1991

Pharmacokinetics of Ceftibuten-cis and Its trans Metabolite in Healthy Volunteers and in Patients with Chronic Renal Insufficiency

Judy Shepard Kelloway
University of Minnesota

Walid M. Awni
University of Minnesota

Chin C. Lin
Schering-Plough Corporation

See next page for additional authors

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1991, p. 2267–2274
0066-4804/91/112267-08$02.00/0

Vol. 35, No. 11

Pharmacokinetics of Ceftibuten-*cis* and Its *trans* Metabolite in Healthy Volunteers and in Patients with Chronic Renal Insufficiency

JUDY SHEPARD KELLOWAY,[1,2] WALID M. AWNI,[1,2] CHIN C. LIN,[3] JOSEPHINE LIM,[3] MELTON B. AFFRIME,[3] WILLIAM F. KEANE,[1] GARY R. MATZKE,[1,2]† AND CHARLES E. HALSTENSON[1,2]*

The Drug Evaluation Unit, Division of Nephrology, Hennepin County Medical Center, Minneapolis, Minnesota 55415[1]; College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455[2]; and Schering-Plough Corporation, Kenilworth, New Jersey 07033[3]

Received 11 March 1991/Accepted 14 August 1991

The impact of renal insufficiency on the dispositions of 300 mg of orally administered ceftibuten-*cis*, a new broad-spectrum oral cephalosporin, and its primary metabolite ceftibuten-*trans* was characterized in 30 adult subjects. Subjects were divided into five groups of six subjects each on the basis of their 24-h ambulatory creatinine clearances (CL_{CR}). The apparent total body clearance (CL_P/F; where F is absolute bioavailability) and renal clearance of ceftibuten-*cis* were significantly lower in subjects with end-stage renal disease (on maintenance hemodialysis; group V) and in those with severe (CL_{CR}, 5 to 29 ml/min; group IV) and moderate (CL_{CR}, 30 to 49 ml/min; group III) renal insufficiency than in those with mild renal insufficiency (CL_{CR}, 50 to 80 ml/min; group II) or normal renal function (CL_{CR}, >80 ml/min; group I). A significant correlation was observed between CL_{CR} and ceftibuten-*cis* CL_P/F. The mean apparent steady-state volume of distribution (V_β/F) of ceftibuten-*cis* ranged from 0.21 to 0.24 liter/kg in subjects in group I, II, III, and IV. V_β/F was significantly greater in the group V subjects with end-stage renal disease (V_β/F, 0.39 ± 0.27 liters/kg). These changes in V_β/F cannot be separated from possible changes in bioavailability. The maximum concentration of ceftibuten-*trans* in plasma was significantly higher and occurred significantly later in group IV subjects than it did in subjects in the other groups. The terminal elimination half-life of ceftibuten-*trans* was significantly and progressively prolonged as CL_{CR} declined (2.63 ± 1.02, 5.37 ± 1.93, 14.29 ± 10.84, and 19.46 ± 9.69 h in groups I, II, III, and IV, respectively). The hemodialysis clearance of ceftibuten-*cis* was 76.9 ± 18.0 ml/min, and the fraction of the administered dose of ceftibuten-*cis* removed during ~3 h of hemodialysis was 39 ± 9%. Ceftibuten dosage adjustments are proposed for subjects with renal insufficiency.

Ceftibuten {(6*R*,7*R*)-7[(2)-2-(2-aminothiazol-4-yl)-4 carboxy-2-butenyolamino]-8-oxo-5-thia-1-azabicyclo [4,2,0] oct-2-ene-2 carboxylic acid; molecular weight, 410.43} (Fig. 1) is an investigational, orally active broad-spectrum cephalosporin that has demonstrated in vitro antibacterial activity against a wide range of gram-negative and gram-positive bacteria (6). In vitro studies have shown that 92% of all members of the family *Enterobacteriaceae* are susceptible to ceftibuten, whereas 78.7 and 45.1% are susceptible to cefixime and cefuroxime, respectively (7). The activity of ceftibuten against 95 respiratory tract pathogens was superior or comparable to that reported for other oral cephalosporins such as cefprozil (BMY-28100), cefuroxime axetil, cefetamet (RO 15-8074), cefteram (RO 19-5247), and cefixime (7).

