IV ethanol study.
Figure 4.10 Baseline-corrected peak change in relative theta power by treatment for IV ethanol study

Figure 4.11 Baseline-corrected peak change in relative alpha power by treatment for IV ethanol study
Figure 4.12 Baseline-corrected peak change in relative beta I power by treatment for IV ethanol study

Figure 4.13 Baseline-corrected peak change in relative beta II power by treatment for IV ethanol study
The $E_{max}^{obs}$ for relative delta power and $E_{min}^{obs}$ for relative theta power showed a trend toward treatment-related differences, but the $p$ values did not reach statistical significance ($p$ value for $E_{max}^{obs}$ for relative delta power = 0.0537, and for $E_{min}^{obs}$ for relative theta power = 0.0972).

There was also a trend toward lower EEG responses for relative delta and relative theta power for female subjects compared to male subjects, but the differences did not reach statistical significance. Statistically significant differences between males and females were observed only for relative alpha power.

Statistical comparison of the $t_{max}$ or $t_{min}$ for the EEG measures revealed significant treatment differences for total power ($p = 0.0023$), relative theta power ($p = 0.042$), relative alpha power ($p = 0.0246$) and relative beta II power ($p = 0.0135$). Multiple comparisons indicated that, in general, treatment A was significantly different from treatments B, C and D for total power, relative theta power and relative beta II power. Residuals were found to be normally distributed for these variables. There was a significant period effect observed for relative theta power and relative alpha power. The baseline response was not a significant covariate for any of the $t_{max}$ or $t_{min}$ estimates for any of the EEG measures evaluated except for relative theta power. The NR score was a significant covariate only for the $t_{min}$ for relative alpha power. Alcohol history (AAAI) was a significant covariate for the $t_{min}$ for relative theta, relative alpha and relative beta II power, indicating that the AAAI may contribute significantly to the overall variability in the timing of the EEG response to ethanol. There were no significant gender
differences observed for any of the $t_{max}$ or $t_{min}$ comparisons.

The increases in relative delta power, along with the decreases in relative theta power as well as the decrease in relative power of the fast bands (alpha and beta) are consistent with the increase in EEG power and a generalized slowing of the EEG following ethanol administration that have been previously reported in the literature (Ehlers and Shuckit, 1990; Begleiter and Platz, 1972; Lukas et al., 1986; Kaplan et al., 1988), although these studies have investigated EEG changes following oral ethanol administration, and there have been no studies prior to this evaluating EEG changes following intravenous ethanol administration. The EEG effects of ethanol show treatment-related changes, and some of the time to peak measures show a significant effect of input-rate on the EEG measures evaluated. Gender differences were observed in the EEG response to ethanol indicating that, in general, females tended to respond less to the effect of ethanol on the increase in slow activity and decrease in alpha activity at the same achieved serum ethanol concentrations compared to the male subjects. Statistically significant gender differences were observed only for relative alpha power.

4.4.3B Psychometric Performance Tests

Baseline-corrected response vs. time profiles for the primary PPT measures evaluated, including reaction time for number vigilance and sensitivity for word recognition are shown in Appendix K. Response-time profiles for the other measures are not included since they did not show any consistent time-related changes. Table 4.16 lists the baseline
Table 4.16 Pharmacodynamic parameters (Means and %COV) for PPT measures across treatments and subjects

Table 4.16a Immediate Recall Accuracy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [-]</th>
<th>$E_{\text{min}}$ [-]</th>
<th>$E_0-E_{\text{min}}$ [-]</th>
<th>$T_{\text{min}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>7.1 (38%)</td>
<td>3.3 (40%)</td>
<td>3.8 (66%)</td>
<td>1.2 (0.3-4.0)</td>
</tr>
<tr>
<td>Females</td>
<td>8.2 (17%)</td>
<td>3.2 (31%)</td>
<td>5.0 (19%)</td>
<td>1.2 (0.3-3.0)</td>
</tr>
<tr>
<td>All</td>
<td>7.7 (28%)</td>
<td>3.3 (35%)</td>
<td>4.4 (44%)</td>
<td>1.2 (0.3-4.0)</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>7.0 (37%)</td>
<td>2.8 (72%)</td>
<td>4.3 (54%)</td>
<td>4.5 (0.3-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>8.1 (15%)</td>
<td>3.1 (41%)</td>
<td>5.1 (34%)</td>
<td>4.5 (1.0-6.7)</td>
</tr>
<tr>
<td>All</td>
<td>7.6 (27%)</td>
<td>2.9 (56%)</td>
<td>4.7 (43%)</td>
<td>4.5 (0.3-7.0)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>8.0 (28%)</td>
<td>2.6 (33%)</td>
<td>5.4 (42%)</td>
<td>1.8 (0.5-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>8.0 (16%)</td>
<td>2.9 (56%)</td>
<td>5.1 (14%)</td>
<td>2.5 (0.8-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>8.0 (22%)</td>
<td>2.8 (46%)</td>
<td>5.3 (31%)</td>
<td>2.0 (0.5-7.0)</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>7.2 (34%)</td>
<td>3.7 (34%)</td>
<td>3.5 (43%)</td>
<td>6.3 (1.3-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>7.3 (18%)</td>
<td>3.7 (32%)</td>
<td>3.6 (40%)</td>
<td>1.8 (0.3- 7.0)</td>
</tr>
<tr>
<td>All</td>
<td>7.2 (26%)</td>
<td>3.7 (32%)</td>
<td>3.5 (40%)</td>
<td>4.5 (0.3-12.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{min}}$ expressed as Median (range)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [msec]</th>
<th>$E_{\text{min}}$ [msec]</th>
<th>$E_0 - E_{\text{min}}$ [msec]</th>
<th>$T_{\text{min}}$ [hr]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>96.3 (9%)</td>
<td>70.8 (39%)</td>
<td>25.4 (103%)</td>
<td>1.7 (0.3-3.0)</td>
</tr>
<tr>
<td>Females</td>
<td>98.8 (2%)</td>
<td>91.7 (9%)</td>
<td>7.1 (134%)</td>
<td>0.5 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>97.5 (6%)</td>
<td>81.3 (28%)</td>
<td>16.3 (131%)</td>
<td>1.3 (0.3-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>99.2 (2%)</td>
<td>65.4 (45%)</td>
<td>33.8 (85%)</td>
<td>6.3 (1.7-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>98.8 (2%)</td>
<td>88.8 (15%)</td>
<td>10.0 (126%)</td>
<td>4.0 (0.8-7.0)</td>
</tr>
<tr>
<td>All</td>
<td>99.0 (2%)</td>
<td>77.1 (33%)</td>
<td>21.9 (113%)</td>
<td>5.5 (0.8-7.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>96.3 (4%)</td>
<td>67.5 (41%)</td>
<td>28.8 (85%)</td>
<td>4.0 (0.3-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>98.3 (3%)</td>
<td>87.9 (14%)</td>
<td>10.4 (99%)</td>
<td>2.5 (1.3-9.0)</td>
</tr>
<tr>
<td>All</td>
<td>97.3 (3%)</td>
<td>77.7 (30%)</td>
<td>19.6 (104%)</td>
<td>3.0 (0.3-9.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>93.8 (6%)</td>
<td>84.2 (18%)</td>
<td>9.6 (145%)</td>
<td>0.8 (0.3-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>97.1 (6%)</td>
<td>89.6 (14%)</td>
<td>7.5 (94%)</td>
<td>1.0 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>95.4 (6%)</td>
<td>86.9 (16%)</td>
<td>8.5 (125%)</td>
<td>1.0 (0.3-6.0)</td>
</tr>
</tbody>
</table>

1: $T_{\text{min}}$ expressed as Median (range)
Table 4.16c  Number Vigilance Reaction Time

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [msec]</th>
<th>$E_{\text{max}}$ [msec]</th>
<th>$E_{\text{max}} - E_0$ [msec]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>422.6 (10%)</td>
<td>549.0 (16%)</td>
<td>126.4 (52%)</td>
<td>1.8 (0.8-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>391.4 (8%)</td>
<td>476.9 (11%)</td>
<td>85.5 (55%)</td>
<td>1.8 (0.8-4.0)</td>
</tr>
<tr>
<td>All</td>
<td>407.0 (10%)</td>
<td>513.0 (15%)</td>
<td>105.9 (56%)</td>
<td>1.8 (0.8-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>413.5 (13%)</td>
<td>537.4 (18%)</td>
<td>123.9 (44%)</td>
<td>5.0 (0.3-9.0)</td>
</tr>
<tr>
<td>Females</td>
<td>393.7 (9%)</td>
<td>473.9 (13%)</td>
<td>80.2 (60%)</td>
<td>6.0 (1.7-7.0)</td>
</tr>
<tr>
<td>All</td>
<td>403.6 (11%)</td>
<td>505.6 (17%)</td>
<td>102.0 (53%)</td>
<td>5.5 (0.3-9.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>415.1 (12%)</td>
<td>566.8 (13%)</td>
<td>151.8 (28%)</td>
<td>3.5 (0.5-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>400.9 (11%)</td>
<td>506.5 (12%)</td>
<td>105.6 (40%)</td>
<td>5.0 (1.3-7.0)</td>
</tr>
<tr>
<td>All</td>
<td>408.0 (11%)</td>
<td>536.7 (14%)</td>
<td>128.7 (37%)</td>
<td>4.0 (0.5-7.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>436.4 (14%)</td>
<td>477.5 (15%)</td>
<td>41.1 (86%)</td>
<td>4.0 (2.0-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>406.6 (15%)</td>
<td>450.0 (15%)</td>
<td>43.5 (66%)</td>
<td>1.2 (0.3-6.3)</td>
</tr>
<tr>
<td>All</td>
<td>421.5 (14%)</td>
<td>463.8 (15%)</td>
<td>42.3 (74%)</td>
<td>3.0 (0.3-7.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{max}}$ expressed as Median (range)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [cm]</th>
<th>$E_{max}$ [cm]</th>
<th>$E_{max}-E_0$ [cm]</th>
<th>$T_{max}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>25.27 (16%)</td>
<td>45.03 (58%)</td>
<td>19.75 (122%)</td>
<td>1.2 (0.3-4.0)</td>
</tr>
<tr>
<td>Females</td>
<td>27.94 (12%)</td>
<td>33.54 (16%)</td>
<td>5.61 (44%)</td>
<td>1.0 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>26.61 (15%)</td>
<td>39.29 (48%)</td>
<td>12.68 (143%)</td>
<td>1.2 (0.3-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>27.57 (17%)</td>
<td>43.04 (51%)</td>
<td>15.47 (126%)</td>
<td>6.3 (1.0-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>26.64 (18%)</td>
<td>33.82 (16%)</td>
<td>7.17 (46%)</td>
<td>6.3 (0.8-7.0)</td>
</tr>
<tr>
<td>All</td>
<td>27.10 (17%)</td>
<td>38.43 (42%)</td>
<td>11.32 (125%)</td>
<td>6.3 (0.8-12.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>24.66 (21%)</td>
<td>38.58 (21%)</td>
<td>13.93 (60%)</td>
<td>3.0 (0.3-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>28.59 (10%)</td>
<td>41.68 (34%)</td>
<td>13.09 (107%)</td>
<td>3.0 (0.3-6.3)</td>
</tr>
<tr>
<td>All</td>
<td>26.62 (17%)</td>
<td>40.13 (28%)</td>
<td>13.51 (82%)</td>
<td>3.0 (0.3-7.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>25.05 (20%)</td>
<td>30.08 (11%)</td>
<td>5.03 (70%)</td>
<td>1.3 (0.3-6.7)</td>
</tr>
<tr>
<td>Females</td>
<td>26.48 (14%)</td>
<td>38.25 (40%)</td>
<td>11.77 (114%)</td>
<td>2.5 (0.3-6.7)</td>
</tr>
<tr>
<td>All</td>
<td>25.76 (17%)</td>
<td>34.16 (34%)</td>
<td>8.40 (120%)</td>
<td>1.8 (0.3-6.7)</td>
</tr>
</tbody>
</table>

$^1$: $T_{max}$ expressed as Median (range)
### Table 4.16e Word Recognition Sensitivity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [-]</th>
<th>$E_{\text{min}}$ [-]</th>
<th>$E_0-E_{\text{min}}$ [-]</th>
<th>$T_{\text{min}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.728 (18%)</td>
<td>0.206 (143%)</td>
<td>0.522 (51%)</td>
<td>2.2 (0.5-4.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.860 (12%)</td>
<td>0.430 (46%)</td>
<td>0.431 (35%)</td>
<td>1.7 (0.3-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.794 (17%)</td>
<td>0.318 (85%)</td>
<td>0.476 (45%)</td>
<td>1.7 (0.3-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.734 (14%)</td>
<td>0.217 (106%)</td>
<td>0.517 (49%)</td>
<td>5.0 (1.7-6.3)</td>
</tr>
<tr>
<td>Females</td>
<td>0.839 (13%)</td>
<td>0.332 (76%)</td>
<td>0.507 (36%)</td>
<td>5.7 (0.3-12.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.787 (15%)</td>
<td>0.274 (88%)</td>
<td>0.512 (42%)</td>
<td>5.0 (0.3-12.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.702 (17%)</td>
<td>-0.007 (532%)</td>
<td>0.710 (39%)</td>
<td>4.0 (1.3-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.855 (22%)</td>
<td>0.310 (75%)</td>
<td>0.545 (21%)</td>
<td>5.0 (0.8-6.7)</td>
</tr>
<tr>
<td>All</td>
<td>0.779 (22%)</td>
<td>0.151 (214%)</td>
<td>0.627 (35%)</td>
<td>4.0 (0.8-7.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.771 (18%)</td>
<td>0.411 (31%)</td>
<td>0.360 (19%)</td>
<td>6.2 (2.0-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0.724 (16%)</td>
<td>0.384 (52%)</td>
<td>0.341 (37%)</td>
<td>4.5 (0.5-12.0)</td>
</tr>
<tr>
<td>All</td>
<td>0.748 (17%)</td>
<td>0.397 (41%)</td>
<td>0.350 (28%)</td>
<td>5.5 (0.5-12.0)</td>
</tr>
</tbody>
</table>

1: $T_{\text{min}}$ expressed as Median (range)
Table 4.16f  Word Recognition Reaction time

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [msec]</th>
<th>$E_{max}$ [msec]</th>
<th>$E_{max}-E_0$ [msec]</th>
<th>$T_{max}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>659.5 (13%)</td>
<td>1286.3 (58%)</td>
<td>626.8 (116%)</td>
<td>1.8 (0.3-4.0)</td>
</tr>
<tr>
<td>Females</td>
<td>602.7 (6%)</td>
<td>745.8 (9%)</td>
<td>143.1 (40%)</td>
<td>0.9 (0.3-2.0)</td>
</tr>
<tr>
<td>All</td>
<td>631.1 (11%)</td>
<td>1016.1 (57%)</td>
<td>385.0 (145%)</td>
<td>1.3 (0.3-4.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>722.4 (19%)</td>
<td>963.8 (24%)</td>
<td>241.4 (74%)</td>
<td>3.5 (0.3-6.7)</td>
</tr>
<tr>
<td>Females</td>
<td>613.0 (9%)</td>
<td>766.9 (13%)</td>
<td>153.9 (45%)</td>
<td>3.5 (0.5-7.0)</td>
</tr>
<tr>
<td>All</td>
<td>667.7 (18%)</td>
<td>865.4 (23%)</td>
<td>197.6 (70%)</td>
<td>3.5 (0.3-7.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>685.7 (13%)</td>
<td>1101.3 (32%)</td>
<td>415.7 (81%)</td>
<td>4.0 (0.5-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>628.4 (11%)</td>
<td>777.7 (14%)</td>
<td>149.3 (36%)</td>
<td>6.0 (3.0-9.0)</td>
</tr>
<tr>
<td>All</td>
<td>657.1 (13%)</td>
<td>939.5 (32%)</td>
<td>282.5 (96%)</td>
<td>5.0 (0.5-9.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>661.2 (16%)</td>
<td>898.8 (35%)</td>
<td>237.6 (112%)</td>
<td>3.8 (1.3-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>637.6 (9%)</td>
<td>758.5 (18%)</td>
<td>120.9 (79%)</td>
<td>4.2 (0.8-12.0)</td>
</tr>
<tr>
<td>All</td>
<td>649.4 (13%)</td>
<td>828.6 (29%)</td>
<td>179.2 (113%)</td>
<td>3.8 (0.8-12.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{max}$ expressed as Median (range)
(E_0), maximum or minimum observed response (E_{max}^{obs} or E_{min}^{obs}) and time of E_{max}^{obs} or E_{min}^{obs} (t_{max} or t_{min}) for each of the PPT measures evaluated. Figures 4.14 - 4.18 show the peak changes in the PPT measures, including accuracy for immediate word recall, accuracy and reaction time for number vigilance, mean tracking error for tracking and sensitivity and reaction time for word recognition.

Response-time profiles for PPT measures indicated that the psychometric test battery was sensitive to ethanol and showed increase in reaction-time for the number vigilance and word recognition tests, decrease in the sensitivity measure of the word recognition test, increase in tracking error and decrease in accuracy of the immediate recall test.

Treatment A showed a greater impairment of psychometric performance as measured by these tests compared to treatment B. Peak increases in speed measures and peak decreases in accuracy measures were comparable for treatments A and C. The psychometric performance impairment during the steady-state phase of treatment C was sustained and no acute tolerance development was observed. Baseline variability for all tests was fairly low across treatments. However, there appeared to be a fatigue effect on some of the tests, indicated by slight changes in performance scores for treatment D (placebo). This may be due to the frequency of the testing, as well as the duration for which these tests were performed during each study period.

Statistical comparison of E_{max}^{obs} for number vigilance reaction time showed significant treatment differences, but no significant gender differences. Multiple comparisons revealed that the active treatments (A, B and C) were significantly different from placebo.
Figure 4.14  Immediate Recall Accuracy (Mean ± S.E.) by treatment for IV ethanol study

Figure 4.15  Number vigilance reaction time (Mean ± S.E.) by treatment for IV ethanol study
Figure 4.16  Tracking Mean Error (Mean ± S.E.) by treatment for IV ethanol study

Figure 4.17  Word Recognition Sensitivity (Mean ± S.E.) by treatment for IV ethanol study
Figure 4.18  Word Recognition reaction time (Mean ± S.E.) by treatment for IV ethanol study
(treatment D), but not from each other. Statistical comparison for $E_{\text{min}}$ for word recognition sensitivity also showed significant treatment differences, but no significant gender differences. Multiple comparisons revealed that the active treatments (A, B and C) were significantly different from placebo (treatment D), and that treatments A and B were different from treatment C, but not from each other. Statistical comparison of the other measures, viz. changes in accuracy measures of the immediate word recall and number vigilance tests, changes in mean tracking error of the tracking test and changes in reaction time for the word recognition test revealed significant treatment differences only for the immediate word recall accuracy, with multiple comparisons indicating that the active treatments were significantly different from placebo.

Statistical comparison of $T_{\text{max}}$ or $T_{\text{min}}$ values revealed significant differences for all the primary and secondary measures. Multiple comparisons indicated, in general, that time of peak impairment for treatment A was significantly different from those of treatments B and C.

For all the statistical tests, treatment-by-gender interactions were not significant. Also, the baseline response was not a significant covariate except for the immediate word recall test. The alcohol history (AAAI) and non-responder score were also not significant covariates, indicating that they did not contribute significantly to the overall variability in the response measures. Also, residual analysis for all the comparisons indicated that the distribution of the residuals were not significantly different from a normal distribution, except for the word recognition reaction-time. Therefore, the statistical
analysis was repeated on the log-transformed data, after which the residuals were found to be normally distributed.

The increase in reaction-time for the number vigilance and word recognition tests, decrease in the sensitivity measure of the word recognition test, increase in tracking error and decrease in accuracy of the immediate recall test are consistent with psychometric impairment. Word recognition sensitivity and number vigilance reaction time were the most sensitive measures of the psychometric performance battery completed by the subjects in this study. The measures showed significant treatment-related differences, as well as significant rate-related differences between treatments A and B for the word recognition sensitivity. The impairment in psychometric performance is consistent with other studies evaluating performance impairment following ethanol administration (Evan et al., 1984; Moskowitz et al., 1976; Wittenborn, 1987; van Harten et al., 1992; Fluckiger et al., 1988). Input-rate had a significant effect on the degree of impairment, with the fast-input treatment resulting in greater psychometric impairment than the slow-input treatment. There were no significant gender difference in the psychometric impairment induced by ethanol across treatments in this study.

4.4.3C Impairment Scales

Baseline-corrected response vs. time profiles for the SRI and ORI measures evaluated, including scores for the items HIGH, DRUNK and ALCOHOL EFFECTS on the SRI scale, as well as scores for the items HIGH and DRUNK on the ORI scale are shown in
Appendix L. Response vs. time profiles for the other items on the SRI and ORI scales are not included since they did not show a consistent response across subjects and treatments.

Table 4.17 lists the baseline \( E_0 \), maximum observed response \( E_{\text{max}}^{\text{obs}} \) and time of \( E_{\text{max}}^{\text{obs}} (t_{\text{max}}) \) for each of the SRI and ORI items listed above. Figures 4.19 - 4.23 show the peak changes in the SRI/ORI measures, including scores for the items HIGH, DRUNK and ALCOHOL EFFECTS on the SRI scale, as well as scores for the items HIGH and DRUNK on the ORI scale.

The SRI and ORI scales were very sensitive to the effects of ethanol, with the most sensitive items being HIGH, DRUNK and ALCOHOL EFFECTS on the SRI scale and HIGH and DRUNK on the ORI scale. There were input-related increases in the \( E_{\text{max}}^{\text{obs}} \) for these items, with both fast and slow input treatments showing increases in \( E_{\text{max}}^{\text{obs}} \) from placebo, however the changes in the scores for treatment B (slow input) increased more gradually relative to the scores for treatment A (fast-input). \( E_{\text{max}}^{\text{obs}} \) values for treatment C were consistent with treatment A, indicating rapid achievement of peak impairment scores.

Two of the eight male subjects (subjects 1 and 8) and four of the eight female subjects (subjects 9, 11, 13 and 15) did not show a consistent response on the SRI and ORI scales, even though they showed EEG changes and psychometric impairment consistent with the other subjects. These subjects were classified as "non-responders". In order to incorporate this in the statistical analysis, these subjects were given a "non-responder"
Table 4.17 Pharmacodynamic parameters (Means and %COV) for SRI/ORI measures across treatments and subjects

Table 4.17a SRI - HIGH

<table>
<thead>
<tr>
<th>Treatment</th>
<th>E₀ [-]</th>
<th>Eₘₐₓ [-]</th>
<th>Eₘₐₓ-E₀ [-]</th>
<th>Tₘₐₓ [hr]¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Males</td>
<td>1 (214%)</td>
<td>30 (93%)</td>
<td>30 (96%)</td>
<td>1.0 (0.3-1.7)</td>
</tr>
<tr>
<td>Females</td>
<td>1 (215%)</td>
<td>13 (119%)</td>
<td>12 (113%)</td>
<td>0.6 (0.3-1.7)</td>
</tr>
<tr>
<td>All</td>
<td>1 (226%)</td>
<td>22 (109%)</td>
<td>21 (112%)</td>
<td>1.0 (0.3-1.7)</td>
</tr>
<tr>
<td>B Males</td>
<td>0 (185%)</td>
<td>15 (102%)</td>
<td>14 (105%)</td>
<td>6.0 (3.0-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>4 (240%)</td>
<td>13 (190%)</td>
<td>9 (172%)</td>
<td>3.5 (1.3-8.0)</td>
</tr>
<tr>
<td>All</td>
<td>2 (319%)</td>
<td>14 (142%)</td>
<td>12 (129%)</td>
<td>5.0 (1.3-8.0)</td>
</tr>
<tr>
<td>C Males</td>
<td>0 (283%)</td>
<td>41 (61%)</td>
<td>41 (62%)</td>
<td>2.0 (0.3-6.0)</td>
</tr>
<tr>
<td>Females</td>
<td>2 (283%)</td>
<td>21 (112%)</td>
<td>19 (111%)</td>
<td>0.8 (0.3-3.0)</td>
</tr>
<tr>
<td>All</td>
<td>1 (374%)</td>
<td>31 (83%)</td>
<td>30 (84%)</td>
<td>1.0 (0.3-6.0)</td>
</tr>
<tr>
<td>D Males</td>
<td>1 (138%)</td>
<td>2 (94%)</td>
<td>1 (107%)</td>
<td>0.4 (0.3-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0 (198%)</td>
<td>1 (113%)</td>
<td>1 (107%)</td>
<td>0.3 (0.3-7.0)</td>
</tr>
<tr>
<td>All</td>
<td>1 (159%)</td>
<td>1 (103%)</td>
<td>1 (114%)</td>
<td>0.3 (0.3-11.0)</td>
</tr>
</tbody>
</table>

¹: Tₘₐₓ expressed as Median (range)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [%]</th>
<th>$E_{\text{max}}$ [%]</th>
<th>$E_{\text{max}} - E_0$ [%]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1 (185%)</td>
<td>56 (63%)</td>
<td>55 (64%)</td>
<td>1.0 (0.5-3.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0 (185%)</td>
<td>15 (114%)</td>
<td>15 (116%)</td>
<td>0.6 (0.3-1.7)</td>
</tr>
<tr>
<td>All</td>
<td>0 (192%)</td>
<td>35 (96%)</td>
<td>35 (97%)</td>
<td>0.8 (0.3-1.7)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0 (283%)</td>
<td>25 (98%)</td>
<td>25 (99%)</td>
<td>4.0 (1.3-7.0)</td>
</tr>
<tr>
<td>Females</td>
<td>1 (283%)</td>
<td>7 (103%)</td>
<td>6 (113%)</td>
<td>4.5 (1.3-6.3)</td>
</tr>
<tr>
<td>All</td>
<td>0 (336%)</td>
<td>16 (124%)</td>
<td>16 (128%)</td>
<td>4.0 (1.3-7.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0 (185%)</td>
<td>58 (57%)</td>
<td>57 (58%)</td>
<td>2.5 (0.8-6.3)</td>
</tr>
<tr>
<td>Females</td>
<td>0 (283%)</td>
<td>20 (84%)</td>
<td>20 (85%)</td>
<td>1.3 (0.3-3.0)</td>
</tr>
<tr>
<td>All</td>
<td>0 (215%)</td>
<td>39 (83%)</td>
<td>38 (83%)</td>
<td>1.7 (0.3-6.3)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1 (119%)</td>
<td>3 (118%)</td>
<td>2 (155%)</td>
<td>0.5 (0.3-4.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0 (198%)</td>
<td>1 (95%)</td>
<td>1 (107%)</td>
<td>0.6 (0.3-11.0)</td>
</tr>
<tr>
<td>All</td>
<td>1 (146%)</td>
<td>2 (145%)</td>
<td>1 (177%)</td>
<td>0.5 (0.3-11.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{max}}$ expressed as Median (range)
Table 4.17c  SRI - ALCOHOL EFFECTS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [-]</th>
<th>$E_{\text{max}}$ [-]</th>
<th>$E_{\text{max}}-E_0$ [-]</th>
<th>$T_{\text{max}}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0 (185%)</td>
<td>61 (57%)</td>
<td>60 (57%)</td>
<td>0.9 (0.5-1.7)</td>
</tr>
<tr>
<td>Females</td>
<td>0 (198%)</td>
<td>30 (103%)</td>
<td>29 (105%)</td>
<td>1.0 (0.5-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0 (193%)</td>
<td>45 (78%)</td>
<td>45 (79%)</td>
<td>1.0 (0.5-6.0)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0 (283%)</td>
<td>40 (72%)</td>
<td>39 (74%)</td>
<td>5.0 (1.7-11.0)</td>
</tr>
<tr>
<td>Females</td>
<td>1 (225%)</td>
<td>18 (76%)</td>
<td>18 (80%)</td>
<td>6.0 (1.7-6.3)</td>
</tr>
<tr>
<td>All</td>
<td>0 (250%)</td>
<td>29 (84%)</td>
<td>28 (87%)</td>
<td>5.5 (1.7-11.0)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0 (283%)</td>
<td>69 (44%)</td>
<td>69 (45%)</td>
<td>2.0 (1.0-12.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0 (0%)</td>
<td>32 (69%)</td>
<td>32 (69%)</td>
<td>1.0 (0.5-6.0)</td>
</tr>
<tr>
<td>All</td>
<td>0 (400%)</td>
<td>51 (63%)</td>
<td>50 (64%)</td>
<td>1.0 (0.5-12.0)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1 (151%)</td>
<td>2 (111%)</td>
<td>2 (133%)</td>
<td>0.5 (0.3-9.0)</td>
</tr>
<tr>
<td>Females</td>
<td>0 (185%)</td>
<td>1 (103%)</td>
<td>1 (107%)</td>
<td>1.4 (0.3-9.0)</td>
</tr>
<tr>
<td>All</td>
<td>0 (165%)</td>
<td>2 (112%)</td>
<td>1 (126%)</td>
<td>0.8 (0.3-9.0)</td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{max}}$ expressed as Median (range)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>$E_0$ [-]</th>
<th>$E_{max}$ [-]</th>
<th>$E_{max}-E_0$ [-]</th>
<th>$T_{max}$ [hr]$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0 (0%)</td>
<td>29 (68%)</td>
<td>29 (68%)</td>
<td>1.0 (0.3-1.3)</td>
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<td>23 (72%)</td>
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<tr>
<td><strong>D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.3 (0.3-0.3)</td>
</tr>
<tr>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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</tr>
<tr>
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$^1$: $T_{max}$ expressed as Median (range)
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<th>$E_{\text{max}}-E_0$ [-]</th>
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</tr>
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<td>34 (65%)</td>
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<td></td>
</tr>
<tr>
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<td>30 (53%)</td>
<td>6.0 (5.0-6.3)</td>
</tr>
<tr>
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<td>20 (73%)</td>
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<td>25 (63%)</td>
<td>25 (63%)</td>
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</tr>
<tr>
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<td>33 (63%)</td>
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</tr>
<tr>
<td>Males</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.3 (0.3-0.3)</td>
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<td>0 (0%)</td>
<td>0.3 (0.3-0.3)</td>
</tr>
<tr>
<td>All</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.3 (0.3-0.3)</td>
</tr>
</tbody>
</table>

$^1$: $T_{\text{max}}$ expressed as Median (range)
Figure 4.19  SRI-HIGH Score (Mean ± S.E.) by treatment for IV Ethanol Study

Figure 4.20  SRI-DRUNK Score (Mean ± S.E.) by treatment for IV Ethanol Study
Figure 4.21  SRI-ALCOHOL EFFECTS Score (Mean ± S.E.) by treatment for IV ethanol study

Figure 4.22  ORI-HIGH Score (Mean ± S.E.) by treatment for IV Ethanol Study
Figure 4.23 ORI-DRUNK Score (Mean ± S.E.) by treatment for IV Ethanol Study
score (NR) of 0, while the other subjects ("responders") were given a score of 1. This score was used as a covariate in the statistical analysis.

Statistical comparison of the $E_{\text{max,obs}}$ and $t_{\text{max}}$ revealed significant treatment differences for all the SRI and ORI variables. Multiple comparisons for the $E_{\text{max,obs}}$ values across treatments indicated that all three active treatments (A, B and C) were significantly different from placebo (treatment D), and that treatment B was significantly different from treatments A and C, but treatments A and C were not significantly different from each other. Multiple comparisons for the $t_{\text{max}}$ values indicated that, in general, treatment B was significantly different from treatments A and C.

Statistical analysis also revealed a significant effect of gender for the $E_{\text{max,obs}}$ for the items DRUNK and ALCOHOL EFFECTS on the SRI scale and the item DRUNK on the ORI scale. This indicates that there was a significant gender difference in the magnitude of the change from baseline on these subjective measures of impairment. Females showed a lower degree of subjective impairment than male subjects, as measured by the SRI and ORI scales.

Residuals were found to be significantly different from normal for some of the variables tested. For these variables, the statistical analysis was performed on the rank-transformed data. There were no significant sequence or period effects. The baseline response was not a significant covariate in the analysis except for the $E_{\text{max,obs}}$ for SRI-HIGH. The NR score was a significant covariate for the $E_{\text{max,obs}}$ for SRI-ALCOHOL EFFECTS and ORI-HIGH. There was no significant effect of Alcohol history (AAA) as a covariate in the
statistical analysis, indicating that differences in Alcohol history did not contribute significantly to the differences between treatments and/or gender.

In summary, the SRI and ORI scales provided sensitive measures of the subjective effects of ethanol in this study. The most sensitive items on the scales were HIGH, DRUNK and ALCOHOL EFFECTS, which showed input-rate-related differences. This provided conclusive proof that the rate of input of ethanol is an important determinant of the degree of subjective impairment perceived by the individual, so that fast-input results in a greater degree of impairment perceived by the individual relative to slow input of ethanol. There were also gender differences observed in this study, indicating that females experienced lower degrees of ethanol-induced subjective impairment compared to the males. Since there were some subjects of each gender that were classified as non-responders (2 out of 8 males and 4 out of 8 females), this may be a confounding factor in the interpretation of this observation. Further research would be necessary to prospectively and systematically evaluate the subjective effects of ethanol in responders and non-responders of both genders to conclusively prove a true difference in perceived impairment induced by ethanol between males and females.

4.4.3D PK-PD Correlation and Tolerance Development

In order to evaluate the PK-PD relationship for ethanol, response vs. serum ethanol concentration profiles were plotted for several of the PD measures evaluated. The PD measures that were correlated to serum concentrations included the relative theta power
from the EEG measures, number vigilance reaction time for the PPT battery, and the score on the item "ALCOHOL EFFECTS" on the SRI scales. Response vs. concentration plots for each of these measures are presented by subject and treatment in Appendix M. A review of the plots for baseline-corrected relative theta power vs. serum ethanol concentrations resulted in the following observations:

1) effect-concentration profiles revealed no consistent patterns across subjects or treatments.

2) For treatments A and B, several of the subjects showed an initial transient increase in relative theta power followed by a later sustained decrease. In general, the changes in relative theta power did not appear to be correlated to concentrations for these treatments.

3) For treatment C, some of the subjects showed a transient increase in relative theta power during the initial phase when concentrations were increasing, followed by a decrease in relative theta power. However, these changes did not appear to be correlated with serum ethanol concentrations.

In order to evaluate the time-course of the change in relative theta power during the "steady-state" infusion phase for treatment C, the relative theta power vs. time profile was superimposed on the serum ethanol concentration vs. time profile for each subject. These plots are presented in Appendix N1 and the plot for one representative subject (subject 9) is shown in figure 4.24.

Five of the subjects (subjects 1, 5, 6, 7, 8) show an initial transient increase in relative...
Figure 4.24 Serum ethanol concentration vs. time and relative theta power vs. time for a representative subject (subject 9) for treatment C of IV ethanol study
theta power during the first infusion followed by a later more sustained decrease in relative theta power that appears to return to baseline values at the end of the second infusion. Eight of the subjects (subjects 2, 3, 9, 11, 12, 13, 14, 15) showed only increases in relative theta power during the ethanol infusions that was sustained, in some cases, during the "steady-state" phase of the treatment, and returned to baseline after the end of the second infusion. The other subjects did not show any consistent time-related changes in relative theta power.

In summary, there was no consistent effect-concentration correlation for the EEG measures evaluated.

A review of the plots for baseline-corrected number vigilance reaction-time vs. serum ethanol concentrations resulted in the following observations:

1) increasing concentrations generally were associated with increases in number vigilance reaction time.

2) for treatment A, most of the subjects showed concentration-related increases in reaction-time consistent with psychometric impairment. Only 2 subjects (subjects 5 and 10) showed a small clockwise hysteresis loop with smaller changes in reaction time at later time points (during the declining phase) compared to the relatively larger changes in reaction time at earlier time-points (during increasing concentrations).

3) for treatment B, most of the subjects showed concentration-related increases in reaction-time consistent with psychometric impairment. Only 3 subjects (subjects 1, 12
and 14) showed a small clockwise hysteresis loop with smaller changes in reaction time at later time points (during the declining phase) compared to the relatively larger changes in reaction time at earlier time-points (during increasing concentrations).

4) for treatment C, most of the subjects showed increases in reaction-time with concentration. Only 2 subjects (subjects 2 and 16) showed a small clockwise hysteresis loop with smaller changes occurring at later time-points (during the declining phase) relative to the changes in reaction-time at earlier time-points during increasing concentrations.

In order to evaluate the time-course of the change in number vigilance reaction-time during the "steady-state" infusion phase for treatment C, the reaction-time vs. time profile was superimposed on the serum ethanol concentration vs. time profile for each subject. These plots are presented in Appendix N2 and the plot for one representative subject (subject 9) is shown in figure 4.25. As the plots indicate, reaction-time increased with an increase in serum concentration during the first hour (Infusion I). During the next five hours (Infusion II), the increase in reaction-time was sustained and followed the serum concentration-time profile, with no acute tolerance development. The response-time profile also followed the serum concentration-time profile during the declining phase after the end of Infusion II. This was observed for all subjects except subject number 7, for whom the response returned to baseline faster than the serum concentration.

In summary, both fast and slow input treatments (A and B) showed psychometric impairment, as measured by increases in reaction-time, consistent with serum ethanol...
Figure 4.25 Serum ethanol concentration vs. time and number vigilance reaction time vs. time for a representative subject (subject 9) for treatment C of IV ethanol study.
concentration. Treatment C showed impairment that was correlated with concentration and which was sustained during the "steady-state" phase of the treatment, indicating that there was concentration-related impairment with no acute tolerance development to the psychometric impairment effects of ethanol.

A review of the plots for baseline-corrected SRI-Alcohol Effect Scores vs. serum ethanol concentrations resulted in the following observations:

1) there was a consistent increase in SRI scores with serum concentrations at earlier time points, i.e., higher concentrations were associated with a higher degree of subjective impairment as assessed by the SRI scores. This was observed during the ascending concentration phase for all treatments.

2) For treatments A and B, at later time-points, the effect appeared to decline faster than serum concentrations resulting in the presence of clockwise hysteresis loops in the effect vs. concentration profiles. Clockwise hysteresis loops were observed in 10 of the 16 subjects for treatment A, in 9 of the 16 subjects for treatment B, and in 10 out of 16 subjects for treatment C. Figure 4.26 shows the SRI-ALCOHOL EFFECT vs. concentration profiles by treatment for a representative subject (subject 3).

3) Two subjects in treatment A (subjects 8 and 15), three subjects in treatment B (subjects 1, 2 and 8), and two subjects in treatment C (subjects 2 and 8) showed inconsistent changes in SRI-ALCOHOL EFFECTS scores with serum ethanol concentration.
Figure 4.26 SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration by treatment for a representative subject (subject 9) for IV ethanol study
4) For treatment C, the serum ethanol concentration vs. time and the SRI-ALCOHOL EFFECTS score vs. time profiles were plotted on the same time scale to compare the time course of the changes in concentration and effect. These plots are presented, by subject, in Appendix N3. The plot for a representative subject (subject 9) is shown in figure 4.27. Evaluation of these profiles revealed that during the first hour (Infusion I), the SRI scores increased with concentration. However, during the "steady state" phase (Infusion II), SRI-ALCOHOL EFFECT scores were not sustained, even though serum concentrations remained fairly constant. This was observed for 14 of the 16 subjects and is consistent with acute pharmacodynamic tolerance development to the subjective effects of ethanol.

Follow-up analysis for other items of the SRI scale, including the items "HIGH" and "DRUNK", as well as for the ORI scale items "HIGH" and "DRUNK" revealed the same pattern of initial concentration-related impairment and the presence of clockwise hysteresis, although the most profound effect was observed for the SRI-Alcohol Effects scores.

In order to evaluate the effect of the rate and extent of ethanol exposure on the pharmacodynamics and the development of acute tolerance, the observed effect at the time corresponding to the peak concentration ($E_{t_{max}}$) was plotted as a function of the $C_{max}$, and as a function of the partial area under the concentration-time curve until the end of the infusion for that treatment ($AUC_{t_{max}}$). The $AUC_{t_{max}}$ provides a measure of the overall exposure to ethanol. These plots were made for the relative theta power, number
Figure 4.27 Serum ethanol concentration vs. time and SRI-ALCOHOL EFFECTS score vs time for a representative subject (subject 9) for treatment C of IV ethanol study
vigilance reaction time, and the SRI-ALCOHOL EFFECTS (SRI-AE) score and are presented in figures 4.28 and 4.29.

An evaluation of the plots of $E_{\text{r}1\text{mA}}$ vs. $C_{\text{m}1\text{mA}}$ reveal that the mean SRI-AE score was lower for the slow-input treatment (treatment B), as well as for treatment C at the end of the infusion (C6), when compared with the fast-input treatment (treatment A), even though the mean $C_{\text{max}}$ estimates were similar across treatments. This plot also demonstrated the decrease in effect from the end of the first infusion (C1) to the end of the second infusion (C6) for treatment C, indicating that the acute tolerance was input-rate-related. The plots for number vigilance reaction time and relative theta power did not show this pattern, indicating the lack of acute tolerance development to these effects of ethanol.

The plots of $E_{\text{r}1\text{max}}$ vs. $\text{AUC}_{\text{r}1\text{max}}$ revealed that the SRI-AE scores decreased as the $\text{AUC}_{\text{r}1\text{max}}$ increased from treatment A to B to C. This was not observed for the number vigilance reaction time or relative theta power, and indicates that the acute tolerance development to the subjective effects of ethanol was exposure-related.

These findings are consistent with the development of acute, exposure-related tolerance development to the subjective impairment effects of ethanol. This means that the degree of subjective impairment perceived by the subject was higher during the ascending limb of the ethanol concentration-time curve than at similar concentrations during the descending limb of the ethanol concentration-time curve. During the drug elimination phase, the effect declined faster than drug concentrations such that subjects did not
Figure 4.28 Mean (S.E.) Effect at Tmax [E(Tmax)] vs. Mean (S.E.) Cmax by treatment for SRI-ALCOHOL EFFECTS Score, Number Vigilance Reaction Time and Relative Theta Power. [A: Trt A; B: Trt B; C1: Trt C at 1 hr; C2: Trt C at 6 hrs]
Figure 4.29 Mean (S.E.) Effect at Tmax (E(Tmax)) vs. Mean (S.E.) AUC(Tmax) by treatment for SRI-ALCOHOL EFFECTS Score, Number Vigilance Reaction Time and Relative Theta Power. [A: Trt A; B: Trt B; C1: Trt C at 1 hr; C2: Trt C at 6 hrs]
perceive themselves to be impaired even though they had significant measurable concentrations of ethanol and exhibited psychometric impairment as measured by the test battery. This means that there was a temporal disparity between perceived impairment and performance impairment during the descending limb of the ethanol concentration-time curve. Also, treatment C allowed the evaluation of the time course of this tolerance development when concentrations of ethanol are sustained at steady-state. The data from treatment C are also consistent with acute exposure-related tolerance development to the subjective effects of ethanol during the period when concentrations are at "steady-state".

These findings are consistent with the results of other studies evaluating the subjective and objective impairment induced by ethanol, which conclude that objective measures of impairment do not show acute tolerance development, while subjective measures of impairment do show consistent development of acute tolerance (Radlow and Hurst, 1985; Jones et al., 1972; Kaplan et al., 1985; Gengo et al., 1990). Results of this study also indicate that the tolerance is input rate-related. Although there was a gender difference in the degree of subjective impairment induced by ethanol, there did not appear to be a gender difference in the development of acute tolerance to ethanol.

4.4.3E PK-PD Modelling of the Acute Tolerance Development to Subjective Effects of Ethanol

A PK-PD model was developed to describe the tolerance development to the subjective
impairment following intravenous ethanol administration. The SRI-ALCOHOL EFFECTS (SRI-AE) measure was selected since it was shown to be the most sensitive subjective measure of ethanol's effect. The SRI-AE and concentration data were fit individually for each subject and treatment. The data sets were constructed in a spreadsheet (Microsoft Excel version 5, Microsoft Inc., WA) and directly imported into the program used for the fitting, Scientist (version 2.0 for Windows, MicroMath Inc., Salt Lake City, UT).

**Model Development:** The model used to fit the individual effect-concentration data was similar to the final model used in the oral ethanol study. The final model used in this study was a two-compartment PK model with capacity-limited elimination; the central compartment was linked to the PD model which related concentration to the primary (direct) effect using the classical $E_{\text{max}}$ model (Holford, 1992) (see figure 4.30). The direct effect of the drug is the driving force that activates the tolerance mechanism, implying that the tolerance development is a result of compensatory feedback mechanisms that are produced to counter-regulate the direct effect.

The direct effect ($E_D$) was modelled as:

$$E_D = \frac{E_{\text{max}} \cdot C^n}{EC_{50}^a + C^a}$$

where $E_{\text{max}}$ is the maximum effect, $EC_{50}$ is the serum concentration required to produce an effect that is 50% of the maximum effect, $n$ is the Hill coefficient, reflecting the steepness of the concentration-effect relationship, and $C$ is the serum ethanol
Figure 4.30 Final PK-PD model for acute tolerance development to subjective effects of intravenous ethanol
concentration.

The feedback effect ($E_{FB}$) was modelled using two rate constants ($k_{on}$ and $k_{off}$). The rate (and extent) of negative feedback is proportional to the magnitude of the direct effect of the drug, i.e., the greater the primary (direct) effect, the greater is the rate of negative feedback. The differential equation for the feedback effect was:

$$E_{FB}' = k_{on}E - k_{off}E_{FB}$$

The net observed effect $E$ was calculated as

$$E = E_d - E_{FB}$$

The final PD model had five parameters: $E_{max}$, $EC_{50}$, $n$, $k_{on}$ and $k_{off}$.

This model was coded in Scientist. Initial parameter estimates for the PD parameters were obtained from simulations using different values of the parameters. The model was fit to the individual concentration-effect (SRI-AE) data. The PK parameters, $V_{max}$, $K_m$, $k_{12}$, $k_{21}$ and $V_{dss}$ were fixed to the final estimates obtained during the PK modelling of the data (done previously, see section 3.4.2). Weights of 1 and $1/y$ were evaluated. Goodness of fit was assessed by evaluating the coefficient of determination ($r^2$), Model Selection Criteria (MSC), parameter estimates and their standard deviations, residual analysis, and visual observation of the observed points and fitted effect-time profiles as well as observed and fitted hysteresis loops (in effect-concentration plots).

Results: Individual fits were determined to be acceptable based on goodness of fit criteria described above. Weights of $1/y$ did not appear to improve the fit. The coefficients of determination for the final model ranged from 0.851 to 0.996, and MSC
ranged from 1.62 to 5.11. Parameter estimates for seven of the 48 data-sets (treatment B for subject 1, treatments B and C for subject 2, treatments A, B and C for subject 8, and treatment A for subject 15) could not be obtained due to inconsistent effect-time profiles and inability of the model to adequately fit the profiles.

Table 4.18 lists the final parameter estimates for the model parameters, $E_{\text{max}}$, $EC_{50}$, n, $k_{\text{on}}$ and $k_{\text{off}}$. Figure 4.31 shows the observed values and fitted curves for the SRI-AE score vs. concentration plots by treatment for a representative subject (subject 3).

As table 4.18 indicates, the estimates for all the parameters did not appear to be different across treatment, however there was a trend toward lower $E_{\text{max}}$ values for female subjects compared to the male subjects across treatments (Mean ± S.D. $E_{\text{max}}$ for male subjects: 122 ± 79, and for female subjects: 55 ± 56). Also, the inter-individual variability in the parameter estimates was quite high, as indicated by the %COVs in table 4.18.

Table 4.18 also lists the mean parameter estimates for responders and non-responders by treatment and across treatments for male and female subjects. Table 4.18 demonstrates that there were no differences in parameter values between responders and non-responders across treatments, except for the $E_{\text{max}}$ which, on average was about 4-fold higher for responders compared to the non-responders. This was seen across treatments for both male and female subjects. Figure 4.32 illustrates the differences between male and female responders and non-responders with respect to their mean (± S.E.) $E_{\text{max}}$ estimates by treatment.

The mean (± S.D.) estimate for $EC_{50}$ was 748 (± 333) mg/L across treatments and
Figure 4.18 Model parameters (means and %COV) by treatment for PK-PD model of subjective effects of intravenous ethanol (Males: n=8, Females: n=8)

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<th>EC$_{50}$ [mg/L]</th>
<th>n [-]</th>
<th>$k_{on}$ [hr$^{-1}$]</th>
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<td>NR$^2$</td>
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<td><strong>A</strong></td>
<td></td>
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<td>0.6 (42%)</td>
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<td>0.7 (57%)</td>
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<td>Males</td>
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<tr>
<td>Across Trts</td>
<td>133 (58%)</td>
<td>34 (51%)</td>
<td>692 (28%)</td>
<td>2.6 (17%)</td>
<td>0.6 (72%)</td>
</tr>
<tr>
<td>Males</td>
<td>84 (76%)</td>
<td>23 (56%)</td>
<td>792 (52%)</td>
<td>2.8 (35%)</td>
<td>0.8 (86%)</td>
</tr>
<tr>
<td>Females</td>
<td>112 (66%)</td>
<td>25 (54%)</td>
<td>748 (45%)</td>
<td>2.7 (29%)</td>
<td>0.7 (84%)</td>
</tr>
</tbody>
</table>

1: R = Responder  2: NR = Non-Responder  3: Unable to fit adequately for both NR males
Figure 4.31 SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for a representative subject (subject 9) for IV ethanol study.
Figure 4.32 PK-PD model estimates for \( E_{\text{max}} \) for male (M) and female (F) responders (R) and non-responders (NR) by treatment for IV ethanol study.
subjects. The mean (± S.D.) estimate for n was 2.7 (± 0.6) across treatments and subjects. The mean (± S.D.) estimate for \( k_{on} \) was 0.7 (± 0.6) hr\(^{-1} \) across treatments and subjects. This translates to an onset half-life of tolerance (\( t_{1/2on} \)) of 1.5 hrs. The mean (± S.D.) estimate for \( k_{off} \) was 1.3 (± 0.6) hr\(^{-1} \) across treatments and subjects. This translates to an offset half-life of tolerance (\( t_{1/2off} \)) of 0.6 hrs.

The PK-PD model used in this study was similar to the PK-PD model used in the oral study, the only exception being that this study used the sigmoidal \( E_{max} \) model to characterize the relationship between the direct effect and the serum ethanol concentration, while the oral study used a linear model to characterize this relationship. This was primarily because higher concentrations of ethanol and higher magnitudes of subjective impairment were achieved in this study, resulting in a levelling off of the effect-concentration relationship, thus necessitating the use of the \( E_{max} \) model in this study compared to the oral ethanol study. The ratio of \( E_{max} \) to EC\(_{50} \) was calculated using the mean values for responders and non-responders. The ratio was determined to be 0.15 for responders and 0.03 for non-responders. These values are in the same range as the mean estimates for the parameter S in the model used in the oral ethanol study, and indicates that the ratio may be used as a measure of the sensitivity to ethanol. The onset and offset rate constants did not appear to be different between the two studies.

One observation from the PK-PD modelling is that the model predicts a rebound effect, i.e., the net effect falls below the baseline. This is cannot be explained by the data since the impairment scales do not permit measurement of effects below the baseline (zero).
In summary, the feedback model of tolerance was adequately fit to the individual effect-concentration data from this study. The estimated $E_{\text{max}}$ for responders was about four-fold higher than for the non-responders, while the estimates for the other parameters did not differ between the two groups. The parameter estimates were associated with fairly high degrees of inter-individual variability, probably reflecting individual differences in the subjective effects of ethanol as well as individual differences in acute tolerance development to these effects of ethanol.

4.4.3F Correlation of Pharmacodynamic Measures

Since one of the aims of this study was to assess the relationship between the EEG changes and changes in PP as well as the relationship between the EEG changes and SRI, linear regression of the $E_{\text{min}}$ for relative theta power on the $E_{\text{max}}$ for number vigilance reaction time, and on the $E_{\text{max}}$ for SRI-ALCOHOL EFFECTS score were performed individually to assess the significance of the relationship between the EEG changes and changes in PP and SRI. Since this was a crossover study, the regression was only performed for observations for treatment A, since the greatest change would be expected for treatment A.