Ceftibuten is administered as the active *cis* isomer and is excreted primarily in the urine. Approximately 70% of ceftibuten-*cis* is excreted unchanged in the urine of healthy volunteers, and the terminal elimination half-life ($t_{1/2\beta}$) is 2 to 3 h (1). Plasma protein binding of ceftibuten-*cis* approximates 65% in healthy subjects and is independent of the ceftibuten-*cis* concentration in plasma (12). During multiple dosing of 200 mg of ceftibuten-*cis* twice daily in normal male volunteers, 94% of the drug was excreted in the urine (and thus absorbed) as unchanged ceftibuten and the *trans* isomer (1). Following oral administration, the metabolite ceftibuten-*trans* (antimicrobial activity, approximately one eighth that of the *cis* isomer) is detected in the plasma and accounts for 7 to 10% of the dose recovered in the urine of healthy subjects with normal renal function (1). In vitro experiments have documented seroconversion of the *cis* and *trans* isomers of ceftibuten (12).

This study was designed to characterize the disposition of ceftibuten-*cis* following the administration of a single oral dose to subjects with various degrees of renal function and to assess the effect of hemodialysis on the disposition of ceftibuten.

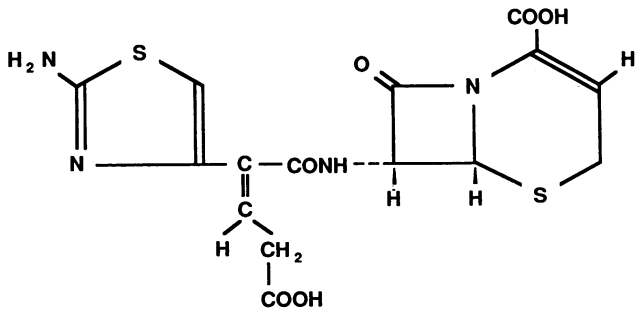

FIG. 1. Structure of ceftibuten.

* Corresponding author.
† Present address: University of Pittsburgh, Pittsburgh, PA 15260.

TABLE 1. Subject demographic data[a]

Subject group[a]	Sex (no. M/ no. F)[b]	Age (yr)	Wt (kg)	Ht (cm)	CL_{CR} (ml/min)	Ceftibuten-*cis* dose (mg/kg)
Group I						
Mean	5/1	37.7	84.4	176.5	117.3	3.6
SD		15.7	11.2	9.7	26.3	0.6
Range		27–57			90.5–161.6	
Group II						
Mean	5/1	56.3[c]	79.7	169.1	75.6	3.9
SD		10.5	14.4	13.3	3.7	0.7
Range		40–68			70.6–79.8	
Group III						
Mean	5/1	53.5	78.5	175.0	36.2	4.0
SD		16.2	17.3	5.2	2.7	1.0
Range		30–70			31.2–38.7	
Group IV						
Mean	3/3	52.5	73.9	171.0	16.1	4.2
SD		13.8	16.7	12.8	7.2	0.9
Range		28–63			7.1–27.3	
Group V						
Mean	3/3	52.2	58.9[d]	166.2	2.9[e]	5.3[f]
SD		11.5	12.3	11.3	4.1	1.0
Range		39–68			2.5–10.3	

[a] There were six subjects in each group.
[b] M, male; F, female.
[c] Versus group I, $P < 0.05$.
[d] Versus groups I, II, and III, $P < 0.05$.
[e] Three subjects were anuric; therefore, $n = 3$ for CL_{CR}.
[f] Versus groups I, II, III, and IV, $P < 0.05$.

MATERIALS AND METHODS

Subjects and study design. Thirty subjects between the ages of 25 and 74 years participated in this study. The subjects were divided into five groups on the basis of their 24-h ambulatory creatinine clearance (CL_{CR}). Subjects in group I had normal renal function (CL_{CR}, >80 ml/min). Those in groups II, III, and IV were nondialyzed subjects with mild (CL_{CR}, 50 to 80 ml/min), moderate (CL_{CR}, 30 to 49 ml/min), or severe (CL_{CR}, 5 to 29 ml/min) renal insufficiency, respectively. Subjects in group V were maintained on chronic hemodialysis three times weekly for a minimum of 12 weeks prior to entry into the study.

The study was approved by the Hennepin County Medical Center's institutional review board. All subjects granted written informed consent before initiation of the study and underwent a complete physical examination, including electrocardiogram, a 24-h ambulatory CL_{CR}, urinalysis, complete blood count with differential, and a multichannel chemistry profile before and after study completion.

None of the subjects had a history of or current evidence of hepatic disease, cardiovascular disorders, respiratory disease, gastrointestinal disorders, blood dyscrasias, rapidly changing renal function as addressed by historical data, or cancer. None of the subjects had received a renal transplant, nor had they received an investigational drug during the 4 weeks prior to the study. Concurrent drug therapy included standard therapy for diseases related to renal insufficiency, such as hypertension, diabetes, and hyperparathyroidism. Subjects were not on concomitant drug therapy known to affect the metabolic capacity or renal handling of drugs. These medications were continued unchanged for at least 14 days prior to the study and during the course of the investigation.