Figure 4.33 shows the plot of $E_{\text{min}}$ for relative theta power vs. the $E_{\text{max}}$ for number vigilance reaction time for treatment A. The coefficient of determination was 0.028, which was not significant, indicating that there did not appear to be a significant correlation between these two objective measures.
Figure 4.33 Baseline-corrected peak change in relative theta power vs. peak change in number vigilance reaction time for treatment A for IV ethanol study.

Figure 4.34 Baseline-corrected peak change in relative theta power vs. peak change in SRI-ALCOHOL EFFECTS score for treatment A for IV ethanol study.
Figure 4.34 shows the plot of $E_{\text{min}}^{\text{obs}}$ for relative theta power vs. the $E_{\text{max}}^{\text{obs}}$ for SRI-Alcohol Effects score for treatment A. As figure 4.34 illustrates, there did not appear to be a consistent relationship between the two variables. Also, the coefficient of determination was 0.190. This indicated that there did not appear to be a relationship between changes in EEG measures and changes in subjective impairment measures. Thus, it appears from comparison of the regressions of EEG measures individually on psychometric performance measures and on subjective impairment measures, that the EEG changes are not related to PPT or to the subject-rated impairment measures. It should be noted that neither of the associations were statistically significant, and that these comparisons were only performed for peak changes in these measures, and that the comparisons were only done for one treatment.

4.5 CONCLUSIONS

The following conclusions can be made from the intravenous ethanol study which was designed to evaluate the effect of input-rate and degree of systemic exposure on the PK-PD relationship for ethanol and development of acute tolerance to the pharmacological effects of ethanol in healthy male and female subjects. Table 4.19 lists the results of the inferential statistical analysis performed for the primary PK and PD measures evaluated in this study.

1) Ethanol, after intravenous administration, follows non-linear, capacity-limited pharmacokinetics. The observed serum ethanol concentration vs. time profiles were best
Table 4.19. Summary of Inferential Statistical Analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Treatment (Trt) Effect</th>
<th>Multiple comparisons for Trt Effect</th>
<th>Gender Effect</th>
<th>Trt-by-Gender Interaction</th>
<th>Baseline as covariate</th>
<th>NR score as covariate</th>
<th>AAAI as covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{\text{max}}$</td>
<td>$p=0.003$</td>
<td>$A \neq C, B \neq C$</td>
<td>NS$^1$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$K_{m}$</td>
<td>NS</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$V_{\text{dss}}$</td>
<td>$p=0.047$</td>
<td>$A \neq C$</td>
<td>$p=0.0015$</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pharmacodynamic Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rel. Theta Power</td>
<td>$E_0 - E_{\text{min}}$</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_0 - E_{\text{min}}$</td>
<td></td>
<td>$p=0.042$</td>
<td>$A \neq B, A \neq C$</td>
<td>NS</td>
<td>NS</td>
<td>$p=0.000$</td>
<td>NS</td>
</tr>
<tr>
<td>$t_{\text{min}}$</td>
<td></td>
<td>$p=0.042$</td>
<td>$A \neq B, A \neq C$</td>
<td>NS</td>
<td>NS</td>
<td>$p=0.046$</td>
<td>NS</td>
</tr>
<tr>
<td>Rel. Alpha Power</td>
<td>$E_0 - E_{\text{min}}$</td>
<td>by gender: M: $p=0.006$</td>
<td>$A, B, C \neq D$</td>
<td>$p=0.034$</td>
<td>$p=0.000$</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>$E_0 - E_{\text{min}}$</td>
<td></td>
<td>F:NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{\text{min}}$</td>
<td></td>
<td>$p=0.025$</td>
<td>$A \neq B, B \neq D$</td>
<td>NS</td>
<td>NS</td>
<td>$p=0.017$</td>
<td>$p=0.049$</td>
</tr>
<tr>
<td>NV RT</td>
<td>$E_{\text{max}} - E_0$</td>
<td>$p=0.000$</td>
<td>$A, B, C \neq D$</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>$p=0.046$</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td></td>
<td>$p=0.004$</td>
<td>$A \neq B, A \neq C$</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Measure</td>
<td>Treatment (Trt) Effect</td>
<td>Multiple comparisons for Trt Effect</td>
<td>Gender Effect</td>
<td>Trt-by-Gender Interaction</td>
<td>Baseline as covariate</td>
<td>NR score as covariate</td>
<td>AAAI as covariate</td>
</tr>
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<td>----------------------</td>
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</tr>
<tr>
<td>WR Sensitivity</td>
<td>p=0.000</td>
<td>A, B ≠ C</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
<tr>
<td>E₀⁻Eₘᵢₙ</td>
<td>p=0.000</td>
<td>A, B ≠ C, A, C ≠ D</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>tₘᵢₙ</td>
<td>p=0.004</td>
<td>A ≠ B, A ≠ D</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SRI-Drunk</td>
<td>p=0.000</td>
<td>A ≠ B, B ≠ C</td>
<td>p=0.011</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Eₘₐₓ⁻E₀</td>
<td>p=0.000</td>
<td>A, B, C ≠ D</td>
<td>p=0.011</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>tₘₐₓ</td>
<td>p=0.000</td>
<td>B ≠ A, C, D</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SRI-Alcohol Effects</td>
<td>p=0.000</td>
<td>B ≠ C</td>
<td>p=0.034</td>
<td>NS</td>
<td>NS</td>
<td>p=0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Eₘₐₓ⁻E₀</td>
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<td>A, B, C ≠ D</td>
<td>p=0.034</td>
<td>NS</td>
<td>NS</td>
<td>p=0.002</td>
<td>NS</td>
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<tr>
<td>tₘₐₓ</td>
<td>p=0.000</td>
<td>A, C, D ≠ B</td>
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<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
<tr>
<td>ORI-Drunk</td>
<td>p=0.000</td>
<td>A ≠ B, B ≠ C</td>
<td>p=0.008</td>
<td>NS</td>
<td>p=0.030</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Eₘₐₓ⁻E₀</td>
<td>p=0.000</td>
<td>A ≠ B, B ≠ C</td>
<td>p=0.008</td>
<td>NS</td>
<td>p=0.030</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>tₘₐₓ</td>
<td>p=0.000</td>
<td>A ≠ B, C, D</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline as covariate</td>
<td></td>
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<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NR score as covariate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>AAAI as covariate</td>
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<td></td>
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</tr>
</tbody>
</table>

1: NS = not significant
described by a two-compartment model with zero-order input into the central compartment, first-order inter-compartmental rate constants, and capacity-limited elimination. The intrinsic PK parameters estimated for ethanol were $V_{\text{max}}$, $K_m$, $k_{12}$, $k_{21}$ and $V_{ds}$. The mean ($\pm$ S.D.) $V_{\text{max}}$ was 349 ($\pm$ 75) mg/L/hr across subjects and treatments; the mean ($\pm$ S.D.) $K_m$ was 252 ($\pm$ 83) mg/L across subjects and treatments; the mean $\pm$ SD $V_{ds}$ was 51 ($\pm$ 9) L across treatments for male subjects, and 38 ($\pm$ 8) L across treatments for female subjects. The mean ($\pm$ S.D.) $k_{12}$ was 0.92 ($\pm$ 0.40) hr$^{-1}$ across subjects and treatments and the mean ($\pm$ S.D.) $k_{21}$ was 2.15 ($\pm$ 1.4) hr$^{-1}$ across subjects and treatments. This corresponds to a distribution half-life of around 0.22 hrs (or around 14 minutes). There was a significant difference in $V_{ds}$ for ethanol between males and females that appeared to be related to differences in their body weight. There were no differences in the elimination PK parameters between males and females observed in this study. The intrinsic PK parameters were independent of input-rate and degree of exposure, but were associated with considerable inter-individual variability. Inter-individual variability was higher than inter-individual variability for all the intrinsic PK parameters. The PK parameters estimated in this study are consistent with previously reported PK parameters for intravenous ethanol (Rangno et al., 1986, Wilkinson et al., 1977, Holford, 1987).

2) Ethanol induced changes in measures of psychometric impairment, as measured by the CDR battery. Word recognition sensitivity and number vigilance reaction time were the most sensitive measures showing significant treatment-related differences. Input-
rate was a significant determinant of the degree of impairment induced by ethanol, with fast input resulting in a higher degree of psychometric impairment than the slow input. The ethanol-induced psychometric impairment appeared to be correlated with serum ethanol concentrations, although a clear quantitative relationship could not be established. Psychometric impairment was sustained during the period when ethanol levels were maintained constant indicating that there was no exposure-related acute tolerance to the psychometric effects of ethanol.

3) EEG measures also showed some ethanol-induced changes, although they were associated with a large degree of inter-individual variability. In general, there was a transient increase in EEG power in the delta band along with corresponding decreases in theta and fast EEG bands (alpha and beta) consistent with slowing of the EEG following ethanol administration. The EEG measures showed input-rate-related differences. Gender differences were observed in the EEG response to ethanol in that female subjects generally showed a lower magnitude of EEG effect, mainly in the decrease in theta and alpha power compared to the male subjects, despite achieving similar concentrations. There was no apparent relationship between ethanol-induced changes in EEG measures and serum ethanol concentrations. Also, there did not appear to be any acute tolerance development to the EEG effects of ethanol observed across treatments and subjects.

4) Ethanol induced significant treatment-related changes in measures of subjective impairment. The SRI and ORI scales proved to be the most sensitive measures of
ethanol's effect. The subjective measures showed input-rate-related changes following intravenous ethanol administration, with the fast-input treatment showing a greater degree of subjective impairment than the slow-input treatment across subjects.

5) There was significant acute, exposure-related tolerance development to the subjective impairment (as measured by the SRI/ORI scales) induced by ethanol. The degree of subjective impairment perceived by the subjects was higher during the ascending limb of the serum-ethanol concentration-time profile than at similar concentrations during the descending limb of the serum ethanol concentration-time profile. Also, during the steady-state infusion for treatment C, subjective responses were not sustained and showed a premature return to baseline, even though concentrations were fairly constant.

The tolerance development could be characterized by a PK-PD model incorporating tolerance as a compensatory feedback mechanism to the direct impairment effect of the drug. Acute tolerance development was not observed for the psychometric performance measures or the EEG measures, indicating a temporal disparity between the perceived and performance impairment induced by ethanol.

6) Two of the 8 male subjects and 4 of the 8 female subjects in the study were classified as "non-responders" based on their lack of subjective response to ethanol administration, even though they demonstrated consistent psychometric impairment and EEG changes.

7) The EEG changes were not correlated to the psychometric impairment or to the
subjective impairment induced by ethanol.
CHAPTER 5
OVERALL CONCLUSIONS

The primary objective of this research was to test the following hypotheses:
1) the rate and degree of ethanol exposure (oral and intravenous) in normal healthy males and females affect the PK and PD of ethanol in a non-linear fashion; 2) the EEG changes after ethanol administration correlate with changes in psychometric performance and subject-rated impairment, as well as serum ethanol concentrations; and 3) acute tolerance develops to the subjective effects of ethanol which is not reflected in changes in EEG activity or psychometric performance.

This research was conducted in two parts: Part I was a pilot study in 6 healthy male subjects to evaluate the effect of dose and dose-rate on the PK and subjective and objective measures of impairment following oral administration of ethanol. Part II was a concentration-controlled, crossover study in 16 healthy subjects (8 males and 8 females) to evaluate the effect of input-rate and degree of systemic exposure on the PK and subjective and objective measures of impairment as well as tolerance development to these measures following intravenous administration of ethanol.

Based on the results obtained in the studies, the following conclusions can be made
regarding the primary objectives:

1) Ethanol, after oral and intravenous administration, follows non-linear, capacity-limited pharmacokinetics. Intrinsic PK parameters, $V_{\text{max}}$, $K_m$ and $V_d$ (or $V_{dss}$) were independent of dose and input-rate, but were associated with fairly high degrees of inter-individual variability. Intra-individual variability was lower than inter-individual variability for the PK parameters.

2) Ethanol, after oral and intravenous administration, induced a transient impairment in psychometric performance. The degree of impairment in psychometric performance appeared to be dose-related as well as input-rate-related (observed in the IV study, but not in the oral study), however, there was a large degree of variability in psychometric impairment induced by ethanol between individuals. The psychometric impairment appeared to be correlated with serum ethanol concentrations, although a clear quantitative relationship could not be established. This may be partly because the magnitude of the changes in psychometric measures was only about 50% from baseline.

3) Ethanol, after oral and intravenous administrations, induced transient changes in EEG activity. The primary effects on the EEG were an increase in EEG power and a generalized slowing of the EEG following ethanol administration. There was, however, a large degree of inter-individual variability in the EEG measures, both at baseline as well as in response to ethanol. The changes in EEG activity following ethanol appeared to be dose-related, as well as input-rate-related, however, a clear quantitative relationship between the EEG changes and serum ethanol concentrations could not be established.
4) Ethanol, after oral and intravenous administration, induced transient changes in measures of subjective impairment. The subjective impairment following ethanol administration was dose-related and input-rate-related and correlated with serum ethanol concentrations across treatments. A subset of subjects (2 out of 6 males in the oral ethanol study, and 2 out of 8 males and 4 out of 8 female subjects in the intravenous study) were classified as "non-responders" based on their lack of subjective response to ethanol, despite serum ethanol concentrations, psychometric impairment and EEG changes that were comparable with the other subjects.

5) There was significant, exposure-related acute tolerance development to the subjective effects of ethanol observed following oral and intravenous administration of different doses at different rates and for different degrees of exposure of ethanol. The acute tolerance development to the subjective effects of ethanol was characterized by a PK-PD model incorporating tolerance as a compensatory feedback mechanism to counter-regulate the direct subjective impairment effect of the drug. Acute tolerance was not observed for the psychometric impairment or changes in EEG activity, indicating that there was a temporal disparity between objective impairment and subjective impairment following ethanol administration.

6) The changes in EEG activity were not correlated with the psychometric impairment or with the subjective impairment following ethanol administration.

7) There was a significant difference observed in the peak concentrations achieved following intravenous ethanol administration, as well as the volume of distribution for
ethanol between male and female subjects. This gender difference may be attributed to differences in body weight and body water content between males and females. There was also a significant gender difference observed with respect to the magnitude of subjective impairment induced by intravenous ethanol, with females showing a lower degree of ethanol induced-subjective impairment, despite achieving similar concentrations in the concentration-controlled study and despite demonstrating similar degrees of psychometric impairment and EEG changes. The gender difference in subjective impairment may be partly confounded by the larger proportion of female "non-responders" compared to the proportion of male "non-responders" in the intravenous ethanol study.

The intravenous ethanol study was unique in its design since it involved the development of an experimental paradigm to study the development of acute tolerance to ethanol's effects. This paradigm involved the evaluation of tolerance development following the administration of IV ethanol infusions at different rates to achieve and maintain a given target concentration (1000 mg/L) for different durations of exposure. Due to the fairly large inter-individual variability in ethanol pharmacokinetics, the infusion-rates were individualized for each subject, based on his/her individual PK parameters estimated from data obtained following a PK screen where a test dose of ethanol was administered as a 1-hour infusion to each subject. A dosing algorithm was developed to calculate the individualized infusion rates for each subject for the concentration-controlled phase of the
study. The results indicated that adequate concentration control was achieved for all subjects and treatments. The PK screen and dose individualization incorporated the PK variability in the achievement of serum ethanol concentrations that were precise and accurate with respect to the target concentrations. This paradigm can be used to evaluate the development of acute tolerance to the effects of ethanol for other measures of ethanol's effects, as well as to compare the tolerance development to the effects of ethanol in different populations of subjects (for e.g., healthy elderly volunteers, alcoholics etc.). This paradigm can also be used to evaluate the development of acute tolerance for other drugs. The necessity of a PK screen for other drugs would depend on the degree of variability in the PK for that drug, nevertheless, this approach would allow the evaluation and modelling of the acute tolerance development for these drugs.
PHARMACOKINETICS AND PHARMACODYNAMICS OF ETHANOL IN HEALTHY VOLUNTEERS: EFFECT OF INPUT-RATE AND DEGREE OF ETHANOL EXPOSURE ON SUBJECTIVE AND OBJECTIVE MEASURES OF IMPAIRMENT

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

by

Vijay A. Ramchandani
B.Pharm.Sc. Bombay University (Bombay, India), 1990

DIRECTOR: Jürgen Venitz, M.D., Ph.D., Associate Professor, Department of Pharmacy and Pharmaceutics

Virginia Commonwealth University
Richmond, Virginia
August 1996
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Wesnes K, Simpson P, Christmas L; The assessment of human information-processing...


APPENDIX A

Protocol and Informed Consent Form for oral ethanol study
Pharmacokinetic-Pharmacodynamic Relationship for Ethanol in Healthy Male Subjects. Assessment of Electroencephalography (EEG), Psychometric Tests and Mood Scales. Effect of Dose and Rate of Ethanol Ingestion.

INVESTIGATORS:
Principal Investigator:
Jürgen Venitz, M.D., Ph.D.
Co-Investigators:
Vijay A. Ramchandani, B. Pharm. Sc. (Bombay, India)
Mark Johns, M.D.

HYPOTHESIS AND SPECIFIC AIMS:

Hypothesis
The hypotheses guiding this research project are that 1) Ethanol induces changes in the electroencephalogram (EEG) that can be used as a surrogate measure to assess alcohol-induced CNS effects; and 2) the rate of alcohol exposure in normal healthy males affects the pharmacokinetics and pharmacodynamics of ethanol in a non-linear fashion.

Specific Aims
The aim of this study is to investigate the pharmacokinetics and pharmacodynamics of ethyl alcohol. The study will assess the changes in the electroencephalogram (EEG) after administration of ethanol as well as changes in performance on psychometric tests and subjective changes in mood. The study will also examine the relationship between EEG changes and 1) serum ethanol concentrations, 2) psychometric performance and 3) subjective mood scales. The study will also evaluate the effect of different rates of oral alcohol administration on the pharmacokinetics and pharmacologic effects of ethanol as measured by the EEG, psychometric performance and subjective measures.

BACKGROUND AND SIGNIFICANCE:

Introduction
Ethanol is probably the most widely used drug in the world. It is commonly self-prescribed rather than prescribed by a clinician and the dose determined either by tradition, social context or the achievement of a pharmacological end-point (1). Almost no other substance has been as comprehensively investigated as ethanol, not only because it is one of the oldest and most ubiquitous abused "drugs" in human history, but also because of its unique dynamic and kinetic behavior (2). Although considered at one time (in the Middle Ages) as the elixir of life, it is now recognized that the therapeutic value of ethanol is extremely limited and that chronic ingestion of excessive amounts is a major social and medical problem (3).
Pharmacokinetics
Ethanol is unusual among drugs in several aspects of its pharmacokinetics. Particularly striking are the great biological inter-subject variabilities in alcohol consumption tolerance and in alcohol elimination, in the pattern of short-term fluctuations from the trend line of the time course of the blood alcohol concentrations and in the partitioning of alcohol between the blood and other body fluids and tissues even at equilibrium (4).

The pharmacokinetics of ethanol has been studied fairly extensively (5,6,7,8). When given orally, it is almost completely absorbed passively from the small intestine. The concentration of alcohol ingested is a determinant of its absorption rate. This is most readily explained by an inhibitory action on gastric emptying (1). Ethanol distributes into total body water and no protein binding has been reported.

Elimination of ethanol occurs primarily through enzymatic oxidation by alcohol dehydrogenase to acetaldehyde in the liver with minute amounts being excreted in the breath (0.7%), sweat (0.1%), and urine (0.3%) (1). The overall elimination process can be described by a capacity-limited model similar to the Michaelis-Menten model for enzyme kinetics first proposed by Lunquist and Wolthers (9,10). The use of the zero-order model of Widmark (11) has been widespread in the past although the limitations of this model have been known for a long time (1).

The alcohol concentration-time profile depends on a number of factors including the dose (10,12,13), the type of alcoholic beverage and the rate of drinking (4,14), the consumption of a meal as well as the composition of the meal (15), sex and body composition (16,17).

In this study, two doses, 0.3 g/kg body weight (low dose corresponding to about 2 drinks of 80 proof vodka) and 0.6 g/kg body weight (moderate dose corresponding to about 4 drinks of 80 proof vodka) will be administered. Based on simulations using a one-compartment model with first order input and capacity-limited elimination, the moderate dose is expected to yield peak serum concentrations close to the legal limit for alcohol (0.1 mg%) (18). To study the effect of rate of drinking, the doses will be administered at two different rates: 1) over 20 minutes to simulate a bolus input, and 2) over 50 minutes to simulate constant rate input.

Differences in pharmacokinetics as well as in psychometric performance and mood states have been observed in males and females (16,17,19). Therefore to reduce variability in response, the study will be conducted in healthy normal male subjects only.

Pharmacodynamics
The relationship of the blood level of a drug to its pharmacologic effect has been the subject of numerous studies. Understanding this relationship is important because it contributes to the inter-individual variability observed in drug response. Ethanol is a
central nervous system depressant and its effects are secondary to CNS depression. These responses characteristically include euphoria, impaired thought processes, and decreased mechanical efficiency (20). Although alcoholic drinks are viewed as stimulating, this apparent stimulation is a result of depression of the inhibitory control mechanisms of the brain (3). However, as intoxication becomes more advanced, there is progressive depression of CNS function that can ultimately lead to respiratory depression, coma and even death.

Ethyl alcohol has been the subject of many studies by investigators interested in the effects of ethanol on the CNS. Its detrimental effects on human performance are well documented (21,22,23). Ethanol also produces numerous behavioral effects ranging from increased alertness to relaxation and a state of well-being or euphoria (24,25). These behavioral effects have been measured by various subjective mood scales such as the Drug Effects Questionnaire (DEQ), Profile of mood states (POMS), and the Subjective High Assessment Scale (SHAS) (26,27). For this study, an alcohol impairment rating scale, adapted from the SHAS (28) will be used. The mood scales will be administered to the subject as well as a blinded observer repeatedly during the study to assess changes in mood following ethanol or placebo administration as well as to study the difference between the subject’s own perception of his degree of intoxication and the observer’s perception of the subject’s degree of intoxication.

The effects of ethanol on psychometric performance have also been studied (20,29,30,31). These psychomotor tests are being used to detect impairment of cerebral function. They provide a non-invasive and quantitative measure of motor and cognitive function and allow comparison between different drugs or between different doses of the same drug. Alcohol has been shown to produce impairment of psychometric function as tested by various tests including tracking, digit symbol substitution, reaction time, body sway, hand steadiness and finger tapping (32). However, these tests are not ideal pharmacodynamic measures. Although some tests can measure some aspects of behavior as a function of drug response, they are somewhat subjective and may not show good reproducibility. Many of these tests are not suitable for repeated measures, since learning and motivational factors can influence performance in subsequent testing (33). Also, the relationship of performance on psychometric tests to the "real life" psychological and behavioral effects of drugs are difficult to define. For this study, the computerized version of the card sorting test, a pen-and-paper digit-symbol substitution test and the computerized finger tapping test have been selected. Card sorting is an excellent example of a performance task which embraces sensory, motor and central components of psychometric performance (33). These assessments are widely used and have been shown to be sensitive to a range of psycho-active drugs including ethanol (34). The digit-symbol substitution task (adapted from the Wechsler Adult Intelligence Battery) (35) has been demonstrated to be a useful indicator of changes in sensory processing performance produced by many drugs including ethanol (18,36). The rate of finger tapping is one of the simplest of human motor activity and has been widely used to measure drug induced
changes in motor activity.

Quantitative EEG is being increasingly used to study the pharmacodynamics of psychoactive drugs. The EEG provides an ongoing record of the neuroelectric activity of the brain, either in the resting state or under different activation procedures (e.g., repetitive photic stimulation, drug ingestion etc.). Although the scalp-recorded EEG is an overall measure of brain activity, it provides one of the best and most direct measures available for assessing the functional state of the CNS (21). Quantitative EEG is objective and non-invasive, and derived parameters change gradually with changes in plasma drug concentrations. Repeated or continuous measures of the EEG can be made, although a familiarization session before the study is advisable to avoid a first-session effect due to anxiety (37,38). Studies investigating the effects of acute ethanol administration on the adult human electroencephalogram (EEG) have been generally consistent (39). Most studies report an increase in voltage and a slowing of the dominant alpha frequency (21,23,40). Studies have also emphasized individual variability in responses to alcohol.

This study aims to assess the relationship between EEG changes and serum ethanol concentrations, psychometric performance and subjective mood scales after oral administration of low to moderate doses of ethanol at different rates. Of particular interest is the question whether alcohol induced EEG changes closely parallel the more or less gradual changes in subjective state and behavior during drinking.

It is well established and universally accepted that the concentration of ethanol, in blood or breath, constitutes the best and most objective indicator of the absence or presence and the degree of alcohol-induced impairment of driving ability in living subjects (4). Hence the understanding and appreciation of the major physiological and pharmacological factors associated with such alcohol concentrations are important for the appropriate use and interpretation of tests for alcohol in traffic law enforcement and in research on mental impairment by alcohol. Recognition of the complexity of the relationships between dose of alcohol, time and pharmacological effect is also essential to both research and public education in this field.

METHODS AND PROCEDURES:
I. SUBJECTS
Six healthy volunteers will participate in the study. Volunteers will be considered for inclusion if they conform to the following criteria:
1. **Demographic:** Subjects must be healthy male volunteers between the ages of 21 and 35 years and must not deviate more than 15% above or below the range of desirable weights according to the 1979 Build Study, Society of Actuaries and Association of Life Insurance Medical Directors of America (Attachment I).
2. **Medical History:** Subjects must have no clinically significant history of renal, hepatic, cardiovascular, gastro-intestinal, neurological, pulmonary,
or hematologic disease; have no history of alcohol abuse, drug addiction, psychological dependence on drugs, or psychiatric illness. Subjects must have no first degree relatives (mother, father, or siblings) with a history of mental illness or alcohol/drug abuse. Subjects must be low to moderate alcohol drinkers with an average intake not greater than 3 oz. (90 ml) of ethanol (approximately six 12 oz. beers) per week (Attachment II).

3. Physical: Subjects must successfully pass a physical examination, demonstrating no evidence of an active disease state or physical or mental impairment (Attachment III).

4. Laboratory screen: Subjects must have no clinically significant abnormal laboratory values on a laboratory screen consisting of 1) SMAC-20, 2) CBC and 3) urinalysis. Subjects must have a negative urine drug test and breath alcohol test (Attachment IV).

5. Electrocardiogram: Subjects must have no clinically significant abnormalities on a 12-lead EKG including a 30 second rhythm strip (Attachment V).

6. Vital signs: Supine and standing systolic and diastolic blood pressure, heart rate, and oral body temperature must be within normal limits. An orthostatic test i.e. systolic and diastolic blood pressure and heart rate at 5, 7 and 10 minutes supine and 0, 1, 3 and 5 minutes standing will have to be clinically acceptable (Attachment VI).

7. Other medications: Subjects must not be taking medications chronically and must not have taken any prescription medication or investigational drugs for at least 4 weeks before entering the study. Subjects must have a normal daily caffeine intake equivalent to or less than two cups of coffee. No medications (including OTC medications and vitamins) or caffeine will be allowed in the 72-hour period before each study day and on each study day. Subjects must also abstain from alcohol starting 72 hours before the first treatment period through the end of the study. Subjects must be non-smokers, meaning that they have abstained from smoking for at least 12 months before the start of the study.

8. Familiarization Period: All subjects participating in the study will undergo an EEG and psychometric test familiarization period before enrolling in the study. Subjects with a high number of artifacts on the EEG or subjects who cannot tolerate wearing the electro-cap for extended periods of time will be excluded.

Within one week after study completion, the physical examination and vital signs, laboratory tests, and EKG will be repeated for all subjects. Possible clinically significant abnormalities will be followed up until return to pre-study values. Subjects for this study will be recruited from within the hospital and schools at MCV/VCU.
II INFORMED CONSENT
Each subject will provide written informed consent for study participation before
the start of the study. The original signed consent forms will be kept in the
subjects’ confidential medical case record as a permanent document and a copy
will be given to the subject.

III PROCEDURE
During each of the five study periods, the following procedure will be followed:

1) Admission to Clinical Research Unit:
Subjects will enter the study facility on the evening of the day prior to each day
of ethanol or placebo dosing and will not be released until the morning after the
day of ethanol or placebo dosing. In addition, a breath alcohol (Alcosenser) test
will be done at the end of each treatment period to ensure that the subjects do not
have detectable ethanol levels. Subjects will fast from midnight on the evening
before ethanol or placebo dosing until the six hours after the dose is administered.
Water will be permitted *ad libitum* throughout each study period.

All subjects must have a negative urine drug screen and breath alcohol test before
each study period before receiving ethanol or placebo. All subjects will complete
a verbal probe concerning recent medical history and medication use (Attachment
VII).

2) Dosing:
During each treatment period, Subjects will receive one of the following five
treatments:
A) ethanol 0.3 g/kg body weight given in four equal "drinks" every 5 minutes
over 20 minutes followed by 2 placebo "drinks" at 30 and 45 minutes after start
of dosing;
B) ethanol 0.6 g/kg body weight given in four equal "drinks" every 5 minutes
over 20 minutes followed by 2 placebo "drinks" at 30 and 45 minutes after start
of dosing;
C) ethanol 0.3 g/kg body weight given in four equal "drinks" every 15
minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the
first "drink";
D) ethanol 0.6 g/kg body weight given in four equal "drinks" every 15
minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the
first "drink";
E) Placebo given in 6 equal "drinks" over 50 minutes (Attachment VIII).
Each treatment will be given exactly once and in random order according to the
randomization sequence (Attachment IX). Both the subjects and the investigators
will be blinded to treatment.
Ethanol will be administered as a 25% solution of 80 proof Vodka in fruit juice. The "drink" will be given ice-cold in an opaque container with a lid and will be sipped with a straw. A vodka-soaked gauze pad will be placed under the lid in an attempt to blind the subject to the contents. The placebo "drink" will consist of fruit juice and will contain a small amount of ethanol (5% of the dose) in a further attempt at blinding the subject.

Doses will be prepared by an unblinded pharmacist, who will assign subjects randomly to one of the randomization sequences. A sealed copy of the reRANDOMization schedule will be available at the research unit in case of an emergency.

3) Pharmacokinetic (PK) Measurements:

**Blood sampling (BAC)**

Prior to dosing, a heparin containing catheter will be inserted into the forearm vein for access to blood sampling.

6 ml samples for determination of ethanol concentration will be collected in red-top tubes with no additives at the following times: pre-dose and 10 min, 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment X). The blood will be allowed to clot, centrifuged (within 1 hour of sampling) for 10 minutes, serum harvested and stored at -20°C until analysis by the TDx Analyzer (Abbott Diagnostics).

The total volume of blood drawn for ethanol determination during the study will be 540 ml over a five-week period.

4) Pharmacodynamic (PD) Measurements:

**Electroencephalography (EEG)**

Five minute segments of 28-channel EEG, using a NeuroScience Brain Imager, will be recorded for each subject with eyes closed at the following times: pre-dose and 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment XI). Subjects will be asked to count back from 500 by threes to maintain constant vigilance during the recordings. The electrodes will be placed using an Electro-cap according to the 10/20 International System with 8 additional electrodes located 50% between the standard 10/20 placement. Linked ears will be used as the reference. Four additional channels will be used to monitor for vertical and lateral eye movements and electromyographic activity. The electrode impedances will be checked before each recording. Impedances should be less than 4.0 kohms and similar between electrodes. Any disturbances in the room or subject movement during the EEG recording will be documented by the EEG technician. The raw EEG will be stored on an optical disk. The objective of each recording is to obtain at least 30 artifact-free frames for further analysis.
Psychometric tests

i. A computerized card-sorting task (CST) (Neuroscan Inc.) will be completed by each subject at the following times: pre-dose and 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment XII).

ii. A computerized motor performance task, finger tapping (FT) (Neuroscan Inc.), will be completed by each subject at the following times: pre-dose and 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment XIII).

iii. A pencil-and-paper digit symbol substitution test (DSST) will be completed by each subject at the following times: pre-dose and 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment XIV).

In the morning before dosing for each period, subjects will practice each psychometric task twice.

Subject rated impairment scale (SRI)
A 100 mm visual analog scale (Attachment XV), based on the Subjective High Assessment Scale (SHAS) will be completed by each subject at the following times: pre-dose and 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment XVI). Subjects will indicate their perceived level of intoxication response for each item by placing a mark on an unnumbered 100 mm scale that ranges from "not at all" to "extremely".

Observer rated impairment scale (ORI)
A 100 mm visual analog scale (Attachment XVII) will be completed by the investigator for each subject at the following times: pre-dose and 20 min, 35 min, 1 hr, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment XVIII). The blinded investigator will indicate his perception of the subject’s level of intoxication by placing a mark on an unnumbered 100 mm scale that ranges from "not at all" to "extremely".

5) Safety measurements:

Vital Signs
Blood pressure (sitting) and heart rate will be measured at the following times: pre-dose and 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing (Attachment XIX).

The study will be conducted by Registered Nurses and the Physician Investigator
(Mark Johns) will be on call throughout each treatment period for each subject.

**Adverse effects**
All subjects will be observed for symptoms and signs of clinical intolerance to the drug or procedures and asked to report any adverse effects. These will be evaluated by the Physician Investigator for their clinical significance and potential need for treatment.

6) **Diet**
On the evening prior to the study, subjects will receive a light snack. No food or beverages, other than water, will be permitted from 10 hours before dosing until 6 hours after ethanol or placebo dosing. Dinner and a snack will be served 10 and 14 hours after dosing respectively. Caffeine-free beverages may be served with meals. The same menu will be served on corresponding days of each study period.

When the above measurements are scheduled at the same time, they will be conducted in the following sequence: 1) blood samples 2) EEG 3) CST 4) DSST 5) FT 6) SRI and ORI scales and 7) vital signs with the blood sample being collected at exactly the scheduled time. If there is any unscheduled delay, measurements may be omitted as needed to conform to the schedule.

A study flow sheet is included (Attachment XX).

**BIOSTATISTICAL DESIGN AND ANALYSIS:**

**Design**
This study will a randomized, double-blind, placebo-controlled five-period crossover study in 6 healthy male volunteers. Subjects will undertake the study one at a time. The start of each treatment period will be separated by a washout period of at least 1 week. Subjects will receive one of five treatments during each treatment period:

A) ethanol 0.3 g/kg body weight given in four equal "drinks" every 5 minutes over 20 minutes followed by 2 placebo "drinks" at 30 and 45 minutes after start of dosing;
B) ethanol 0.6 g/kg body weight given in four equal "drinks" every 5 minutes over 20 minutes followed by 2 placebo "drinks" at 30 and 45 minutes after start of dosing;
C) Ethanol 0.3 g/kg body weight given in four equal "drinks" every 15 minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the first "drink";
D) Ethanol 0.6 g/kg body weight given in four equal "drinks" every 15 minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the first "drink";
E) Placebo given in 6 equal "drinks" over 50 minutes (see attachment). Each subject will be assigned to one of the randomization sequences by an unblinded pharmacist and will receive each treatment exactly once.

**Data analysis**

I. Pharmacokinetic (PK) Analysis

The serum concentration of ethanol obtained during the study will be presented in tabular and graphic form for each subject and treatment. Pertinent pharmacokinetic parameters for ethanol, including apparent volume of distribution (Vd/F), apparent total body clearance (CLtot/F), area under the concentration-time curve (AUC), maximum concentration (Cmax) and time to maximum concentration (tmax) will be estimated for each subject and treatment. Descriptive statistics will be calculated for each parameter.

Extensive pharmacokinetic modelling to estimate the maximum elimination rate constant (Vmax) and Michaelis-Menten constant (Km) will be performed.

**Statistical Analysis:**

Pharmacokinetic parameters will be compared by means of analysis of variance (ANOVA) with treatment, sequence and subject as factors. Residuals will be tested for normality. If the data is not normally distributed, either the data will be transformed or appropriate non-parametric methods will be used. The level of significance (α) will be set at 0.05; in case no significant differences are observed, a power analysis will be performed.

II. Electroencephalography (EEG)

Each of the 5-minute recordings will be reviewed and edited to remove each 2.5 second epoch that is contaminated with artifacts (eye movement, muscle movement, electrode artifacts, or other disturbances noted during the recording). The remaining 2.5 second epochs or artifact-free frames will be averaged to form an average topographical map for each recording. The amplitude, power, and relative power of the EEG signal in the five classical frequency bands (delta: 0.39 - 3.0 Hz; theta: 4.3 - 7.8 Hz; alpha: 8.2 - 11.7 Hz; beta I: 12.1 -16.0 Hz; and beta II: 16.4 - 30 Hz) at each electrode will be determined for each average topographical map. The total amplitude and power for each average map will be calculated. Differences of each treatment from baseline as well as from placebo for each of these parameters will be calculated.

III. Psychometric Tests

1. Card Sorting Task (CST)
The total number of categories completed as well as the number of erroneous responses will be determined at each time point.

2. Finger Tapping Task (FT)
The average rate (taps per second) of finger tapping for the non-dominant hand will be determined based on three trials at each time point.

3. Digit Symbol Substitution Task (DSST)
The total number of substitutions completed in the 90 second testing interval as well as the number of correct responses will be determined at each time point.

IV. Rating Scales (SRI/ORI)
A score between 0 and 100 will be obtained for each item on the visual analog scale at each time point by measuring the number of millimeters between the left end of the scale and the mark placed by the subject.

V. Pharmacodynamic Analysis
Response-time profiles i.e. plots of change in response variable from predose baseline vs. time plots for each subject during each treatment period will be tabulated and plotted for each response measure. Pertinent pharmacodynamic parameters including baseline response, maximal observed response (Emax), time to reach maximum response, and area under the effect-time curve (AUE) will be determined and descriptive statistics for each of the above will be calculated. Pharmacokinetic-pharmacodynamic modelling will be performed, if appropriate.

Statistical Analysis
Results of the above pharmacodynamic response measures for each treatment will be compared using statistical techniques appropriate for a 5-way crossover study design with repeated measures. Residuals will be tested for normality. If normally distributed, a repeated measures analysis of variance (ANOVA) with subject, treatment, sequence and time as factors will be performed. If the data is not normally distributed, either the data will be transformed or appropriate non-parametric tests will be used. The significance level for $\alpha$ will be set at 0.05; in case of no significant differences, a power analysis will be performed.

HUMAN SUBJECT CONCERNS:
Subjects enrolled in the study will receive ethanol orally, have blood samples drawn for ethanol determination, and undergo a series of tests including EEG, psychometric tests and rating scales, repeatedly over a 12 hour period on 5 occasions. Subjects will remain in the study facility from the night before the study day until the morning after the study
day (approximately 36 hours for each treatment period) to preclude any motor or other accidents that may result from the impairment caused by alcohol.

I. Study drug
Subjects will receive ethanol, in doses of 0.3 g/kg and 0.6 g/kg, orally as a solution of vodka (80 proof) in fruit juice in four equivalent "drinks" in a crossover fashion.

Alcohol (ethyl alcohol) may produce the following side-effects: gastric irritation, nausea, vomiting, flushing and feeling of warmth, changes in heart rate and blood pressure, diaphoresis, diuresis, dizziness, changes in sexual desire, drowsiness, euphoria or false feeling of confidence and well being (3).

Subjects will be monitored for the development of adverse effects to the study drug by nurses in the study facility. Vital signs (blood pressure and heart rate) will be determined periodically during the study. Adverse effects will be managed as deemed necessary by the medical monitor.

At the end of each treatment period (24 hours after dosing) it is anticipated that ethanol levels would have dropped to zero. However, a breath alcohol test will be performed to ensure that the subject does not have any detectable ethanol levels.

II. Blood sampling
Subjects will have eighteen 6-ml blood samples drawn during each treatment period. A total of 540 ml of blood will be drawn during the study over a period of five weeks.

III. Test Battery
The test battery consists of EEG, psychomotor tests and rating scales and will be administered periodically during each treatment period. The risk associated with these tests is minimal. Subjects will be expected to wear the electro-caps throughout the treatment period, which may result in some discomfort.

IV. Pre- and post-study physical exam and laboratory tests
Subjects may experience some discomfort during the physical exam, EKG and laboratory tests to be performed during screening and at the end of the study.

Subjects will receive no personal benefits to their health from participating in the study, but the procedures will be conducted at no cost to them and they will receive an honorarium for their participation. Any information obtained about subjects from this research will be kept strictly confidential. Subjects will provide written informed consent and have the right to withdraw from the study at any time.
REFERENCES:


38. Slattum P; Personal communication.


### DOSING SCHEDULE

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\[ x := \text{ethanol dose} \]
\[ p := \text{placebo} \]

Treatment A: Ethanol 0.3 g/kg body weight given in four equal "drinks" every 5 minutes over 20 minutes followed by 2 placebo "drinks".

Treatment B: Ethanol 0.6 g/kg body weight given in four equal "drinks" every 5 minutes over 20 minutes followed by 2 placebo "drinks".

Treatment C: Ethanol 0.3 g/kg body weight given in four equal "drinks" every 15 minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the first "drink".

Treatment D: Ethanol 0.6 g/kg body weight given in four equal "drinks" every 15 minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the first "drink".

Treatment E: Placebo given in 6 equal "drinks" over 50 minutes.
RANDOMIZATION SEQUENCE

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A: Ethanol 0.3 g/kg body weight given in four equal "drinks" every 5 minutes over 20 minutes followed by 2 placebo "drinks".

B: Ethanol 0.6 g/kg body weight given in four equal "drinks" every 5 minutes over 20 minutes followed by 2 placebo "drinks".

C: Ethanol 0.3 g/kg body weight given in four equal "drinks" every 15 minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the first "drink".

D: Ethanol 0.6 g/kg body weight given in four equal "drinks" every 15 minutes over 50 minutes with 2 placebo "drinks" at 5 and 10 minutes after the first "drink".

E: Placebo given in 6 equal "drinks" over 50 minutes.
## STUDY PERIOD FLOW SHEET

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SAC: Serum Samples for Alcohol Determination, EEG: Electroencephalography, PPT: Psychometric Performance Battery, SRI/ORI: Subject Rated Impairment & Observer Rated Impairment Scale, VS: Vital Signs (blood pressure, heart rate, temperature)
CONSENT FORM

Pharmacokinetic-Pharmacodynamic Relationship of Ethanol in Healthy Male Subjects - Assessment of Electroencephalography (EEG), Psychometric Tests and Mood Scales: Effect of Dose and Rate of Ethanol Ingestion.

Investigators
Jürgen Venitz, M.D., Ph.D.
Vijay A. Ramchandani, B.Pharm.Sc.(Bombay, India)
Mark Johns, M.D. (Medical Monitor)

Introduction
You are being asked to participate in this study because you are healthy and not taking any stimulant drugs or medication on a chronic basis. This study is designed to study the relationship between changes in your brain waves (electroencephalogram) and other mental tests after taking different doses of alcohol (ethanol) at different rates.

If you agree to participate, you will be expected to provide information about your medical history, have laboratory tests done (including blood and urine tests), have a physical examination, and have an EKG (electric tracing of the heart) to determine whether you have any medical condition that would prevent you from participating in the study. Your urine will be tested for drugs of abuse. You will not be permitted to take any prescription medications for four weeks before the start of the study. You will not be permitted to take any over-the-counter medication (such as antacids, aspirin, vitamins or cold preparations) or any beverages containing caffeine for the 72 hours before each study day and on each study day. You will not be permitted to drink any alcohol starting 72 hours before the first study day through the last day of the study. Prior to the start of the study, you will undergo a practice session with the EEG (measuring your brain waves) and other tests that will be used during the study.

You will be expected to report to the study facility for a total of five (5) study periods on five consecutive weeks. During each period, you will come to the unit at 8:00 p.m. on the evening prior to ethanol dosing and will not be released until the morning after the day of dosing. On the night before dosing, you will begin a fast that will continue until six hours after the start of dosing (about 2:00 p.m. on the day of dosing). At the end of each study period, a breath alcohol test will be done to ensure that you have no detectable ethanol levels.

On the morning of dosing, a catheter will be inserted into your forearm vein and a blood sample (about 6 ml or 1.25 teaspoonful) will be drawn. You will then receive six "drinks" containing alcohol (0.3 or 0.6 g/kg body weight) in the form of vodka in fruit juice or placebo ("drink" with no alcohol) over 50 minutes during each period. You will have received all five treatments once by the end of the study. You will not be told
which treatment you are receiving during a given period.

During and after dosing, sixteen (16) additional blood samples will be collected through the catheter during each period. A total of 540 ml (about 1 pint) of blood, (approximately equal to the volume of blood collected in a single blood donation) will be collected during the entire study. If the catheter fails to work, a new catheter will be inserted or it may become necessary to obtain blood samples by sticking a needle directly into the vein.

Beginning just prior to dosing, you will take a series of tests repeatedly throughout the day. These tests include: two computerized tests, one paper-and-pencil test, one questionnaire about your mood and the EEG (brain wave) recording. Each of the tests takes less than two minutes to complete and the EEG recording takes about five minutes. To have the EEG recorded, you must wear a bathing cap-like apparatus with 28 disks (electrodes). Through a hole in each electrode, your scalp will be cleaned and a small amount of jelly-like substance will be applied to the scalp to make a good contact. In addition, two small, round electrodes will be attached, one to each earlobe and four more electrodes will be taped to your face (above and below your eyes). The cap will remain on your head for most of the day. The tests will be repeated several times during each study period (EEG and the mood questionnaire: 16 times; other tests: 14 times). Your heart rate and blood pressure will be monitored periodically throughout the day.

You will not be able to leave the unit until the morning after dosing. In addition, a breath alcohol test will be performed to ensure that you have no detectable alcohol levels.

For your safety, the pre-study physical examination and laboratory tests will be repeated at the end of the study.

Benefits
You are being asked to participate in this study as a volunteer. The study is of no direct medical benefit to you. There will be no charge to you for the screening examination and the results will be made available to you, if you want them.

You will be paid $700.00 for the completion of the study. If you withdraw early or are discontinued by the Medical Monitor, the fee will be prorated (see Withdrawal).

Alternative Therapy
There is no therapeutic benefit to you for participating in this study. Your participation is entirely voluntary. The alternative is not to participate in the study.

Risks, Inconveniences, Discomforts
A total of 85 blood samples will be drawn during the study period of five weeks. The total amount of blood will be 540 ml or about 1 pint over the five weeks of the study.
To obtain the blood samples a small catheter will be inserted into a vein in your arm. This procedure may cause some discomfort, pain, or slight bruising around the site of the needle stick. If the catheter fails to work, a new catheter will be inserted or blood samples will be collected through a needle inserted into the vein. While on the unit you will eat only the meals provided by the investigators at the times prescribed by the investigators. You will be required to remain at the study unit for about 36 hours during each study period. You may receive phone calls during the study, but no visitors will be allowed.

Alcohol (ethyl alcohol) may cause the following side-effects: gastric irritation, nausea, vomiting, flushing and feeling of warmth, changes in heart rate and blood pressure, diaphoresis (sweating), diuresis (increase in urine output), changes in sexual desire, headache, drowsiness, euphoria or false feeling of confidence and well-being.

If any undesirable effects occur, you should report them directly to the investigators. Dr. Mark Johns is the Medical Monitor for this study and is the person you contact in the case of a medical emergency. If you cannot reach Dr. Mark Johns, you may contact any of the study investigators.

None of the tests in the study carry any significant medical risk. There may be some discomfort associated with the EEG cap that you have to wear throughout the study period. Although the tape and gel used for the EEG recording are hypoallergenic, they may rarely cause skin irritation. After the cap is removed, you will be able to wash your hair.

There may be some discomfort associated with the physical exam, EKG, and laboratory tests conducted before and after the study.

Costs of Participation
There will be no charge to you for any laboratory tests, physical examination, hospital care, or other tests related to the conduct of this study. This is a time-consuming study that may interfere with your employment or other activities. You will be confined to the study unit for two nights and an entire day on each of the 5 study periods. You must provide your own transportation to and from the study site.

Research Related Injury
Every effort will be made to prevent any injury that could result from your participation in the study. In the event of any physical or mental injury resulting from your participation in this research project, Virginia Commonwealth University/Medical College of Virginia will not provide any compensation. If any injury occurs, medical treatment will be available at MCV hospitals. Fees for such treatment will be billed to you or appropriate third party insurance.
Confidentiality of Records
The investigators will treat your identity with professional standards of confidentiality. It may be important for the United States Food and Drug Administration (FDA) to be able to inspect the results of this study. By signing this consent form, you authorize release of the portion of your medical records related to this study to the FDA. Information obtained from this study may be published, but your identity will not be revealed.

Withdrawal
Your participation in this study is voluntary. If you decide to participate, you may withdraw at any time. Neither refusal to participate nor withdrawal will result in any penalty to loss of benefits to which you are otherwise entitled. If you have any questions at any time concerning the study procedures, you may contact the study investigators:

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<th>Name</th>
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<tr>
<td>Jürgen Venitz</td>
<td>786-8317</td>
<td>330-4615</td>
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<tr>
<td>Vijay A. Ramchandani</td>
<td>786-8372</td>
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Dr. Mark Johns is the Medical Monitor for this study. He can be reached during office hours at (beeper #) *60 1193 and at other times at 739-1030 (home phone).

If you do not complete the study due to premature withdrawal, the honorarium will be prorated based on the amount of usable information which has been collected. If the Medical Monitor terminates your participation in the study you will receive the entire amount.

You will receive a copy of this consent form.

I have read the above information, and I have had an opportunity to ask questions to help me understand what my participation will involve. I freely give my consent to participate in this study. If I have any questions regarding my rights as a volunteer in a clinical research study, I can contact the Committee on the Conduct of Human Research (CCHR) at the Medical College of Virginia at 786-0868.

Signed ___________________________ Date __________  
(volunteer)

Signed ___________________________ Date __________  
(witness)

Signed ___________________________ Date __________  
(investigator)
Protocol Revisions

CCHR #: 9108-2R

Title: Pharmacokinetic-Pharmacodynamic Relationship for Ethanol in Healthy Male Subjects. Assessment of Electroencephalography (EEG), Psychometric tests, and Mood scales. Effect of Dose and Rate of Ethanol ingestion.

The following revisions have been made to the protocol: (1) An additional baseline (predose) measurement of the EEG, psychometric tests and mood scales will be obtained in order to better define the predose response of the subject. (2) Additional measurements will be made during the first two hours after the start of dosing in order to better characterize the pharmacokinetics and pharmacodynamics of ethanol. Please note that the total volume of blood drawn during the study will remain the same and also that the revisions would not increase the minimal risk associated with the test battery. The changes are highlighted in the attached Modified Study Period Flow Sheet.

Revision 1: Protocol Section III, 3. **Blood sampling (BAC)** (p.8): Change timing of samples to read "6 ml samples for determination of ethanol concentration will be collected in red-top tubes with no additives at the following times: predose and 10 min, 20 min, 35 min, 50 min, 65 min, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing" (see Attachment).

Revision 2: Protocol Section III, 4. **Electroencephalography (EEG)** (p.8): Change timing of measurements to read "Five minute segments of 28-channel EEG, using a Neuroscience Brain Imager, will be recorded for each subject with eyes closed at the following times: twice pre-dose and 20 min, 35 min, 50 min, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing" (see Attachment).

Revision 3: Protocol Section III, 4. **Psychometric tests** - i., ii., and iii. (p.9): Change timing of measurements for all three tests (Card-Sorting Task, Finger Tapping Task and Digit-Symbol Substitution Test) to read:

*i.* A computerized card-sorting task (CST) (Neuroscan Inc.) will be completed by each subject at the following times: twice pre-dose and 50 min, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing.

**ii.** A computerized motor performance task, finger tapping (FT) (Neuroscan Inc.), will be completed by each subject at the following times: twice pre-dose and 20 min, 35 min, 50 min, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6
iii. A pencil-and-paper digit symbol substitution test (DSST) will be completed by each subject at the following times: twice pre-dose and 50 min, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing. (see Attachment).

Revision 4: Protocol Section III, 4. Subject rated impairment scale (SRI) (p.9): Change timing of measurements to read "A 100 mm visual analog scale (Attachment XV), based on the Subjective High Assessment Scale (SHAS) will be completed by each subject at the following times: twice pre-dose and 20 min, 35 min, 50 min, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing" (see Attachment).

Revision 5: Protocol Section III, 4. Observer rated impairment scale (ORD) (p.9): Change timing of measurements to read "A 100 mm visual analog scale (Attachment XVII) will be completed by the investigator for each subject at the following times: twice pre-dose and 20 min, 35 min, 50 min, 1.25 hr, 1.5 hr, 1.75 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr and 12 hr after ethanol or placebo dosing" (see Attachment).
# MODIFIED STUDY PERIOD FLOW-SHEET

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(Discharge from Clinical Research Unit)

**Time:** hours relative to ethanol (or placebo) dosing  
**BAC:** Sample for Blood Alcohol Concentration  
**EEG:** Electroencephalography  
**CST:** Card Sorting Task  
**DSST:** Digit-Symbol Substitution Task  
**FT:** Finger Tapping task  
**SRI:** Subject Rated Impairment scale  
**ORI:** Observer Rated Impairment scale  
**VS:** Vital Signs (blood pressure & heart rate)
APPENDIX B

Individual concentration-time profiles for oral ethanol study

B1 Individual serum ethanol concentration vs. time profiles by treatment and subject

B2 Individual serum ethanol concentration vs. time profiles (observed values and curves fitted by compartmental analysis by treatment and subject)

B3 Individual serum ethanol concentration vs. time profiles (observed values and curves fitted by simultaneous compartmental analysis of treatments by subject)
Figure B1.1 Serum ethanol concentration vs. time for Subject 1 by treatment for oral ethanol study
Figure B1.2  Serum ethanol concentration vs. time for Subject 2 by treatment for oral ethanol study
Figure B1.3 Serum ethanol concentration vs. time for Subject 3 by treatment for oral ethanol study
Figure B1.4 Serum ethanol concentration vs. time for Subject 4 by treatment for oral ethanol study
Figure B1.5  Serum ethanol concentration vs. time for Subject 5 by treatment for oral ethanol study
Figure B1.6 Serum ethanol concentration vs. time for Subject 6 by treatment for oral ethanol study
Figure B2.1 Serum Ethanol concentration vs. time profiles (observed points and fitted curves by individual fitting) for Subject 1.
Figure B2.2 Serum Ethanol concentration vs. time profiles (observed points and fitted curves by individual fitting) for Subject 2.
Figure B2.3 Serum Ethanol concentration vs. time profiles (observed points and fitted curves by individual fitting) for Subject 3.
Figure B2.4 Serum Ethanol concentration vs. time profiles (observed points and fitted curves by individual fitting) for Subject 4.
Figure B2.5 Serum Ethanol concentration vs. time profiles (observed points and fitted curves by individual fitting) for Subject 5.
Figure B2.6 Serum Ethanol concentration vs. time profiles (observed points and fitted curves by individual fitting) for Subject 6.
Figure B3.1 Serum ethanol concentration vs. time profiles (observed points and curves by simultaneous fitting) for Subject 1.
Figure B3.2  Serum ethanol concentration vs. time profiles (observed points and curves by simultaneous fitting) for Subject 2.
Figure B3.3 Serum ethanol concentration vs. time profiles (observed points and curves by simultaneous fitting) for Subject 3.
Figure B3.4 Serum ethanol concentration vs. time profiles (observed points and curves by simultaneous fitting) for Subject 4.
Figure B3.5 Serum ethanol concentration vs. time profiles (observed points and curves by simultaneous fitting) for Subject 5.
Figure B3.6 Serum ethanol concentration vs. time profiles (observed points and curves by simultaneous fitting) for Subject 6.
APPENDIX C

Individual baseline-corrected response-time profiles for EEG measures

C1 total power across all bands vs. time by treatment and subject
C2 relative delta power vs. time by treatment and subject
C3 relative theta power vs. time by treatment and subject
C4 relative alpha power vs. time by treatment and subject
C5 relative beta I power vs. time by treatment and subject
C6 relative beta II power vs. time by treatment and subject
C7 spectral edge vs. time by treatment and subject
Figure C1.1 Total Power vs. time by treatment for Subject 1.
Figure C1.2 Total Power vs. time by treatment for Subject 2.
Figure C1.3 Total Power vs. time by treatment for Subject 3.
Figure C1.4 Total Power vs. time by treatment for Subject 4.
Figure C1.5 Total Power vs. time by treatment for Subject 5.
Figure C1.6 Total Power vs. time by treatment for Subject 6.
Figure C2.1 Relative Delta Power vs. time by treatment for Subject 1.
Figure C2.2 Relative Delta Power vs. time by treatment for Subject 2.
Figure C2.3 Relative Delta Power vs. time by treatment for Subject 3.
Figure C2.4 Relative Delta Power vs. time by treatment for Subject 4.
Figure C2.5 Relative Delta Power vs. time by treatment for Subject 5.
Figure C2.6 Relative Delta Power vs. time by treatment for Subject 6.
Figure C3.1 Relative Theta Power vs. time by treatment for Subject 1.
Figure C3.2 Relative Theta Power vs. time by treatment for Subject 2.
Figure C3.3 Relative Theta Power vs. time by treatment for Subject 3.
Figure C3.4 Relative Theta Power vs. time by treatment for Subject 4.
Figure C3.5 Relative Theta Power vs. time by treatment for Subject 5.
Figure C3.6 Relative Theta Power vs. time by treatment for Subject 6.
Figure C4.1 Relative Alpha Power vs. time by treatment for Subject I.
Figure C4.2 Relative Alpha Power vs. time by treatment for Subject 2.
Figure C4.3 Relative Alpha Power vs. time by treatment for Subject 3.
Figure C4.4 Relative Alpha Power vs. time by treatment for Subject 4.
Figure C4.5 Relative Alpha Power vs. time by treatment for Subject 5.
Figure C4.6 Relative Alpha Power vs. time by treatment for Subject 6.
Figure C5.1 Relative Beta I Power vs. time by treatment for Subject 1.
Figure C5.2 Relative Beta I Power vs. time by treatment for Subject 2.
Figure C5.3 Relative Beta I Power vs. time by treatment for Subject 3.
Figure C5.4 Relative Beta I Power vs. time by treatment for Subject 4.
Figure C5.5 Relative Beta I Power vs. time by treatment for Subject 5.
Figure C5.6 Relative Beta I Power vs. time by treatment for Subject 6.
Figure C6.1 Relative Beta II Power vs. time by treatment for Subject 1.
Figure C6.2 Relative Beta II Power vs. time by treatment for Subject 2.
Figure C6.3 Relative Beta II Power vs. time by treatment for Subject 3.
Figure C6.4 Relative Beta II Power vs. time by treatment for Subject 4.
Figure C6.5 Relative Beta II Power vs. time by treatment for Subject 5.
Figure C6.6 Relative Beta II Power vs. time by treatment for Subject 6.
Figure C7.1  Spectral Edge vs. time by treatment for Subject 1.
Figure C7.2 Spectral Edge vs. time by treatment for Subject 2.
Figure C7.3 Spectral Edge vs. time by treatment for Subject 3.
Figure C7.4 Spectral Edge vs. time by treatment for Subject 4.
Figure C7.5 Spectral Edge vs. time by treatment for Subject 5.
Figure C7.6 Spectral Edge vs. time by treatment for Subject 6.
APPENDIX D

Individual baseline-corrected response-time profiles for PPT measures

D1 average tap-rate for dominant hand for FT vs. time by treatment and subject

D2 average tap-rate for non-dominant hand for FT vs. time by treatment and subject
Figure D1.1 Dominant hand tap-rate vs. time by treatment for Subject 1.
Figure D1.2 Dominant hand tap-rate vs. time by treatment for Subject 2.
Figure D1.3 Dominant hand tap-rate vs. time by treatment for Subject 3.
Figure D1.4 Dominant hand tap-rate vs. time by treatment for Subject 4.
Figure D1.5 Dominant hand tap-rate vs. time by treatment for Subject 5.
Figure D1.6 Dominant hand tap-rate vs. time by treatment for Subject 6.
Figure D2.1 Non-dominant hand tap-rate vs. time by treatment for Subject 1.
Figure D2.2 Non-dominant hand tap-rate vs. time by treatment for Subject 2.
Figure D2.3 Non-dominant hand tap-rate vs. time by treatment for Subject 3.
Figure D2.4 Non-dominant hand tap-rate vs. time by treatment for Subject 4.
Figure D2.5 Non-dominant hand tap-rate vs. time by treatment for Subject 5.
Figure D2.6 Non-dominant hand tap-rate vs. time by treatment for Subject 6.
APPENDIX E

Individual baseline-corrected response-time profiles for SRI/ORI measures

E1 SRI-HIGH score vs. time by treatment and subject
E2 SRI-DRUNK score vs. time by treatment and subject
E3 SRI-ALCOHOL EFFECTS score vs. time by treatment and subject
E4 ORI-HIGH score vs. time by treatment and subject
E5 ORI-DRUNK score vs. time by treatment and subject
Figure E1.1 SRI-HIGH score vs. time by treatment for Subject 1.
Figure E1.2 SRI-HIGH score vs. time by treatment for Subject 2.
Figure E1.3 SRI-HIGH score vs. time by treatment for Subject 3.
Figure B1.4 SRI-HIGH score vs. time by treatment for Subject 4.
Figure E1.5 SRI-HIGH score vs. time by treatment for Subject 5.
Figure E1.6 SRI-HIGH score vs. time by treatment for Subject 6.
Figure E2.1 SRI-DRUNK score vs. time by treatment for Subject 1.
Figure E2.2 SRI-DRUNK score vs. time by treatment for Subject 2.
Figure E2.3 SRI-DRUNK score vs. time by treatment for Subject 3.
Figure E2.4 SRI-DRUNK score vs. time by treatment for Subject 4.
Figure E2.5 SRI-DRUNK score vs. time by treatment for Subject 5.
Figure E2.6 SRI-DRUNK score vs. time by treatment for Subject 6.
Figure E3.1 SRI-ALCOHOL EFFECTS score vs. time by treatment for Subject 1.
Figure E3.2 SRI-ALCOHOL EFFECTS score vs. time by treatment for Subject 2.
Figure E3.3 SRI-ALCOHOL EFFECTS score vs. time by treatment for Subject 3.
Figure E3.4 SRI-ALCOHOL EFFECTS score vs. time by treatment for Subject 4.
Figure E3.5 SRI-ALCOHOL EFFECTS score vs. time by treatment for Subject 5.
Figure E3.6 SRI-ALCOHOL EFFECTS score vs. time by treatment for Subject 6.
Figure E4.1 ORI-HIGH score vs. time by treatment for Subject 1.
Figure E4.2  ORI-HIGH score vs. time by treatment for Subject 2.
Figure E4.3 ORI-HIGH score vs. time by treatment for Subject 3.
Figure E4.4 ORI-HIGH score vs. time by treatment for Subject 4.
Figure E4.5 ORI-HIGH score vs. time by treatment for Subject 5.
Figure E4.6 ORI-HIGH score vs. time by treatment for Subject 6.
Figure E5.1 ORI-DRUNK score vs. time by treatment for Subject 1.
Figure E5.2 ORI-DRUNK score vs. time by treatment for Subject 2.
Treatment A

Treatment B

Treatment C

Treatment D

Figure E5.3 ORI-DRUNK score vs. time by treatment for Subject 3.
Figure E5.4 ORI-DRUNK score vs. time by treatment for Subject 4.
Figure E5.5 ORI-DRUNK score vs. time by treatment for Subject 5.
Figure E5.6 ORI-DRUNK score vs. time by treatment for Subject 6.
APPENDIX F

Individual baseline-corrected response-concentration profiles for PD measures for oral ethanol study

F1  Baseline-corrected relative theta power vs. concentration by treatment and subject

F2  Baseline-corrected non-dominant hand tap-rate for FT vs. concentration by treatment and subject

F3  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. concentration by treatment and subject
Figure F1.1 Baseline-corrected Relative Theta Power vs. serum ethanol concentration by treatment for Subject 1.
Figure F1.2 Baseline-corrected Relative Theta Power vs. serum ethanol concentration by treatment for Subject 2.
Figure F1.3 Baseline-corrected Relative Theta Power vs. serum ethanol concentration by treatment for Subject 3.
Figure F1.4 Baseline-corrected Relative Theta Power vs. serum ethanol concentration by treatment for Subject 4.
Figure F1.5 Baseline-corrected Relative Theta Power vs. serum ethanol concentration by treatment for Subject 5.
Figure F1.6 Baseline-corrected Relative Theta Power vs. serum ethanol concentration by treatment for Subject 6.
Figure F2.1 Baseline-corrected Non-dominant hand Tap-rate vs. Serum ethanol concentration by treatment for Subject 1.
Figure F2.2 Baseline-corrected Non-dominant hand Tap-rate vs. Serum ethanol concentration by treatment for Subject 2.
Figure F2.3 Baseline-corrected Non-dominant hand Tap-rate vs. Serum ethanol concentration by treatment for Subject 3.
Figure F2.4 Baseline-corrected Non-dominant hand Tap-rate vs. Serum ethanol concentration by treatment for Subject 4.
Figure F2.5 Baseline-corrected Non-dominant hand Tap-rate vs. Serum ethanol concentration by treatment for Subject 5.
Figure F2.6  Baseline-corrected Non-dominant hand Tap-rate vs. Serum ethanol concentration by treatment for Subject 6.
Figure F3.1 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration by treatment for Subject 1.
Figure F3.2 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration by treatment for Subject 2.
Figure F3.3 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration by treatment for Subject 3.
Figure F3.4 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration by treatment for Subject 4.
Figure F3.5 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration by treatment for Subject 5.
Figure F3.6 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration by treatment for Subject 6.
APPENDIX G

Individual response vs. time and response vs. concentration profiles (observed values and fitted curves) for SRI-ALCOHOL EFFECTS score for oral ethanol study

G1 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment and subject

G2 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment and subject
Figure G1.1 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 1.
Figure G1.2  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 2.
Figure G1.3 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 3.
Figure G1.4 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 4.
Figure G1.5  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 5.
Figure G1.6 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 6.
Figure G2.1  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentrations (observed values and fitted curves) by treatment for Subject 1.
Figure G2.2 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentrations (observed values and fitted curves) by treatment for Subject 2.
Figure G2.3  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentrations (observed values and fitted curves) by treatment for Subject 3.
Figure G2.4 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentrations (observed values and fitted curves) by treatment for Subject 4.
Figure G2.5  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentrations (observed values and fitted curves) by treatment for Subject 5.
Figure G2.6  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum ethanol concentrations (observed values and fitted curves) by treatment for Subject 6.
APPENDIX H

Protocol and Informed Consent Form for intravenous ethanol study
Pharmacokinetic-Pharmacodynamic Relationship for Intravenous Ethanol in Healthy Male and Female Subjects.
**Part II:** Modelling the Development of Tolerance to the Effects of Intravenous Ethanol administration in Healthy Male and Female Subjects: Effect of Systemic Input Rate and Degree of Ethanol Exposure.

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**HYPOTHESIS AND SPECIFIC AIMS**

**Hypothesis**
The hypotheses guiding this research project are that 1) the rate and degree of intravenous (IV) ethanol exposure in normal healthy males and females affect the pharmacokinetics and pharmacodynamics of ethanol in a non-linear fashion; and 2) acute tolerance, which is defined as a diminished effect at a given serum level during declining concentrations compared to the effect at the same serum level during ascending concentrations, develops to the subjective effects of prolonged exposure to ethanol which is not reflected in electroencephalographic activity or psychometric performance.

**Specific Aims**
The aim of this study is to investigate the pharmacokinetics and pharmacodynamics of different doses and dose rates of intravenous ethyl alcohol and the development of acute tolerance to ethanol in healthy male and female subjects. The study will assess changes in the electroencephalogram (EEG) after IV administration of ethanol as well as changes in performance on psychometric tests and subjective changes in mood. The study will examine the relationship between changes in the EEG and changes in psychometric performance and subjective mood scales to compare the sensitivity of the EEG to serum ethanol concentrations with that of psychometric performance and mood. The study will also evaluate the effect of different rates of infusions, designed to achieve and maintain "steady-state" concentrations of ethanol for different durations, on the pharmacokinetic profile and pharmacologic effects of ethanol as measured by the EEG, psychometric performance and subjective measures of mood. The study will also examine differences between male and female subjects with respect to pharmacokinetics as well as EEG changes, psychometric performance and mood changes following IV ethanol administration.
BACKGROUND AND SIGNIFICANCE

Ethanol is probably the most widely used drug in the world. It is commonly self-prescribed rather than prescribed by a clinician and the dose determined either by tradition, social context or the achievement of a pharmacological end-point (1). Almost no other substance has been as comprehensively investigated as ethanol, not only because it is one of the oldest and most ubiquitous abused “drugs” in human history, but also because of its unique dynamic and kinetic behavior (2). Although considered at one time (in the Middle Ages) as the elixir of life, it is now recognized that the therapeutic value of ethanol is extremely limited and that chronic ingestion of excessive amounts is a major social and medical problem (3).

Pharmacokinetics
Ethanol is unusual among drugs in several aspects of its pharmacokinetics. Particularly striking are the great biological inter-subject variabilities in alcohol consumption patterns and in alcohol elimination, in the pattern of short-term fluctuations from the trend line of the time course of the blood alcohol concentrations and in the partitioning of alcohol between the blood and other body fluids and tissues even at equilibrium (4).

The pharmacokinetics of intravenous ethanol have been studied fairly extensively (5,6,7,8). Ethanol distributes into total body water and no protein binding has been reported. Elimination of ethanol occurs primarily through enzymatic oxidation by alcohol dehydrogenase to acetaldehyde in the liver with minute amounts being excreted in the breath (0.7%), sweat (0.1%), and urine (0.3%) (1). The overall elimination process can be described by a capacity-limited model similar to the Michaelis-Menten model for enzyme kinetics first proposed by Lunquist and Wolthers (9,10). The use of the zero-order model of Widmark (11) has been widespread in the past although the limitations of this model have been known for a long time (1).

The alcohol concentration-time profile depends on a number of factors including the dose (10,12,13), the type of alcoholic beverage and the rate of drinking (4,14), the consumption of a meal as well as the composition of the meal (15), sex and body composition (16,17).

Differences in pharmacokinetics as well as in psychometric performance and mood states have been observed in males and females (16,17,19). This study will examine the differences between male and female subjects with respect to their pharmacokinetics as well as pharmacodynamic effects following IV ethanol administration.

Pharmacodynamics
The relationship of the blood level of a drug to its pharmacologic effect has been the subject of numerous studies. Understanding this relationship is important because it contributes to the inter-individual variability observed in drug response. Ethanol is
considered to be a central nervous system depressant and its responses characteristically include euphoria, impaired thought processes, and decreased mechanical efficiency (20). Although alcoholic drinks are viewed as stimulating, this apparent stimulation is a result of depression of the inhibitory control mechanisms of the brain (3). However, as intoxication becomes more advanced, there is progressive depression of CNS function that can ultimately lead to respiratory depression, coma and even death.

Ethyl alcohol has been studied by investigators interested in its behavioral effects. The detrimental effects of alcohol on human performance are well documented (21,22,23). Ethanol produces numerous behavioral effects ranging from increased alertness to relaxation and a state of well-being or euphoria (24,25). These behavioral effects have been measured by various subjective mood scales such as the Drug Effects Questionnaire (DEQ), Profile of mood states (POMS), and the Subjective High Assessment Scale (SHAS) (26,27).

The effects of ethanol on psychometric performance have also been studied (20,29,30,31). These psychomotor tests provide a non-invasive and quantitative measure of motor and cognitive function and allow comparison between different drugs or between different doses of the same drug. Alcohol has been shown to produce impairment of psychometric function as tested by various tests including tracking, digit symbol substitution, reaction time, body sway, hand steadiness and finger tapping (32). However, these tests are not ideal pharmacodynamic measures. Although some tests can measure some aspects of behavior as a function of drug response, they are somewhat subjective and may not show good reproducibility. Many of these tests are not suitable for repeated measures, since learning and motivational factors can influence performance in subsequent testing (33). Also, the relationship of performance on psychometric tests to the "real life" psychological and behavioral effects of drugs are difficult to define.

Quantitative EEG is being increasingly used to study the pharmacodynamics of psychoactive drugs. The EEG provides an ongoing record of the neuroelectric activity of the brain, either in the resting state or under different activation procedures (e.g. repetitive photic stimulation, drug administration etc.). Although the scalp-recorded EEG is an overall measure of brain activity, it provides one of the best and most direct measures available for assessing the functional state of the CNS (21). Quantitative EEG is objective and non-invasive, and derived parameters change gradually with changes in plasma drug concentrations. Repeated or continuous measures of the EEG can be made, although a familiarization session before the study is advisable to avoid a first-session effect due to anxiety (37,38). Studies investigating the effects of acute ethanol administration on the adult human electroencephalogram (EEG) have been generally consistent (39). Most studies report an increase in voltage and a slowing of the dominant alpha frequency (21,23,40). Studies have also emphasized individual variability in responses to alcohol.
Tolerance

Acute tolerance to alcohol was first described by Mellanby, who reported a lower impairment at a given blood alcohol level in the descending limb of the blood alcohol curve than at the same level in the ascending limb of the curve (36). Since then, several studies have characterized the development of acute tolerance to single doses of ethanol, although there are reports describing the lack of tolerance to alcohol's effects (36,43,44,45,46). One explanation for this inconsistency may be the end point used to measure the pharmacological effects of ethanol. In general, data from studies measuring subjective assessments are consistent with the development of acute tolerance. The opposite conclusion is reached when objective psychological functions are assessed. Generally, studies measuring psychomotor performance fail to show significant acute tolerance to ethanol. The rate of change of concentration, direction of change of concentration, as well as the degree and rate of exposure to ethanol may also be important determinants of the development of acute tolerance to ethanol.

Several paradigms can be used to study the development of acute tolerance to the effects of drugs, specially alcohol. One method would be to compare effects at the same concentrations during the ascending and descending limbs of the alcohol concentration-time curve. Another method would be to study the time course of the effects of ethanol at "steady-state" i.e. when concentrations are constant. In such a paradigm, a diminishing of the effects of ethanol, despite maintaining constant concentrations, can be interpreted as the development of acute tolerance. Since ethanol follows non-linear capacity-limited pharmacokinetics, this is not true "steady-state", however, a dosing regimen can be designed to control the rate of input such that levels can be maintained fairly constant over prolonged durations. Intravenous administration of ethanol can provide good control of the input rate, which is critical to the achievement of these constant levels.

In Part I of this study, six (6) healthy male volunteers were given two different doses of ethanol (0.3 g/kg and 0.6 g/kg), each ingested at two different rates (20 minutes and 50 minutes). Serial blood samples (for serum alcohol concentrations) were drawn, and EEG recordings, psychometric tests and mood scales were completed by the subjects during each period. Preliminary analysis of the psychometric performance and mood data indicated that, in general, some of the items of the mood scale (viz. "HIGH", "DRUNK", "ALCOHOL EFFECTS") were fairly sensitive in discriminating different doses of ethanol, and also distinguishing dose rates at the high dose for some subjects. The psychometric tests indicated some trends toward dose-related impairment which were not significant. Practice effects were evident. Two of the six subjects were classified as "non-responders" based on their lack of response on the mood scales. The data also seemed to indicate that the rate of input may not have been controlled well enough to assess the effects of rate of input on the effects of ethanol.

In this study, subjects will be administered an individualized regimen consisting of intravenous infusions of ethanol calculated to achieve and maintain concentrations of
ethanol at or about 1000 mg/L (the legal limit). This will be accomplished by determining the subjects’ individual pharmacokinetic parameters from serum concentrations after administration of a test dose of ethanol during the Pharmacokinetic Screening and Familiarization period. These individual parameters can then be used to calculate a dosing regimen that will be designed to achieve the desired alcohol level and maintain it for different durations of exposure. Several pharmacodynamic end points: EEG, psychometric performance and mood will be measured and the relationship between these end-points and serum concentrations will be assessed to study the pharmacokinetic-pharmacodynamic relationship for IV ethanol as well as the development of acute tolerance to the effects of different rates and degrees of ethanol exposure.

Relevance of the complexity of the relationships between alcohol dose, time and pharmacological effects is essential for the development of a paradigm for measuring the influence of factors such as gender, age and concomitant drugs on the effects of ethanol. Ethanol can also be examined as a model CNS depressant for the evaluation of objective pharmacodynamic end-points, such as EEG and psychometric tests, and subjective measures of mood and behavior, for other psychoactive drugs in order to correlate these surrogate measures with concentration or dose.

METHODS AND PROCEDURES

I. SUBJECTS
Sixteen (16) healthy volunteers, (eight male and eight female), will participate in the study. Volunteers will be considered for inclusion if they conform to the following criteria:

1. Demographic: Subjects must be healthy male or non-pregnant female volunteers between the ages of 21 and 35 years and must not deviate more than 15% above or below the range of desirable weights according to the 1979 Build Study, Society of Actuaries and Association of Life Insurance Medical Directors of America.

2. Medical History: Subjects must have no clinically significant history of renal, hepatic, cardiovascular, gastro-intestinal, neurological, pulmonary, or hematologic disease. Subjects must have no history of alcohol abuse, drug addiction, psychological dependence on drugs, or psychiatric illness. Subjects must have no first degree relatives (mother, father, or siblings) with a history of mental illness or alcohol/drug abuse.

To participate in the study, female subjects must meet the following criteria: As determined by thorough enquiry, women must be found to practice acceptable methods of birth control and have a negative serum beta-hCG pregnancy test. Abstention, vaginal contraceptives, intra-uterine devices, or use of contraceptives by the women’s partner, do not constitute acceptable birth control. Acceptable methods will be limited to oral contraceptives only. The method of birth control must be recorded in the subject’s medical history.
3. **Alcohol History:** Subjects must complete an alcohol drinking history questionnaire based on the Khavari Alcohol Test and the Short Michigan Alcoholism Screening Test to quantify their alcohol intake and patterns of use (47). Subjects will also complete an alcohol use diary starting from the date of screening through the end of the study, approximately 5 - 6 weeks.

4. **Physical:** Subjects must successfully pass a physical examination, demonstrating no evidence of an active disease state or physical or mental impairment.

5. **Laboratory screen:** Subjects must have no clinically significant abnormal laboratory values on a laboratory screen consisting of 1) SMAC-20, 2) CBC and 3) urinalysis. Subjects must have a negative urine drug test and breath alcohol test. Female subjects must have a negative serum beta-hCG test.

6. **Electrocardiogram:** Subjects must have no clinically significant abnormalities on a 12-lead EKG including a 30 second rhythm strip.

7. **Vital signs:** Supine and standing systolic and diastolic blood pressure, heart rate, and oral body temperature must be within normal limits. An orthostatic test i.e. systolic and diastolic blood pressure and heart rate at 5, 7 and 10 minutes supine and 0, 1, 3 and 5 minutes standing will have to be clinically acceptable.

8. **Other medications:** Subjects must not be taking medications chronically and must not have taken any prescription medication or investigational drugs for at least 4 weeks before entering the study. Female subjects will be permitted to continue their oral contraceptive medication. Subjects must have a normal daily caffeine intake equivalent to or less than two cups of coffee. No medications (including OTC medications and vitamins) or caffeine will be allowed in the 72-hour period before each study day and on each study day. Subjects must also abstain from alcohol starting 72 hours before the first treatment period through the end of the study. Subjects must be non-smokers, meaning that they have abstained from smoking for at least 12 months before the start of the study.

Within one week after study completion, the physical examination and vital signs, laboratory tests, and EKG will be repeated for all subjects. Possible clinically significant abnormalities will be followed up until return to pre-study values.

Subjects for this study will be recruited from within the hospital and schools at MCV/VCU.

II **INFORMED CONSENT**

Each subject will provide written informed consent for study participation before the start of the study. The original signed consent forms will be kept in the subjects’ confidential medical case record as a permanent document and a copy will be given to the subject.

III **PROCEDURES**

The study will be conducted in two phases:

Subjects who have successfully passed the medical screening will first undergo an open-labelled Pharmacokinetic Screen and Familiarization Period (Leg 0); to assess their individual pharmacokinetic parameters, which will be used to design an appropriate
regimen, as well as to familiarize them with the study procedures, especially the EEG. After this, subjects will be randomized to the double-blind, four-treatment crossover phase (Legs 1 through 4) of the study. The washout period between treatments will be at least one week.

Leg 0
During the Pharmacokinetic screen and Familiarization Period, the following procedure will be followed:

1. **Admission to Clinical Research Unit**
   Subjects will enter the study facility on the evening of the day prior to the day of dosing. A urine sample will be collected for a urine drug screen test and a breath alcohol test (Alcosensor) will also be completed. A blood sample will be collected from female subjects for a serum beta-hCG test. Subjects must test negative on both the urine drug screen as well as the breath alcohol test. Female subjects must test negative on the beta-hCG test. All subjects will complete a probe concerning recent medical history and medication use.

2. **Dosing**
   On the morning of dosing, subjects will receive a one-hour infusion of ethanol administered via an indwelling catheter in the dominant arm. A total dose of 0.6 g ethanol/kg body weight for male subjects and 0.5 g ethanol/kg body weight for female subjects will be administered as a 10% solution in normal saline over 1 hour. Doses will be prepared by the investigational pharmacy and the treatment will be open-labelled.

3. **Pharmacokinetic (PK) Measurements**
   **Blood sampling (SAC)**
   Prior to dosing, a heparin containing catheter will be inserted into the forearm vein of the non-dominant arm (contra-lateral to ethanol infusion) for access to blood sampling. 6 ml samples for determination of ethanol concentration will be collected in red-top tubes with no additives at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the ethanol infusion. The blood will be allowed to clot, centrifuged (within 1 hour of sampling) for 10 minutes, serum harvested and stored at -20°C until analysis by the TDx Analyzer (Abbott Diagnostics).

4. **Pharmacodynamic (PD) Measurements**
   **Electroencephalography (EEG)**
   Four minute segments of 28-channel EEG, using a Neuroscan Brain Imager, will be recorded for each subject with eyes closed at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the ethanol infusion. Subjects will be asked to count back from 500 by threes to maintain constant vigilance during the recordings. The electrodes will be placed using an Electro-cap according to the 10/20 International System with 8 additional electrodes located 50% between the standard 10/20 placement. Linked ears will be used as the reference. Four additional channels will be used to monitor for vertical and lateral eye movements and electromyographic activity. The electrode impedances will be
checked before each recording. Impedances should be less than 5.0 kohms and similar between electrodes. Any disturbances in the room or subject movement during the EEG recording will be documented by the EEG technician. The raw EEG will be stored on an optical disk. The objective of each recording is to obtain at least 30 artifact-free frames for further analysis.

Psychometric Performance Tests (PP)
The Wesnes Test Battery (Cognitive Drug Research Computerized Assessment System) of psychometric tests will be administered to each subject at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the ethanol infusion. The Wesnes test battery assesses cognitive function and the tasks include simple and choice reaction times, vigilance tests, tracking, memory scanning and immediate and delayed word recognition. A selection of these tests, Word Recognition, Number Vigilance, Immediate Word Recall and Visual Tracking, will be administered, and parallel forms of the tests will be presented at each session. All the tasks are computerized, the information being presented on high resolution monitors, and the responses recorded via response modules containing two buttons, one marked "NO" and the other "YES".

On the evening prior to the day of dosing, subjects will practice each psychometric task twice.

Subject Rated Impairment Scale (SRI)
A 100 mm visual analog scale, based on the Subjective High Assessment Scale (SHAS) will be completed by each subject at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the ethanol infusion. Subjects will indicate their perceived level of intoxication response for each item by placing a mark on an unnumbered 100 mm scale that ranges from "not at all" to "extremely".

Observer Rated Impairment Scale (ORI)
A 100 mm visual analog scale will be completed by the investigator for each subject at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the ethanol infusion. The blinded investigator will indicate his perception of the subject’s level of intoxication by placing a mark on an unnumbered 100 mm scale that ranges from "not at all" to "extremely".

5. Safety measurements

Vital Signs
Blood pressure (sitting), heart rate and oral body temperature will be measured at the following times: twice pre-dose and 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the ethanol infusion.

Skin (facial) temperature, using the Genius tympanic thermometer (First Temp Inc.), will be measured at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr after the start of the ethanol infusion.
These measurements will be made by Registered Nurses and the Medical Monitor will be on call throughout the treatment period for each subject.

**Adverse effects**

All subjects will be observed for symptoms and signs of clinical intolerance to the drug or procedures and asked to report any adverse effects. These will be evaluated by the Medical Monitor for their clinical significance and potential need for treatment.

6. **Diet**

On the evening prior to dosing, subjects will receive a light snack. No food or beverages will be permitted starting 10 hours prior to dosing. A light standardized meal will be served at 4 hours after the start of ethanol infusion. Dinner and a snack will be served at 9 and 14 hours after start of dosing respectively. Caffeine-free beverages may be served with meals. The same menu will be served on corresponding days of each study period. Water will be permitted *ad libitum*.

When the above measurements are scheduled at the same time, they will be conducted in the following sequence: 1) blood sample, 2) mood scales, 3) EEG, 4) psychometric tests, and 5) vital signs, with the blood sample being collected at exactly the scheduled time. If there is any unscheduled delay, measurements may be omitted as needed to conform to the schedule.

7. **Discharge from Clinical Research Unit**

At the end of the treatment period (24 hours after dosing), it is anticipated that ethanol levels would be below the detectable limit. However, to ensure subject safety, an alcohol breath test (Alcosensor) will be performed. If the test is negative, subjects will be discharged with instructions to return for the crossover phase of the study.

A study flow sheet is included.

**Legs 1-4**

During each of the four randomized crossover legs of the study, the following procedure will be followed:

1. **Admission to Clinical Research Unit**

Subjects will enter the study facility on the evening of the day prior to the day of dosing. A urine sample will be collected for a urine drug screen test and a breath alcohol test (Alcosensor) will also be completed. A blood sample will be collected from female subjects for a serum beta-hCG test. Subjects must test negative on both the urine drug screen as well as the breath alcohol test. Female subjects must test negative on the beta-hCG test. All subjects will complete a probe concerning recent medical history and medication use.

2. **Dosing**

On the morning of dosing, subjects will receive the infusion of ethanol administered via an indwelling catheter in the dominant arm. Dosing will consist of two infusions: Infusion I will be administered for 1 hour, followed by Infusion II which will be administered over the next 5 hours. The total dose of ethanol, which will be individualized for each subject based on his pharmacokinetic parameters, will be administered as a 10% solution in normal saline. Placebo doses will consist of normal
saline. Doses will be prepared by an unblinded pharmacist, who will assign subjects to one of the four randomization sequences such that 2 male and 2 female subjects will be randomized to each sequence. Each treatment will be given exactly once and in random order according to the randomization sequence. Both the subjects and the investigators will be blinded to treatment. A sealed copy of the randomization schedule will be available at the research unit in case of an emergency.

3. Pharmacokinetic (PK) Measurements

Blood sampling (SAC)

Prior to dosing, a heparin containing catheter will be inserted into the forearm vein for access to blood sampling.

6 ml samples for determination of ethanol concentration will be collected in red-top tubes with no additives at the following times: pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The blood will be allowed to clot, centrifuged (within 1 hour of sampling) for 10 minutes, serum harvested and stored at \(-20^\circ\) C until analysis by the TDx Analyzer (Abbott Diagnostics).

The total volume of blood drawn for ethanol determination during the study will be about 560 ml over a five to six week period.

4. Pharmacodynamic (PD) Measurements

Electroencephalography (EEG)

Four minute segments of 28-channel EEG, using a Neuroscan Brain Imager, will be recorded for each subject with eyes closed at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. Subjects will be asked to count back from 500 by threes to maintain constant vigilance during the recordings. The electrodes will be placed using an Electro-cap according to the 10/20 International System with 8 additional electrodes located 50% between the standard 10/20 placement. Linked ears will be used as the reference. Four additional channels will be used to monitor for vertical and lateral eye movements and electromyographic activity. The electrode impedances will be checked before each recording. Impedances should be less than 5.0 kohms and similar between electrodes. Any disturbances in the room or subject movement during the EEG recording will be documented by the EEG technician. The raw EEG will be stored on an optical disk. The objective of each recording is to obtain at least 30 artifact-free frames for further analysis.

Psychometric Performance Tests (PP)

The Wesnes Test Battery (Cognitive Drug Research Computerized Assessment System) of psychometric tests will be administered to each subject at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The Wesnes test battery assesses cognitive function and the tasks include simple and choice reaction times, vigilance tests, tracking, memory scanning and immediate and delayed word recognition. A selection of these tests, Word Recognition, Number
Vigilance, Immediate Word Recall and Visual Tracking, will be administered, and parallel forms of the tests will be presented at each session. All the tasks are computerized, the information being presented on high resolution monitors, and the responses recorded via response modules containing two buttons, one marked "NO" and the other "YES". On the evening prior to the day of dosing, subjects will practice each psychometric task once.

Subject Rated Impairment Scale (SRI)
A 100 mm visual analog scale, based on the Subjective High Assessment Scale (SHAS) will be completed by each subject at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. Subjects will indicate their perceived level of intoxication response for each item by placing a mark on an unnumbered 100 mm scale that ranges from "not at all" to "extremely".

Observer Rated Impairment Scale (ORI)
A 100 mm visual analog scale will be completed by the investigator for each subject at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The blinded investigator will indicate his perception of the subject's level of intoxication by placing a mark on an unnumbered 100 mm scale that ranges from "not at all" to "extremely".

5. Safety measurements

Vital Signs
Blood pressure (sitting), heart rate and oral body temperature will be measured at the following times: twice pre-dose and 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 6 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr, 14 hr, and 24 hr after the start of the ethanol infusion.

Skin (facial) temperature, using the Genius tympanic thermometer (First Temp Inc.), will be measured at the following times: twice pre-dose and 15 min, 30 min, 45 min, 1 hr, 1.33 hr, 1.66 hr, 2 hr, 2.25 hr, 2.5 hr, 2.75 hr, 3 hr, 3.25 hr, 3.5 hr, 3.75 hr, 4 hr, 4.25, 4.5 hr, 4.75 hr, 5 hr, 5.25, 5.5 hr, 5.75 hr, 6 hr, 6.33 hr, 6.66 hr, 7 hr, 8 hr, 9 hr, 11 hr, 12 hr and 14 hr after the start of Infusion I. The study will be conducted by Registered Nurses and the Medical Monitor will be on call throughout each treatment period for each subject.

Adverse effects
All subjects will be observed for symptoms and signs of clinical intolerance to the drug or procedures and asked to report any adverse effects. These will be evaluated by the Physician Investigator for their clinical significance and potential need for treatment.

6. Diet
On the evening prior to dosing, subjects will receive a light snack.

No food or beverages will be permitted starting 10 hours prior to dosing. A light standardized meal will be served at 4 hours after the start of ethanol infusion. Dinner and a snack will be served at 9 hours and 14 hours after start of dosing respectively. Caffeine-free beverages may be served with meals. The same menu will be served on corresponding days of each study period. Water will be permitted ad libitum.
When the above measurements are scheduled at the same time, they will be conducted in the following sequence: 1) blood sample, 2) mood scales, 3) EEG, 4) psychometric tests, and 5) vital signs, with the blood sample being collected at exactly the scheduled time. If there is any unscheduled delay, measurements may be omitted as needed to conform to the schedule.

7. Discharge from Clinical Research Unit
At the end of each treatment period (24 hours after dosing), it is anticipated that ethanol levels would be below the detectable limit. However, to ensure subject safety, an alcohol breath test (Alcosensor) will be performed. If the test is negative, subjects will be discharged with instructions to return on the following week for the next treatment. At the end of the last treatment period, subjects will return the alcohol diary prior to leaving the unit.
A study flow sheet is included.

BIOSTATISTICAL DESIGN AND ANALYSIS

Design
This study is designed as a randomized, double-blind, placebo-controlled four-period crossover concentration-controlled trial in sixteen (eight male and eight female) healthy volunteers. Subjects will undertake the study one at a time and will receive each treatment exactly once. The start of each treatment period will be separated by a washout period of at least one week. Prior to randomization, subjects will undergo a single-blind Pharmacokinetic Screen and Familiarization Period to obtain individual pharmacokinetic parameters that can then be used to determine the appropriate infusion rate to be administered to achieve and maintain desired concentrations in the different legs of the study. Pharmacodynamic data obtained during this period may be used as covariates to classify subjects as "responders" and "non-responders".

Sixteen healthy volunteers (eight male and eight female) will complete the study. Since this is a pilot study, no formal sample size calculations were performed, the number of subjects selected is the minimum required to ensure that exactly two male and two female subjects will be randomized to each treatment sequence. After the medical screening, and the Pharmacokinetic screening period, subjects will be randomized to one of the four sequences, and will receive each of the following treatments exactly once:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Infusion I</th>
<th>Infusion II</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ethanol</td>
<td>placebo</td>
</tr>
<tr>
<td>B</td>
<td>placebo</td>
<td>ethanol</td>
</tr>
<tr>
<td>C</td>
<td>ethanol</td>
<td>ethanol</td>
</tr>
<tr>
<td>D</td>
<td>placebo</td>
<td>placebo</td>
</tr>
</tbody>
</table>

Exactly two males and two females will be assigned to each of the four treatment sequences. The appropriate dose and infusion rate of the ethanol solutions administered intravenously will be determined based on the subject’s individual pharmacokinetic
parameters which will be assessed from the serum concentration data obtained during Leg 0. Placebo treatments will consist of normal saline infusions.

Data analysis

I. Pharmacokinetic (PK) Analysis

1. Pharmacokinetic (PK) Methods

The serum concentration of ethanol obtained during the study will be presented in tabular and graphic form for each subject and treatment. Pertinent pharmacokinetic parameters for ethanol, including volume of distribution (V_d), total body clearance (CL_d), area under the concentration-time curve (AUC), maximum concentration (C_max) and time to maximum concentration (t_max) will be estimated for each subject and treatment. Descriptive statistics will be calculated for each parameter.

If appropriate, pharmacokinetic modelling will be performed to estimate the maximum elimination rate constant (V_max) and Michaelis-Menten constant (K_m).

2. Statistical Analysis

Pharmacokinetic parameters will be compared using univariate analysis of variance (ANOVA) to fit a crossover model to the data of the form:

\[ Y_{ijklm} = \mu + \delta_i + \pi_j + \xi_{ki} + \tau_l + \alpha_m + \lambda_{(m-1)} + \epsilon_{ijklm} \quad \ldots \text{eq. 1} \]

where \( Y_{ijklm} \) is the response for the kth subject of the lth gender in the ith sequence in the jth period after the mth treatment, \( \mu \) is the overall mean, \( \delta_i \) is the effect of the ith sequence, \( \pi_j \) is the effect of the jth period, \( \xi_{ki} \) is the effect of the kth subject within the ith sequence, \( \tau_l \) is the effect of the lth gender, \( \alpha_m \) is the effect of the mth treatment, \( \lambda_{(m-1)} \) is the carryover effect of the (m-1)st treatment, and \( \epsilon_{ijklm} \) is the random error associated with \( Y_{ijklm} \). The \( \epsilon_{ijklm} \) are assumed to be normally distributed random variables with mean of 0 and variance \( \sigma^2 \).

The residuals will be tested for normality. If the data are not normally distributed, the data may be transformed. The level of significance (\( \alpha \)) will be set at 0.05. In case of significant differences, multiple comparisons will be performed. In case no statistical differences are observed, a 'post-hoc' power analysis will be performed to assess the discriminative ability of the statistical tests performed for future studies in the same setting, and to calculate appropriate sample sizes for future studies. Because the calculation of power for crossover models is quite complex, the power of the F test for analysis of variance (associated with the first period data) will be determined. This estimation of power does not take into account the crossover design of the study and therefore is a conservative estimate. The Pearson-Hartley charts of the power of the F test will be used to determine power (41).

II. Pharmacodynamic (PD) Analysis
1. Electroencephalography (EEG)
Each of the 5-minute recordings will be reviewed and edited to remove each 2.5 second epoch that is contaminated with artifacts (eye movement, muscle movement, electrode artifacts, or other disturbances noted during the recording). The remaining 2.5 second artifact-free frames will be averaged to form an average topographical map for each recording. The amplitude, power, and relative power of the EEG signal in the five classical frequency bands (delta: 0.39 - 3.0 Hz; theta: 4.3 - 7.8 Hz; alpha: 8.2 - 11.7 Hz; beta I: 12.1 - 16.0 Hz; and beta II: 16.4 - 30 Hz) at each electrode will be determined for each average topographical map. The total amplitude and power for each average map will be calculated. Differences of each treatment from baseline as well as from placebo for each of these parameters will be calculated.

2. Psychometric Performance (PP) Tests
The following measures will be derived from the Wesnes test battery:

<table>
<thead>
<tr>
<th>Task</th>
<th>Primary Measure</th>
<th>Secondary Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word Recognition</td>
<td>Sensitivity</td>
<td>Speed (msec)</td>
</tr>
<tr>
<td>Number Vigilance</td>
<td>Accuracy (%)</td>
<td>Speed (msec)</td>
</tr>
<tr>
<td>Tracking</td>
<td>Mean errors (cm)</td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>Accuracy (%)</td>
<td></td>
</tr>
</tbody>
</table>

3. Rating Scales (SRI/ORI)
A score between 0 and 100 will be obtained for each item on the visual analog scale at each time point by measuring the number of millimeters between the left end of the scale and the mark placed by the subject.

4. Pharmacodynamic (PD) Methods
Response-time profiles, i.e., plots of change in response variable from predose baseline vs. time plots for each subject during each treatment period will be tabulated and plotted for each response measure obtained from the EEG, PP tests and SRI/ORI scales. Pertinent summary pharmacodynamic parameters including baseline response, maximal observed response ($E_{max}$), time to reach maximum response ($T_{max}$), and area under the effect-time curve (AUE) will be determined and descriptive statistics for each of the above will be calculated.

Effect-concentration profiles will be plotted for each subject at each treatment. Tolerance development will be assessed by visual observation of these plots. Pharmacokinetic-pharmacodynamic modelling will be performed, if appropriate.

5. Statistical Analysis
Because there are many variables of interest in this statistical analysis, the multiplicity of desired inferential statements about the data become problematic. Adjusting the level of significance ($\alpha$) for the multiple statistical comparisons, as made in traditional confirmatory analysis, would result in extremely small $\alpha$ values and virtually no likelihood of detecting any statistically significant differences. Therefore, using the concept of exploratory data analysis, expected differences between treatments based on previously reported studies and patterns apparent from examining the data may be evaluated statistically without adjusting the level of significance. The results of these analyses will be used to make descriptive inferential statements about the data, but not
to reject the null hypothesis. Hypotheses generated by this study would have to be confirmed by prospective studies involving a larger number of subjects.

Primary pharmacodynamic measures that will be evaluated include: changes in relative EEG power in the delta, theta, and alpha bands, changes in primary measures of the Wesnes battery, and changes in the items, "HIGH", "DRUNK", "DROWSY", and "ALCOHOL EFFECTS" on the SRI scales. Statistical comparisons for the other pharmacodynamic parameters will be treated as exploratory data analysis. These will be used to generate hypothesis rather than to make formal conclusions based on the data.

Results of the summary pharmacodynamic parameters \( E_{\text{max}}, T_{\text{max}}, \text{AUE} \) for each response measure for each treatment will be compared using statistical techniques appropriate for a 4-way crossover design with repeated measures. The model used to fit the data would be identical in form to the model described above in eq. 1 (see Statistical Analysis for the Pharmacokinetic (PK) Analysis).

The residuals will be tested for normality. If the data are not normally distributed, the data may be transformed. The level of significance \( (\alpha) \) will be set at 0.05. In case of significant differences, multiple comparisons will be performed. In case no significant differences are observed, a power analysis similar to the one described above (see Statistical Analysis under PK analysis) will be performed.

Since one of the aims of this study is to assess the relationship between the different PD measures viz. EEG changes, psychometric performance and mood changes, linear regression (using a mixed effects regression model) of the EEG parameters on the different psychometric performance and mood parameters will be performed to determine the significance of the relationship between the different PD response measures. The model will incorporate different variance structure matrices (simple, unspecified and autoregressive) to model the variance of the response measure \( (42) \). Residuals will be tested for normality. The level of significance \( (\alpha) \) will be set at 0.05.

**HUMAN SUBJECT CONCERNS**

Subjects enrolled in the study will receive ethanol intravenously, have blood samples drawn for ethanol determination, and undergo a series of tests including EEG, psychometric tests and rating scales, repeatedly over a 12 hour period on 5 occasions. Subjects will remain in the study facility from the night before the study day until the morning after the study day (approximately 36 hours for each treatment period) to preclude any motor or other accidents that may result from the impairment caused by alcohol.

1. **Study drug**

Subjects will receive infusions of 10% v/v ethanol, over a one or six hour period in a crossover fashion. These infusions may produce some local irritation to the veins. Alcohol (ethyl alcohol) may produce the following side-effects: local irritation, nausea, vomiting, flushing and feeling of warmth, changes in heart rate and blood pressure, diaphoresis, diuresis, dizziness, changes in sexual desire, drowsiness, euphoria or false feeling of confidence and well being \( (3) \). Alcohol is known to be teratogenic and if used in pregnant women, it can result in morphological and neurological abnormalities in the
child, called fetal alcohol syndrome. The features of this syndrome include CNS dysfunction, slowness of growth, characteristic facial abnormalities and a variable set of major and minor malformations (3).

Subjects will be monitored for the development of adverse effects to the study drug by nurses in the study facility. Vital signs (blood pressure, heart rate and temperature) will be determined periodically during the study. Adverse effects will be managed as deemed necessary by the medical monitor.

At the end of each treatment period (24 hours after dosing) it is anticipated that ethanol levels would have dropped to zero. However, a breath alcohol test will be performed prior to discharge to ensure that the subject does not have any detectable ethanol levels.

II. Blood sampling
Subjects will have fourteen 6-ml blood samples drawn during Leg 0 and twenty 6-ml blood samples drawn during each treatment period (Legs 1-4). A total of about 560 ml of blood will be drawn during the study over a period of five to six weeks.

III. Test Battery
The test battery consists of EEG, psychomotor tests and rating scales and will be administered periodically during each treatment period. The risk associated with these tests is minimal. Subjects will be expected to wear the Electro-caps throughout the treatment period, which may result in some discomfort.

IV. Pre- and post-study physical exam and laboratory tests
Subjects may experience some discomfort during the physical exam, EKG and laboratory tests to be performed during screening and at the end of the study.

Subjects will receive no personal benefits to their health from participating in the study, but the procedures will be conducted at no cost to them and they will receive an honorarium for their participation. Any information obtained about subjects from this research will be kept strictly confidential. Subjects will provide written informed consent and have the right to withdraw from the study at any time.
REFERENCES:

24. Ekman G et al; Effects of alcohol intake on subjective and objective variables over a five


38. Slattum P; Personal communication (1992).


Medical Screening

Pharmacokinetic Screen and Familiarization Period
Males: 0.6 g/kg IV Ethanol infused over 1 hour
Females: 0.5 g/kg IV Ethanol infused over 1 hour
Leg 0

Assessment of PK parameters
\( V_{\text{max}}, K_m, V_d \)
Dose Individualization

RANDOMIZATION
Four-way Crossover (Legs 1 - 4)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Infusion I</th>
<th>Infusion II</th>
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<tbody>
<tr>
<td></td>
<td>(1 hour)</td>
<td>(5 hours)</td>
</tr>
<tr>
<td>A</td>
<td>ethanol</td>
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<tr>
<td>B</td>
<td>placebo</td>
<td>ethanol</td>
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<tr>
<td>C</td>
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<td>ethanol</td>
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<tr>
<td>D</td>
<td>placebo</td>
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Randomization sequences for intravenous ethanol study

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Leg 1</th>
<th>Leg 2</th>
<th>Leg 3</th>
<th>Leg 4</th>
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<tbody>
<tr>
<td>I</td>
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<td>III</td>
<td>C</td>
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<td>IV</td>
<td>D</td>
<td>C</td>
<td>B</td>
<td>A</td>
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</table>

Trt A: Infusion I: Ethanol  Infusion II: Saline
Trt B: Infusion I: Saline  Infusion II: Ethanol
Trt C: Infusion I: Ethanol  Infusion II: Ethanol
Trt D: Infusion I: Saline  Infusion II: Saline

Infusion I: 0 - 1 hr, Infusion II: 1 - 6 hrs.
### Study Period Flow Sheet for Leg 0 of intravenous ethanol study

<table>
<thead>
<tr>
<th>Time</th>
<th>-12</th>
<th>-10</th>
<th>-1</th>
<th>0</th>
<th>0.25</th>
<th>0.5</th>
<th>0.75</th>
<th>1.0</th>
<th>1.33</th>
<th>1.66</th>
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<th>4.0</th>
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<td><strong>Admission</strong></td>
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<td><strong>Infusion</strong></td>
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<tr>
<td><strong>SAC</strong></td>
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<tr>
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<td><strong>Discharge</strong></td>
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</table>

SAC: Serum Samples for Alcohol Determination, EEG: Electroencephalography, PP: Psychometric Performance Battery, SRI/ORI: Subject Rated Impairment & Observer Rated Impairment Scale, VS: Vital Signs (blood pressure, heart rate, temperature)
Study Period Flow Sheet for Legs 1-4 of intravenous ethanol study

|       | -12 | -10 | -1  | 0   | 0.25 | 0.5 | 0.75 | 1   | 1.33 | 1.66 | 2   | 3   | 4   | 6   | 6.33 | 6.66 | 7   | 8   | 9   | 11  | 12  | 14  | 16  | 24  |
|-------|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Admission | X   |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Infusion |     |     |     |     |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| SAC     | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |
| EEG     | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |
| PP      | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |
| SRI/ORI | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |
| VS      | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |
| Skin Temp | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   | X   |     |
| Meals/Snacks | X   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Discharge |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | X   |

SAC: Serum Samples for Alcohol Determination, EEG: Electroencephalography, PP: Psychometric Performance Battery, SRI/ORI: Subject Rated Impairment & Observer Rated Impairment Scale, VS: Vital Signs (blood pressure, heart rate, temperature), *: Skin temperature measured every 15 minutes during this period
DETERMINATION OF DOSING REGIMENS

1. Estimation of Pharmacokinetic Parameters from Pharmacokinetic Screen and Familiarization period (Leg 0)

The following patient-specific parameters will be estimated from the individual serum concentration-time data from Leg 0 (Pharmacokinetic Screen and Familiarization Period) (1):

- $V_{\text{max}}$: Maximum elimination rate
- $K_m$: Michaelis-Menten constant
- $V_d$: Volume of distribution.

1. Population Estimates

Population parameter estimates for the parameters, $V_{\text{max}}$, $K_m$, and $V_d$ (see table) will be used as a plausibility reference for the estimates obtained for each subject (2,3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Estimate ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{\text{max}}$ [mg/L/hr]</td>
<td>232 ± 26</td>
</tr>
<tr>
<td>$K_m$ [mg/L]</td>
<td>82.1 ± 28.7</td>
</tr>
<tr>
<td>$V_d$ [L/70 kg]</td>
<td>37.3 ± 2.9</td>
</tr>
</tbody>
</table>

2. Initial Estimates

Initial estimates for the pharmacokinetic parameters will be obtained from the slopes of the linear and semi-log concentration-time plots as follows:

- $V_{\text{max}}$ will be estimated as the slope of the initial linear (apparent zero-order) part of the linear concentration-time plot.
- $K_m$ will be estimated from the terminal slope of the log concentration-time plot using equation 1.

\[
K_m = - \frac{V_{\text{max}}}{2.303 \times \text{slope}}
\]  

\(1\)

- $V_d$ can be estimated using equation 2:

\[
V_d = CL \times MRT
\]  

\(2\)

where CL is the total clearance and MRT is the mean residence time calculated by non-compartmental methods (1).

3. Model Fitting

A one compartment model with capacity-limited elimination model will be used to fit the concentration-time data for each subject using MINSQ (Scientific Software Inc.). The model equations are as follows:

during infusion:
\[ \frac{dC}{dt} = \frac{Ko}{V_d} - \frac{(V_{\text{max}} \cdot C)}{(K_m + C)} \]

after infusion:

\[ \frac{dC}{dt} = -\frac{(V_{\text{max}} \cdot C)}{(K_m + C)} \]

The final estimates of the parameters, \( V_{\text{max}} \), \( K_m \), and \( V_d \), will be used in the determination of an appropriate dosing regimen for that subject for the remaining four legs of the study.

II. Calculation of Doses for Legs 1 - 4

1. The dose for Infusion I (Dose I) will be calculated from the patient's individual parameters to achieve a target concentration (\( C_{\text{target}} \)) of 1000 mg/L (± 10%) at the end of the infusion (1 hour).

The dose for Infusion II (Dose II) will be calculated to maintain concentrations at the target level (1000 mg/L ± 10%) over the next 5 hours.

2. A nomogram based on the complete pharmacokinetic model with capacity-limited elimination will be developed to determine the doses required for each leg of the study for each subject based on his/her individual pharmacokinetic parameters.

3. The following treatments will be administered according to the randomization sequences:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Infusion I</th>
<th>Infusion II</th>
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<tbody>
<tr>
<td>A</td>
<td>Dose I</td>
<td>placebo</td>
</tr>
<tr>
<td>B</td>
<td>placebo</td>
<td>Dose II</td>
</tr>
<tr>
<td>C</td>
<td>Dose I</td>
<td>Dose II</td>
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<tr>
<td>D</td>
<td>placebo</td>
<td>placebo</td>
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</table>

Dose I will be administered as a 10%v/v ethanol solution over 1 hour. Dose II will be administered as a 10%v/v ethanol solution over the next 5 hours. Placebo solutions will consist of 0.9% (normal) saline.

4. Dose calculations and dose preparation will be performed by an unblinded pharmacist.

References:
CONSENT FORM

Pharmacokinetic-Pharmacodynamic Relationship for Intravenous Ethanol in Healthy Male and Female Subjects.
Part II: Modeling the Development of Tolerance to the Effects of Intravenous Ethanol Administration in Healthy Male and Female Subjects: Effect of Systemic Input Rate and Degree of Ethanol Exposure

1. Investigators

Vijay A. Ramchandani, B.Pharm.Sc. (Bombay, India)
Jürgen Venitz, M.D., Ph.D.
Alan R. Towne, M.D. (Medical Monitor)
Indravadan Gatiwala, M.D.

2. Introduction

I am being asked to participate in this study because I am healthy and not taking any stimulant drugs or medication on a chronic basis. This study is designed to study the effects of intravenous alcohol (ethanol) on my brain wave recordings (electroencephalogram or EEG) and other psychological tests, as well as on my mood and behavior.

Screening
If I agree to participate, I will be expected to provide information about my medical history and alcohol use, have laboratory tests done (including blood and urine tests and a breath alcohol test), have a physical examination, and have an EKG (electric tracing of the heart) to detect whether I have any medical condition that would prevent me from participating in the study. My urine will be tested for drugs of abuse.
I will not be allowed to take any prescription medications for four weeks before the start of the study. I will not be allowed to take any over-the-counter medication (such as antacids, aspirin, vitamins or cold preparations) or any beverages containing caffeine for the 72 hours before each study day and on each study day. I will not be allowed to drink any alcohol starting 72 hours before the first study day through the last day of the study.
For Female Subjects: A blood sample will be collected for a pregnancy test. This test must be negative in order to qualify for participation in the study. This test will be repeated during each visit, on the night before dosing.

Pharmacokinetic Screen and Familiarization Period
After I complete the medical screening examination successfully, I will also have to undergo a Pharmacokinetic Screen and Familiarization Period; the following description explains the procedures to be followed during this period:
I will come to the Clinical Research Unit the night before the study (about 6:00 p.m.)
and will not be released until the morning after the day of dosing; I will have to spend a total of two (2) nights and one (1) day. On the night before dosing (at about 10:00 p.m.), I will start a fast that will continue until nine (9) hours after the start of dosing (about 5:00 p.m. on the day of dosing). On the morning of dosing, two (2) catheters will be inserted, one in each of my forearm veins. I will then receive a one (1) hour infusion of ethanol through one catheter. This dose is expected to achieve a blood alcohol level of about 0.1 mg%, slightly higher than the legal limit for alcohol in Virginia, which is 0.08mg% effective July 1, 1994 (approximately the same concentration resulting from two (2) alcoholic drinks). During and after the infusion, I will have to take the following tests several times during the day: a series of computerized tests, a questionnaire about my mood, and a recording of my brain waves (EEG). Each of these tests takes no more than five (5) minutes. My heart rate, blood pressure and temperature will be monitored throughout the period. During and after the infusion, fourteen (14) blood samples will be collected through the other catheter during this period. If the catheter fails to work, a new catheter will be inserted or it may become necessary to obtain blood samples by sticking a needle directly into the vein. At the end of the period, a breath alcohol test will be done to ensure that I have no detectable ethanol levels, before I am discharged the following day.

Study Periods
After I complete the first phase as described above, I will have to return to the Clinical Research Unit for a total of four (4) study periods over four (4) consecutive weeks. I will have to spend a total of four (4) days and eight (8) nights during this phase of the study. During each period, I will come to the unit at 6:00 p.m. on the evening before ethanol dosing and will not be released until the morning after the day of dosing (a total of two (2) nights and one (1) day for each period). On the night before dosing, I will begin a fast that will continue until four (4) hours after the start of dosing (about noon on the day of dosing).

During each study period, on the morning of dosing, two (2) catheters will be inserted, one in each of my forearm veins. I will then receive a six-hour infusion divided into two parts: the first infusion (Infusion I) will last for one (1) hour, and the second infusion (Infusion II) will start as soon as the first infusion ends and last for another five (5) hours. Depending on the treatment assigned to the period, I will receive the following treatments, Infusion I will contain alcohol, Infusion II will be placebo (Treatment A), Infusion I will be placebo, Infusion II will contain alcohol (Treatment B), Infusion I and Infusion II will both contain alcohol (Treatment C), or Infusion I and Infusion II will both contain placebo (Treatment D). This dose is expected to achieve a blood alcohol level of about 0.1 mg%, slightly higher than the legal limit for alcohol in Virginia, which is 0.08mg% effective July 1, 1994 (approximately the same concentration resulting from two (2) alcoholic drinks). I will have received all four treatments once by the end of the study. Neither I nor the Investigators will know which treatment I am receiving during a given period, however a sealed copy of the treatments will be available on the Clinical Research Unit in case of an emergency.
During and after the infusion, I will have to take the following tests several times during the day: a series of computerized tests, a questionnaire about my mood, and a recording of my brain waves (EEG). Each of these tests takes no more than five (5) minutes. My heart rate, blood pressure and temperature will be monitored throughout the period. During and after the infusion, nineteen (19) additional blood samples will be collected through the catheter during this period. If the catheter fails to work, a new catheter will be inserted or it may become necessary to obtain blood samples by sticking a needle directly into the vein.

At the end of the period, i.e., on the morning of the second day, a breath alcohol test will be done to ensure that I have no detectable ethanol levels before I am discharged. For my safety, the pre-study physical examination, EKG, and laboratory tests will be repeated at the end of the study, i.e., after completion of all four periods. If I discontinue the study prematurely, the physical examination, EKG and laboratory tests would be repeated.

This study is being conducted at the Virginia Commonwealth University/Medical College of Virginia by Vijay A. Ramchandani B.Pharm.Sc., Jürgen Venitz M.D., Ph.D., Alan R. Towne, M.D., and Indravadan Gatiwala, M.D. Dr. Towne is the Medical Monitor for this study and is the first person to be contacted in the case of a medical emergency.

3. Benefits

I am being asked to participate in this study as a volunteer. The study is of no direct medical benefit to me. There will be no charge to me for the screening examination and the results will be made available to me, if I want them. I will be paid $800.00 for the completion of the study. If I withdraw early or am discontinued by the Medical Monitor, the fee will be prorated (see Section 9).

4. Alternative Therapy

There is no therapeutic benefit to me for participating in this study. My participation is entirely voluntary. The alternative is not to participate in the study.

5. Risks, Inconveniences, Discomforts

During the study, I will receive infusions of ethanol, either over a one or six hour period. These infusions may produce some local irritation to the veins. Alcohol (ethyl alcohol) may cause the following side-effects: local irritation, nausea, vomiting, flushing and feeling of warmth, changes in heart rate and blood pressure, diaphoresis (sweating), diuresis (increase in urine output), changes in sexual desire, headache, drowsiness, euphoria or false feeling of confidence and well-being.

For female subjects: Alcohol is known to be harmful to the fetus, and if used in a pregnant woman, it can cause a condition called fetal alcohol syndrome in the baby. The features of this syndrome include low birth weight, decreased brain function and
development, facial abnormalities as well as other malformations.
A total of 94 blood samples will be drawn during the study period of five to six weeks. The total amount of blood will be 560 ml (a little over 1 pint) over the entire duration of the study. To obtain the blood samples as well as to administer the infusions, two (2) small catheters will be inserted into a vein in each of my forearms. This procedure may cause some discomfort, pain, or slight bruising around the site of the needle stick. Sometimes fainting or infection may occur. If the catheter fails to work, a new catheter will be inserted or blood samples will be collected through a needle inserted into the vein.
I will be observed for evidence of any untoward effects and I will be treated promptly and appropriately for any adverse effects, should they occur. I will be informed of any changes in the study and of any new risks that become evident; any new information obtained during the study that may be related to my willingness to continue participation will be provided to me. If any undesirable effects occur, I should report them directly to the investigators. Dr. Alan R. Towne is the Medical Monitor for this study and is the person I should contact in the case of a medical emergency. If I cannot reach Dr. Alan R. Towne, I may contact any of the study investigators.
To have the EEG recorded, I must wear a bathing cap-like apparatus with 28 disks (electrodes). Through a hole in each electrode, my scalp will be cleaned and a small amount of jelly-like substance will be applied to the scalp to make a good contact. In addition, two small, round electrodes will be attached, one to each earlobe and four more electrodes will be taped to my face (above and below my eyes). The cap will remain on my head for most of the day. There may be some discomfort associated with the EEG cap. Although the tape and gel used for the EEG recording are hypoallergenic, they may rarely cause skin irritation. After the cap is removed, I will be able to wash my hair. None of the other tests in the study carry any significant medical risk.
There may be some discomfort associated with the physical exam, EKG, and laboratory tests conducted before and after the study.
While on the Clinical Research Unit I will eat only the meals provided by the investigators at the times prescribed by the investigators. I will be required to remain at the Clinical Research Unit for about 36 hours during each study period. I may receive phone calls during the study, but no visitors will be allowed.

6. Costs of Participation

There will be no charge to me for any laboratory tests, physical examination, hospital care, or other tests related to the conduct of this study. This is a time-consuming study that may interfere with my employment or other activities. I confirm that I understand this before the beginning of the study. I will be confined to the study unit for two nights and an entire day on each of the 5 study periods. I must provide my own transportation to and from the study site.
7. Pregnancy

For Female Subjects: I am aware that every effort will be made to have females enter the study on an equal basis with male subjects. Medically accepted birth control is required to enter this study. This will be limited only to regular use of birth control pills. Use of IUDs, condoms, diaphragms, implants, jellies, foams, sponges, being surgically sterile, abstention, or being in a post-menopausal state are not acceptable methods of birth control for this study. However, no birth control method completely eliminates the risk of pregnancy. If pregnancy occurs, there may be a risk of miscarriage, birth-defects, or other unforeseen medical conditions. A pregnancy test will be conducted during each period of the study, before dosing. If I am found to be pregnant, I will be withdrawn from the study.

8. Research Related Injury

Every effort will be made to prevent any injury that could result from my participation in the study. In the event of any physical or mental injury resulting from my participation in this research project, Virginia Commonwealth University/Medical College of Virginia will not provide any compensation. If any injury occurs, medical treatment will be available at MCV hospitals. Fees for such treatment will be billed to me or the appropriate third party insurance.

9. Confidentiality of Records

The investigators will treat my identity with professional standards of confidentiality. Information obtained from this study may be published, but my identity will not be revealed.

10. Withdrawal

My participation in this study is voluntary. If I decide to participate, I may withdraw at any time. Neither refusal to participate nor withdrawal will result in any penalty to loss of benefits to which I am otherwise entitled. If I have any questions at any time concerning the study procedures, I may contact the study investigators:

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<thead>
<tr>
<th>Name</th>
<th>Pager</th>
<th>Office</th>
<th>Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vijay A. Ramchandani</td>
<td>756-1034</td>
<td>828-5429</td>
<td>648-6808</td>
</tr>
<tr>
<td>Jürgen Venitz</td>
<td>756-4106</td>
<td>828-9720</td>
<td>379-5568</td>
</tr>
<tr>
<td>Alan R. Towne</td>
<td>828-0840</td>
<td>743-8299</td>
<td></td>
</tr>
<tr>
<td>Indravadan Gatiwala</td>
<td>*60-1801</td>
<td>828-0840</td>
<td>743-8299</td>
</tr>
</tbody>
</table>

Dr. Alan Towne is the Medical Monitor for this study. He is the first person to be contacted in the case of an emergency.
If I do not complete the study due to premature withdrawal, the honorarium will be prorated based on the amount of usable information which has been collected. If the Medical Monitor terminates my participation in the study I will receive the entire amount.

I have received a copy of this consent form. I have read the above information, and I have had an opportunity to ask questions to help me understand what my participation will involve.

I freely give my consent to participate in this study. If I have any questions regarding my rights as a volunteer in a clinical research study, I can contact the Committee on the Conduct of Human Research (CCHR) at the Medical College of Virginia at 828-0868.

Signed ________________________________ Date _________
(volunteer)

Signed ________________________________ Date _________
(witness)

Signed ________________________________ Date _________
(investigator)
APPENDIX I

Individual concentration-time profiles for intravenous ethanol study

I1 Individual serum ethanol concentration vs. time profiles by subject for Leg 0

I2 Individual serum ethanol concentration vs. time profiles by treatment and subject for treatments A, B and C

I3 Individual serum ethanol concentration vs.time profiles (observed values and curves fitted by compartmental analysis by treatment and subject for treatments A, B and C.
Figure 11.1 Serum ethanol concentration vs. time profile for Leg 0 for Subject 1.

Figure 11.2 Serum ethanol concentration vs. time profile for Leg 0 for Subject 2.

Figure 11.3 Serum ethanol concentration vs. time profile for Leg 0 for Subject 3.

Figure 11.4 Serum ethanol concentration vs. time profile for Leg 0 for Subject 4.
Figure 11.5 Serum ethanol concentration vs. time profile for Leg 0 for Subject 5.

Figure 11.6 Serum ethanol concentration vs. time profile for Leg 0 for Subject 6.

Figure 11.7 Serum ethanol concentration vs. time profile for Leg 0 for Subject 7.

Figure 11.8 Serum ethanol concentration vs. time profile for Leg 0 for Subject 8.
Figure 11.9 Serum ethanol concentration vs. time profile for Leg 0 for Subject 9.

Figure 11.10 Serum ethanol concentration vs. time profile for Leg 0 for Subject 10.

Figure 11.11 Serum ethanol concentration vs. time profile for Leg 0 for Subject 11.

Figure 11.12 Serum ethanol concentration vs. time profile for Leg 0 for Subject 12.
Figure II.13 Serum ethanol concentration vs. time profile for Leg 0 for Subject 13.

Figure II.14 Serum ethanol concentration vs. time profile for Leg 0 for Subject 14.

Figure II.15 Serum ethanol concentration vs. time profile for Leg 0 for Subject 15.

Figure II.16 Serum ethanol concentration vs. time profile for Leg 0 for Subject 16.
Figure 12.1 Serum ethanol concentration vs. time profile for Treatment A for Subject 1.

Figure 12.2 Serum ethanol concentration vs. time profile for Treatment A for Subject 2.

Figure 12.3 Serum ethanol concentration vs. time profile for Treatment A for Subject 3.

Figure 12.4 Serum ethanol concentration vs. time profile for Treatment A for Subject 4.
Figure 12.5 Serum ethanol concentration vs. time profile for Treatment A for Subject 5.

Figure 12.6 Serum ethanol concentration vs. time profile for Treatment A for Subject 6.

Figure 12.7 Serum ethanol concentration vs. time profile for Treatment A for Subject 7.

Figure 12.8 Serum ethanol concentration vs. time profile for Treatment A for Subject 8.
Figure 12.9 Serum ethanol concentration vs. time profile for Treatment A for Subject 9.

Figure 12.10 Serum ethanol concentration vs. time profile for Treatment A for Subject 10.

Figure 12.11 Serum ethanol concentration vs. time profile for Treatment A for Subject 11.

Figure 12.12 Serum ethanol concentration vs. time profile for Treatment A for Subject 12.
Figure 12.13 Serum ethanol concentration vs. time profile for Treatment A for Subject 13.

Figure 12.14 Serum ethanol concentration vs. time profile for Treatment A for Subject 14.

Figure 12.15 Serum ethanol concentration vs. time profile for Treatment A for Subject 15.

Figure 12.16 Serum ethanol concentration vs. time profile for Treatment A for Subject 16.
Figure I2.17 Serum ethanol concentration vs. time profile for Treatment B for Subject 1.

Figure I2.18 Serum ethanol concentration vs. time profile for Treatment B for Subject 2.

Figure I2.19 Serum ethanol concentration vs. time profile for Treatment B for Subject 3.

Figure I2.20 Serum ethanol concentration vs. time profile for Treatment B for Subject 4.
Figure 12.21  Serum ethanol concentration vs. time profile for Treatment B for Subject 5.

Figure 12.22  Serum ethanol concentration vs. time profile for Treatment B for Subject 6.

Figure 12.23  Serum ethanol concentration vs. time profile for Treatment B for Subject 7.

Figure 12.24  Serum ethanol concentration vs. time profile for Treatment B for Subject 8.
Figure 12.25 Serum ethanol concentration vs. time profile for Treatment B for Subject 9.

Figure 12.26 Serum ethanol concentration vs. time profile for Treatment B for Subject 10.

Figure 12.27 Serum ethanol concentration vs. time profile for Treatment B for Subject 11.

Figure 12.28 Serum ethanol concentration vs. time profile for Treatment B for Subject 12.
Figure 12.29 Serum ethanol concentration vs. time profile for Treatment B for Subject 13.

Figure 12.30 Serum ethanol concentration vs. time profile for Treatment B for Subject 14.

Figure 12.31 Serum ethanol concentration vs. time profile for Treatment B for Subject 15.

Figure 12.32 Serum ethanol concentration vs. time profile for Treatment B for Subject 16.
Figure 12.33 Serum ethanol concentration vs. time profile for Treatment C for Subject 1.

Figure 12.34 Serum ethanol concentration vs. time profile for Treatment C for Subject 2.

Figure 12.35 Serum ethanol concentration vs. time profile for Treatment C for Subject 3.

Figure 12.36 Serum ethanol concentration vs. time profile for Treatment C for Subject 4.
Figure 12.37 Serum ethanol concentration vs. time profile for Treatment C for Subject 5.

Figure 12.38 Serum ethanol concentration vs. time profile for Treatment C for Subject 6.

Figure 12.39 Serum ethanol concentration vs. time profile for Treatment C for Subject 7.

Figure 12.40 Serum ethanol concentration vs. time profile for Treatment C for Subject 8.
Figure 12.41 Serum ethanol concentration vs. time profile for Treatment C for Subject 9.

Figure 12.42 Serum ethanol concentration vs. time profile for Treatment C for Subject 10.

Figure 12.43 Serum ethanol concentration vs. time profile for Treatment C for Subject 11.

Figure 12.44 Serum ethanol concentration vs. time profile for Treatment C for Subject 12.
Figure 12.45 Serum ethanol concentration vs. time profile for Treatment C for Subject 13.

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PHARMACOKINETICS AND PHARMACODYNAMICS OF ETHANOL IN HEALTHY VOLUNTEERS: EFFECT OF INPUT-RATE AND DEGREE OF ETHANOL EXPOSURE ON SUBJECTIVE AND OBJECTIVE MEASURES OF IMPAIRMENT

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

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APPENDIX J

Individual baseline-corrected response-time profiles for EEG measures

J1 total power across all bands vs. time by treatment and subject
J2 relative delta power vs. time by treatment and subject
J3 relative theta power vs. time by treatment and subject
J4 relative alpha power vs. time by treatment and subject
J5 relative beta I power vs. time by treatment and subject
J6 relative beta II power vs. time by treatment and subject
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Figure J1.3  Total Power vs. time profiles by treatment for Subject 3.
Figure J1.4 Total Power vs. time profiles by treatment for Subject 4.
Figure J1.5  Total Power vs. time profiles by treatment for Subject 5.
Figure J1.6  Total Power vs. time profiles by treatment for Subject 6.
Figure J1.7 Total Power vs. time profiles by treatment for Subject 7.
Figure J1.8 Total Power vs. time profiles by treatment for Subject 8.
Figure J1.9 Total Power vs. time profiles by treatment for Subject 9.
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Figure J1.15 Total Power vs. time profiles by treatment for Subject 15.
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Figure J2.3 Relative Delta Power vs. time profiles by treatment for Subject 3.
Figure J2.4 Relative Delta Power vs. time profiles by treatment for Subject 4.
Figure J2.5 Relative Delta Power vs. time profiles by treatment for Subject 5.
Figure J2.6  Relative Delta Power vs. time profiles by treatment for Subject 6.
Figure J2.7 Relative Delta Power vs. time profiles by treatment for Subject 7.
Figure J2.8 Relative Delta Power vs. time profiles by treatment for Subject 8.
Figure J2.9 Relative Delta Power vs. time profiles by treatment for Subject 9.
Figure J2.10 Relative Delta Power vs. time profiles by treatment for Subject 10.
Figure J2.11  Relative Delta Power vs. time profiles by treatment for Subject 11.
Figure J2.12 Relative Delta Power vs. time profiles by treatment for Subject 12.
Figure J2.13  Relative Delta Power vs. time profiles by treatment for Subject 13.
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Figure J3.5 Relative Theta Power vs. time profiles by treatment for Subject 5.
Figure J3.6  Relative Theta Power vs. time profiles by treatment for Subject 6.
Figure J3.7  Relative Theta Power vs. time profiles by treatment for Subject 7.
Figure J3.8 Relative Theta Power vs. time profiles by treatment for Subject 8.
Figure J3.9 Relative Theta Power vs. time profiles by treatment for Subject 9.
Figure J3.10 Relative Theta Power vs. time profiles by treatment for Subject 10.
Figure J3.11  Relative Theta Power vs. time profiles by treatment for Subject 11.
Figure J3.12 Relative Theta Power vs. time profiles by treatment for Subject 12.
Figure J3.13 Relative Theta Power vs. time profiles by treatment for Subject 13.
Figure J3.14 Relative Theta Power vs. time profiles by treatment for Subject 14.
Figure J3.15  Relative Theta Power vs. time profiles by treatment for Subject 15.
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Figure J4.3 Relative Alpha Power vs. time profiles by treatment for Subject 3.
Figure J4.4  Relative Alpha Power vs. time profiles by treatment for Subject 4.
Figure J4.5 Relative Alpha Power vs. time profiles by treatment for Subject 5.
Figure J4.6 Relative Alpha Power vs. time profiles by treatment for Subject 6.
Figure J4.7 Relative Alpha Power vs. time profiles by treatment for Subject 7.
Figure J4.8  Relative Alpha Power vs. time profiles by treatment for Subject 8.
Figure J4.9 Relative Alpha Power vs. time profiles by treatment for Subject 9.
Figure J4.10 Relative Alpha Power vs. time profiles by treatment for Subject 10.
Figure J4.11 Relative Alpha Power vs. time profiles by treatment for Subject 11.
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Figure J4.13 Relative Alpha Power vs. time profiles by treatment for Subject 13.
Figure J4.15 Relative Alpha Power vs. time profiles by treatment for Subject 15.
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Figure J5.2  Relative Beta I Power vs. time profiles by treatment for Subject 2.
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Figure J5.5 Relative Beta I Power vs. time profiles by treatment for Subject 5.
Figure J5.6 Relative Beta I Power vs. time profiles by treatment for Subject 6.
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Figure J5.8 Relative Beta I Power vs. time profiles by treatment for Subject 8.
Figure J5.9 Relative Beta I Power vs. time profiles by treatment for Subject 9.
Figure J5.10  Relative Beta I Power vs. time profiles by treatment for Subject 10.
Figure J5.11 Relative Beta I Power vs. time profiles by treatment for Subject 11.
Figure J5.12 Relative Beta I Power vs. time profiles by treatment for Subject 12.
Figure J5.13 Relative Beta I Power vs. time profiles by treatment for Subject 13.
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Figure J5.15 Relative Beta I Power vs. time profiles by treatment for Subject 15.
Figure J5.16 Relative Beta I Power vs. time profiles by treatment for Subject 16.
Figure J6.1 Relative Beta II Power vs. time profiles by treatment for Subject 1.
Figure J6.2 Relative Beta II Power vs. time profiles by treatment for Subject 2.
Figure J6.3 Relative Beta II Power vs. time profiles by treatment for Subject 3.
Figure J6.4  Relative Beta II Power vs. time profiles by treatment for Subject 4.
Figure J6.5  Relative Beta II Power vs. time profiles by treatment for Subject 5.
Figure J6.6  Relative Beta II Power vs. time profiles by treatment for Subject 6.
Figure J6.7 Relative Beta II Power vs. time profiles by treatment for Subject 7.
Figure J6.8 Relative Beta II Power vs. time profiles by treatment for Subject 8.
Figure J6.9 Relative Beta II Power vs. time profiles by treatment for Subject 9.
Figure J6.10  Relative Beta II Power vs. time profiles by treatment for Subject 10.
Figure J6.11  Relative Beta II Power vs. time profiles by treatment for Subject 11.
Figure J6.12 Relative Beta II Power vs. time profiles by treatment for Subject 12.
Figure J6.13 Relative Beta II Power vs. time profiles by treatment for Subject 13.
Figure J6.14 Relative Beta II Power vs. time profiles by treatment for Subject 14.
Figure J6.15  Relative Beta II Power vs. time profiles by treatment for Subject 15.
Figure J6.16 Relative Beta II Power vs. time profiles by treatment for Subject 16.
APPENDIX K

Individual baseline-corrected response-time profiles for PPT measures

K1  number vigilance reaction time vs. time by treatment and subject

K2  word recognition sensitivity vs. time by treatment and subject
Figure K1.1  Number Vigilance Reaction Time vs. time profile by treatment for Subject 1.
Figure K1.2  Number Vigilance Reaction Time vs. time profile by treatment for Subject 2.
Figure K1.3  Number Vigilance Reaction Time vs. time profile by treatment for Subject 3.
Figure K1.4 Number Vigilance Reaction Time vs. time profile by treatment for Subject 4.
Figure K1.5  Number Vigilance Reaction Time vs. time profile by treatment for Subject 5.
Figure K1.6  Number Vigilance Reaction Time vs. time profile by treatment for Subject 6.
Figure K1.7 Number Vigilance Reaction Time vs. time profile by treatment for Subject 7.
Figure K1.8  Number Vigilance Reaction Time vs. time profile by treatment for Subject 8.
Figure K1.9  Number Vigilance Reaction Time vs. time profile by treatment for Subject 9.
Figure K1.10  Number Vigilance Reaction Time vs. time profile by treatment for Subject 10.
Figure K1.11  Number Vigilance Reaction Time vs. time profile by treatment for Subject 11.
Figure K1.12  Number Vigilance Reaction Time vs. time profile by treatment for Subject 12.
Figure K1.13  Number Vigilance Reaction Time vs. time profile by treatment for Subject 13.
Figure K1.14  Number Vigilance Reaction Time vs. time profile by treatment for Subject 14.
Figure K1.15  Number Vigilance Reaction Time vs. time profile by treatment for Subject 15.
Figure K1.16 Number Vigilance Reaction Time vs. time profile by treatment for Subject 16.
Figure K2.1  Word Recognition Sensitivity vs. time profile by treatment for Subject 1.
Figure K2.2  Word Recognition Sensitivity vs. time profile by treatment for Subject 2.
Figure K2.3  Word Recognition Sensitivity vs. time profile by treatment for Subject 3.
Figure K2.4 Word Recognition Sensitivity vs. time profile by treatment for Subject 4.
Figure K2.5  Word Recognition Sensitivity vs. time profile by treatment for Subject 5.
Figure K2.6  Word Recognition Sensitivity vs. time profile by treatment for Subject 6.
Figure K2.7 Word Recognition Sensitivity vs. time profile by treatment for Subject 7.
Figure K2.8 Word Recognition Sensitivity vs. time profile by treatment for Subject 8.
Figure K2.9  Word Recognition Sensitivity vs. time profile by treatment for Subject 9.
Figure K2.10  Word Recognition Sensitivity vs. time profile by treatment for Subject 10.
Figure K2.11  Word Recognition Sensitivity vs. time profile by treatment for Subject 11.
Figure K2.12  Word Recognition Sensitivity vs. time profile by treatment for Subject 12.
Figure K2.13  Word Recognition Sensitivity vs. time profile by treatment for Subject 13.
Figure K2.14  Word Recognition Sensitivity vs. time profile by treatment for Subject 14.
Figure K2.15  Word Recognition Sensitivity vs. time profile by treatment for Subject 15.
Figure K2.16  Word Recognition Sensitivity vs. time profile by treatment for Subject 16.
APPENDIX L

Individual baseline-corrected response-time profiles for SRI/ORI measures

L1 SRI-HIGH score vs. time by treatment and subject
L2 SRI-DRUNK score vs. time by treatment and subject
L3 SRI-ALCOHOL EFFECTS score vs. time by treatment and subject
L4 ORI-HIGH score vs. time by treatment and subject
L5 ORI-DRUNK score vs. time by treatment and subject
Figure L1.1 SRI-HIGH Score vs time by treatment for Subject 1.
Figure L1.2  SRI-HIGH Score vs time by treatment for Subject 2.
Figure L1.3  SRI-HIGH Score vs time by treatment for Subject 3.
Figure L1.4  SRI-HIGH Score vs time by treatment for Subject 4.
Figure L1.5  SRI-HIGH Score vs time by treatment for Subject 5.
Figure L1.6  SRI-HIGH Score vs time by treatment for Subject 6.
Figure L1.7  SRI-HIGH Score vs time by treatment for Subject 7.
Figure L1.8  SRI-HIGH Score vs time by treatment for Subject 8.
Figure L1.9  SRI-HIGH Score vs time by treatment for Subject 9.
Figure L1.10  SRI-HIGH Score vs time by treatment for Subject 10.
Figure L1.11  SRI-HIGH Score vs time by treatment for Subject 11.
Figure L1.12  SRI-HIGH Score vs time by treatment for Subject 12.
Figure L1.13 SRL-HIGH Score vs time by treatment for Subject 13.
Figure L1.14 SRI-HIGH Score vs time by treatment for Subject 14.
Figure L1.15  SRI-HIGH Score vs time by treatment for Subject 15.
Figure L1.16  SRI-HIGH Score vs time by treatment for Subject 16.
Figure L2.1  SRI-DRUNK Score vs time by treatment for Subject 1.
Figure L2.2 SRI-DRUNK Score vs time by treatment for Subject 2.
Figure L2.3  SRI-DRUNK Score vs time by treatment for Subject 3.
Figure L2.4  SRI-DRUNK Score vs time by treatment for Subject 4.
Figure L2.5  SRI-DRUNK Score vs time by treatment for Subject 5.
Figure L2.6  SRI-DRUNK Score vs time by treatment for Subject 6.
Figure L2.7  SRI-DRUNK Score vs time by treatment for Subject 7.
Figure 1.2.8  SRI-DRUNK Score vs time by treatment for Subject 8.
Figure L2.9 SRI-DRUNK Score vs time by treatment for Subject 9.
Figure L2.10 SRI-DRUNK Score vs time by treatment for Subject 10.
Figure L2.11  SRI-DRUNK Score vs time by treatment for Subject 11.
Figure L2.12  SRI-DRUNK Score vs time by treatment for Subject 12.
Figure 1.2.13  SR1-DRUNK Score vs time by treatment for Subject 13.
Figure L2.14  SRI-DRUNK Score vs time by treatment for Subject 14.
Figure L2.15  SRI-DRUNK Score vs time by treatment for Subject 15.
Figure L2.16 SRI-DRUNK Score vs time by treatment for Subject 16.
Figure L3.1  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 1.
Figure L3.2  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 2.
Figure L3.3 SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 3.
Figure L3.4  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 4.
Figure L3.5  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 5.
Figure L3.6 SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 6.
Figure L3.7  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 7.
Figure 1.3.8  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 8.
Figure L3.9  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 9.
Figure L3.10 SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 10.
Figure L3.11  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 11.
Figure L3.12  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 12.
Figure L3.13  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 13.
Figure L3.14  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 14.
Figure L3.15  SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 15.
Figure L3.16 SRI-ALCOHOL EFFECTS Score vs time by treatment for Subject 16.
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Figure L4.2  ORI-HIGH Score vs time by treatment for Subject 2.
Figure L4.3  ORI-HIGH Score vs time by treatment for Subject 3.
Figure L4.4 ORI-HIGH Score vs time by treatment for Subject 4.
Figure L4.5  ORI-HIGH Score vs time by treatment for Subject 5.
Figure L4.6  ORI-HIGH Score vs time by treatment for Subject 6.
Figure L4.7 ORI-HIGH Score vs time by treatment for Subject 7.
Figure L4.8  ORI-HIGH Score vs time by treatment for Subject 8.
Figure L4.9  ORI-HIGH Score vs time by treatment for Subject 9.
Figure L4.10  ORI-HIGH Score vs time by treatment for Subject 10.
Figure L4.11 ORI-HIGH Score vs time by treatment for Subject 11.
Figure I4.12  ORI-HIGH Score vs time by treatment for Subject 12.
Figure L4.13 ORI-HIGH Score vs time by treatment for Subject 13.
Figure L4.14  ORI-HIGH Score vs time by treatment for Subject 14.
Figure L4.15  ORI-HIGH Score vs time by treatment for Subject 15.
Figure L4.16  ORI-HIGH Score vs time by treatment for Subject 16.
Figure L5.1 ORI-DRUNK Score vs time by treatment for Subject 1.
Figure L5.2 ORI-DRUNK Score vs time by treatment for Subject 2.
Figure L5.3  ORI-DRUNK Score vs time by treatment for Subject 3.
Figure L5.4 ORI-DRUNK Score vs time by treatment for Subject 4.
Figure L5.5 ORI-DRUNK Score vs time by treatment for Subject 5.
Figure L5.6  ORI-DRUNK Score vs time by treatment for Subject 6.
Figure L5.7  ORI-DRUNK Score vs time by treatment for Subject 7.
Figure L5.8 ORI-DRUNK Score vs time by treatment for Subject 8.
Figure L5.9  ORI-DRUNK Score vs time by treatment for Subject 9.
Figure L5.10  ORI-DRUNK Score vs time by treatment for Subject 10.
Figure L5.11  ORI-DRUNK Score vs time by treatment for Subject 11.
Figure L5.12  ORI-DRUNK Score vs time by treatment for Subject 12.
Figure L5.13  ORI-DRUNK Score vs time by treatment for Subject 13.
Figure L5.14  ORI-DRUNK Score vs time by treatment for Subject 14.
Figure L5.15  ORI-DRUNK Score vs time by treatment for Subject 15.
Figure L5.16 ORI-DRUNK Score vs time by treatment for Subject 16.
APPENDIX M

Individual baseline-corrected response-concentration profiles for PD measures for intravenous ethanol study

M1 Baseline-corrected relative theta power vs. concentration by treatment and subject

M2 Baseline-corrected non-dominant hand tap-rate for FT vs. concentration by treatment and subject

M3 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. concentration by treatment and subject
Figure M1.1  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 1.
Figure M1.2  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 2.
Figure M1.3 Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 3.
Figure M1.4  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 4.
Figure M1.5  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 5.
Figure M1.6  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 6.
Figure M1.7 Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 7.
Figure M1.8  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 8.
Figure M1.9  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 9.
Figure M1.10  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 10.
Figure M1.11  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 11.
Figure M1.12  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 12.
Figure M1.13 Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 13.
Figure M1.14  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 14.
Figure M1.15  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 15.
Figure M1.16  Baseline-corrected Relative Theta Power vs. Serum ethanol concentration profiles by treatment for Subject 16.
Figure M2.1 Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 1.
Figure M2.2  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 2.
Figure M2.3  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 3.
Figure M2.4  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 4.
Figure M2.5  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 5.
Figure M2.6  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 6.
Figure M2.7  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 7.
Figure M2.8  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 8.
Figure M2.9  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 9.
Figure M2.10  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 10.
Figure M2.11  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 11.
Figure M2.12  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 12.
Figure M2.13  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 13.
Figure M2.14  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 14.
Figure M2.15  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 15.
Figure M2.16  Number Vigilance Reaction Time vs. Serum Ethanol Concentration profiles by treatment for Subject 16.
Figure M3.1 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 1.
Figure M3.2 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 2.
Figure M3.3  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 3.
Figure M3.4 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 4.
Figure M3.5 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 5.
Figure M3.6 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 6.
Figure M3.7 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 7.
Figure M3.8 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 8.
Figure M3.9 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 9.
Figure M3.10 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 10.
Figure M3.11 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 11.
Figure M3.12 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 12.
Figure M3.13 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 13.
Figure M3.14  Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 14.
Figure M3.15 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 15.
Figure M3.16 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. Serum Ethanol Concentration profiles by treatment for Subject 16.
APPENDIX N

Individual response vs. time and serum ethanol concentration vs. time profiles for treatment C for intravenous ethanol study

N1 Relative theta power vs. time and serum ethanol concentration vs. time profiles by subject for treatment C

N2 Number vigilance reaction time vs. time and serum ethanol concentration vs. time profiles by subject for treatment C

N3 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time profiles by subject for treatment C
Figure N1.1 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 1.

Figure N1.2 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 2.

Figure N1.3 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 3.

Figure N1.4 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 4.
Figure N1.5 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 5.

Figure N1.6 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 6.

Figure N1.7 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 7.

Figure N1.8 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 8.
Figure N1.9 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 9.

Figure N1.10 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 10.

Figure N1.11 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 11.

Figure N1.12 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 12.
Figure N1.13 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 13.

Figure N1.14 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 14.

Figure N1.15 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 15.

Figure N1.16 Relative Theta Power vs. time and serum ethanol concentration vs. time for treatment C for Subject 16.
Figure N2.1 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 1.

Figure N2.2 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 2.

Figure N2.3 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 3.

Figure N2.4 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 4.
Figure N2.5 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 5.

Figure N2.6 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 6.

Figure N2.7 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 7.

Figure N2.8 Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 8.
Figure N2.9  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 9.

Figure N2.10  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 10.

Figure N2.11  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 11.

Figure N2.12  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 12.
Figure N2.13  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 13.

Figure N2.14  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 14.

Figure N2.15  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 15.

Figure N2.16  Number Vigilance Reaction Time vs. time and serum ethanol concentration vs. time for treatment C for Subject 16.
Figure N3.1 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 1.

Figure N3.2 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 2.

Figure N3.3 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 3.

Figure N3.4 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 4.
Figure N3.5 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 5.

Figure N3.6 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 6.

Figure N3.7 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 7.

Figure N3.8 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 8.
Figure N3.9 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 9.

Figure N3.10 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 10.

Figure N3.11 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 11.

Figure N3.12 SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 12.
Figure N3.13  SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 13.

Figure N3.14  SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 14.

Figure N3.15  SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 15.

Figure N3.16  SRI-ALCOHOL EFFECTS score vs. time and serum ethanol concentration vs. time for treatment C for Subject 16.
APPENDIX O

Individual response vs. time and response vs. concentration profiles (observed values and fitted curves) for SRI-ALCOHOL EFFECTS score for intravenous ethanol study

01 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment and subject

02 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed and fitted) by treatment and subject
Figure O1.1 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 1.
Figure O1.2 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 2.
Figure O1.3 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 3.
Figure O1.4 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 4.
Figure 01.5 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 5.
Figure O1.6 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 6.
Figure O1.7 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 7.
Figure O1.8 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 8.
Figure O1.9 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 9.
Figure O1.10 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 10.
Figure 01.11 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 11.
Figure O1.12 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 12.
Figure O1.13 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 13.
Figure O1.14 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 14.
Figure O1.15 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 15.
Figure O1.16 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. time (observed values and fitted curves) by treatment for Subject 16.
Figure O2.1 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 1.
Figure O2.2 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 2.
Figure O2.3 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 3.
Figure O2.4 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 4.
Figure O2.5 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 5.
Figure O2.6 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 6.
Figure O2.7 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 7.
Figure 02.8 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 8.
Figure O2.9 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 9.
Figure O2.10 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 10.
Figure O2.11 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 11.
Figure 02.12 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 12.
Figure 02.13 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 13.
Figure O2.14 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 14.
Figure O2.15 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 15.
Figure O2.16 Baseline-corrected SRI-ALCOHOL EFFECTS score vs. serum ethanol concentration (observed values and fitted curves) by treatment for Subject 16.
APPENDIX P

Impairment Scales

P1  Subject-Rated Impairment (SRI) Scale
P2  Observer-Rated Impairment (ORI) Scale
SUBJECT - RATED ALCOHOL IMPAIRMENT SCALE

S. #: ____________________________
S. Init: ____________________________
Leg: ____________________________
Date: ____________________________
Time: ____________________________

Please mark on the line below how you feel right now with respect to each of the following:

1. high
   not at all ____________________________ extremely

2. drunk
   not at all ____________________________ extremely

3. confused
   not at all ____________________________ extremely

4. dizzy
   not at all ____________________________ extremely

5. clumsy
   not at all ____________________________ extremely

6. floating
   not at all ____________________________ extremely

7. uncomfortable
   not at all ____________________________ extremely

8. slurred speech
   not at all ____________________________ extremely

9. feel great
   not at all ____________________________ extremely

10. feel terrible
    not at all ____________________________ extremely

11. drowsy
    not at all ____________________________ extremely

12. alcohol effects
    not at all ____________________________ extremely

sri.frn//VAR::6/19/96
OBSERVER - RATED ALCOHOL IMPAIRMENT SCALE

S. #: ___________________________        Leg: ___________________________
S. Init: ___________________________       Date: ___________________________
Observer Init.: ___________________________
Time: ___________________________

Please mark on the line below how you perceive the subject feels right now with respect to each of the following:

1. high
   not at all ___________________________ extremely □

2. drunk
   not at all ___________________________ extremely □

3. confused
   not at all ___________________________ extremely □

4. drowsy
   not at all ___________________________ extremely □
APPENDIX Q

Program code for model equations in Scientist

Q1 One compartment body model for oral ethanol
Q2 PK-PD model for acute tolerance to SRI effects of oral ethanol
Q3 One compartment body model for intravenous ethanol
Q4 Two compartment body model for intravenous ethanol
Q5 PK-PD model for acute tolerance to SRI effects of intravenous ethanol
// ETOH ORAL PK
// Zero order input into absorption compartment, First order absorption
// One compartment body model with Michaelis-Menten elimination

IndVars: T
DepVars: C
Params: VMAX, KM, V, KA, D, TINF

// Zero order input
CRATEA = (D/V)/TINF
CRATEB = 0
FLAG = UNIT(T-TINF)
CRATE = CRATEA*(1-FLAG) + CRATEB
// First order absorption
A' = CRATE-(KA*A)
// One compartment body model with saturable elimination
C' = KA*A-(VMAX*C/(KM+C))
// Initial conditions
T = 0
A = 0
C = 0
***
PK-PD Model for Acute Tolerance to SRI effects of Oral Ethanol

IndVars: T
DepVars: C, CSAL
Params: VMAX, KM, V, KA, D, TINF, S, kon, koff

PK
Zero order input into absorption compartment, First order absorption
One compartment body model with Michaelis-Menten elimination

PD
Direct effect linearly related to concentration
Feedback effect (tolerance) related to direct effect by first-order process
Effect: SRI-ALCOHOL EFFECTS Score

// Drug-induced direct effect - Linear
CSALD = S*C

// Feedback effect
CSALFB' = kon*CSALD-koff*CSALFB

// Total effect
CSAL = CSALD-CSALFB

// Initial conditions
T=0
A=0
C=0
CSALFB=0

***
// PK Model for Intravenous Ethanol (1-compartment)  
// ethanol1.eqn Version 1.0  
// VAR and JV June 3, 1994  
//  
// ETOH infusion PK  
// 1 compartment model with zero-order input and Michaelis-Menten elimination  
//  
IndVars: T  
DepVars: C  
Params: VMAX, KM, D1, D2, V, TINF1, TINF2  
//  
// Dose administration as two consecutive IV infusions  
// INFUSION 1  
CRATE1A=(D1/V)/TINF1  
CRATE1B=0  
FLAG1=UNIT(T-TINF1)  
CRATE1=CRATE1A*(1-FLAG1)+CRATE1B*FLAG1  
// INFUSION 2  
CRATE2A=(D2/V)/(TINF2-TINF1)  
CRATE2B=0  
FLAG2=UNIT(T-TINF2)  
CRATE2=CRATE2A*FLAG1*(1-FLAG2)+CRATE2B*FLAG2  
CRATE=CRATE1+CRATE2  
//  
// One compartment body model with saturable elimination  
C'=CRATE-VMAX*C/(KM+C)  
// Initial conditions  
T=0  
C=0  
***
PK Model for Intravenous Ethanol (2-compartment)

ethivpk.eqn Version 2.0

VAR and JV March 13, 1996

//
// ETOH infusion PK
// 2 compartment model with zero-order input, first-order distribution,
// Michaelis-Menten elimination
//
IndVars: T
DepVars: C
Params: D1, D2, TINF1, TINF2, VMAX, KM, V, K12, K21

// Dose administration as two consecutive IV infusions
// INFUSION 1
CRATE1A = (D1/V)/TINF1
CRATE1B = 0
FLAG1 = UNIT(T-TINF1)
CRATE1 = CRATE1A*(1-FLAG1) + CRATE1B*FLAG1

// INFUSION 2
CRATE2A = (D2/V)/(TINF2-TINF1)
CRATE2B = 0
FLAG2 = UNIT(T-TINF2)
CRATE2 = CRATE2A*FLAG1*(1-FLAG2) + CRATE2B*FLAG2
CRATE = CRATE1 + CRATE2

// Two compartment body model with saturable elimination
C' = CRATE-VMAX*C/(KM+C)-K12*C+K21*CT
CT' = K12*C-K21*CT

// Initial conditions
T = 0
C = 0
CT = 0
CSALFB = 0

***
PK-PD Model for Acute Tolerance to SRI Effects of Intravenous Ethanol

ETHEMAX2.EQN Version 2.0
VAR and JV March 13, 1996

PK-PD Modelling of Subjective Effects of Ethanol

IndVars: T
DepVars: C, CSAL
Params: D1, D2, TINF1, TINF2, VMAX, KM, V, K12, K21, Emax, Ec50, n, Kon, Koff

PK

2-compartment model with zero-order input, first-order distribution, Michaelis-Menten elimination

Dose administration as two consecutive IV infusions

INFUSION 1
CRATE1A = (D1/V)/TINF1
CRATE1B = 0
FLAG1 = UNIT(T-TINF1)
CRATE1 = CRATE1A*(1-FLAG1) + CRATE1B*FLAG1

INFUSION 2
CRATE2A = (D2/V)/(TINF2-TINF1)
CRATE2B = 0
FLAG2 = UNIT(T-TINF2)
CRATE2 = CRATE2A*FLAG1*(1-FLAG2) + CRATE2B*FLAG2
CRATE = CRATE1 + CRATE2

Two compartment body model with saturable elimination
C' = CRATE-VMAX*C/(KM+C)-K12*C+K21*C
CT' = K12*C-K21*CT

PD

Direct effect related to concentration by sigmoidal Emax model

Feedback effect (tolerance) related to direct effect by first-order process

Effect: SRI-ALCOHOL EFFECTS Score

Drug-induced Effect - sigmoidal Emax model
CSALD = (Emax*(C^n))/((Ec50^n)+(C^n))
Feedback Effect
CSALFB' = Kon*CSALD-Koff*CSALFB
Total Effect
CSAL = CSALD-CSALFB

Initial conditions
T = 0
C = 0
CT = 0
CSALFB = 0

***