Subjects reported to the Clinical Research Unit of the Drug Evaluation Unit the evening prior to drug administration. During the 10 h prior to dosing they fasted, with the exception of water and concomitant medications such as antihypertensive and oral antidiabetic agents. Drugs that could alter absorption characteristics (i.e., antacids and phosphate binders), gastrointestinal motility (i.e., metoclopramide and bisacodyl), or that were not essential (i.e., vitamin replacements) were not administered until 4 h after

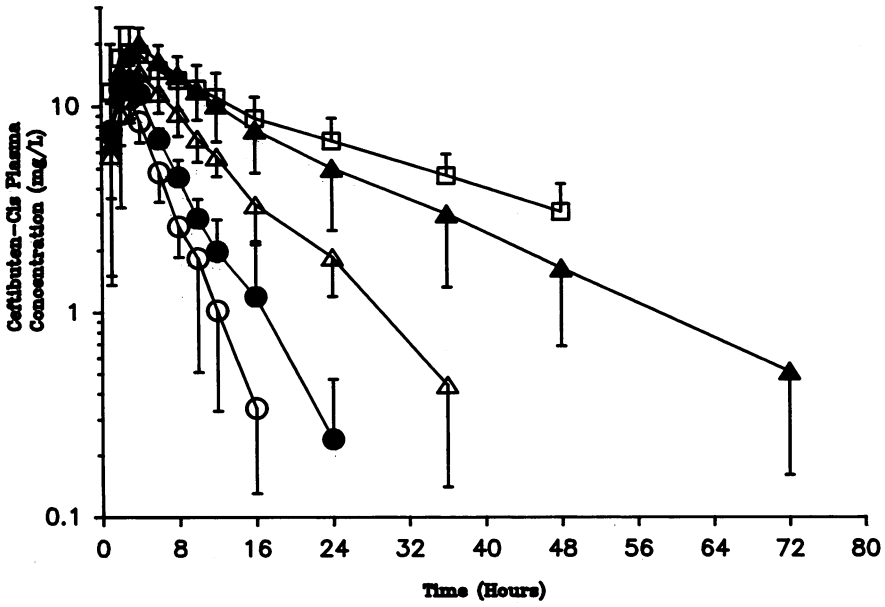

FIG. 2. Ceftibuten-cis plasma concentration-versus-time profiles (mean ± SD) for group I (○), group II (●), group III (△), group IV (▲), and group V (interdialytic dose; □) subjects following a 300-mg oral dose of ceftibuten.

TABLE 2. Ceftibuten-*cis* pharmacokinetic parameters

Subject group	C_{max} (mg/liter)	C_{max} (mg/liter/kg)	T_{max} (h)	$AUC_{0-\infty}$ (mg · h/liter)	β (h^{-1})	$t_{1/2\beta}$ (h)	V_β/F (liter/kg)	CL_P/F (ml/min)	% of total dose recovered in urine as *cis*	CL_R (ml/min)	CL_{NR}/F (ml/min)
Group I											
Mean	11.7	0.14	2.67	65.6	0.26[a,b,c,d]	2.70	0.21	76.7[a,b,c,d]	67.7[a,b,c,d]	51.7[a,b,c,d]	25.0[c,d]
SD	2.3	0.04	0.52	5.5	0.05	0.58	0.03	6.8	9.5	6.4	8.7
Group II											
Mean	13.9	0.18	2.83	94.1	0.19[b,c,d]	3.85	0.22	54.7[b,c,d]	52.6[c,d]	28.6[b,c,d]	26.1[b,c,d]
SD	2.0	0.04	0.75	18.5	0.06	1.26	0.05	9.8	9.5	6.6	8.2
Group III											
Mean	13.0	0.16	3.17	167.7[e]	0.10[d]	7.07	0.24	30.2[c,d]	41.1[d]	12.2[c,d]	18.0
SD	6.5	0.08	0.75	18.3	0.02	1.43	0.07	3.2	11.2	2.8	5.0
Group IV											
Mean	20.7[b,e]	0.31[a,b,e]	4.33[a,b,d,e]	362.9[a,b,e]	0.07	13.39[a,b,e]	0.22	16.2	31.0[d]	5.6	10.6
SD	7.4	0.16	1.37	144.6	0.05	4.67	0.05	7.7	14.6	5.3	3.6
Group V[f]											
Mean	19.5[e]	0.34[a,b,e]	3.0	472.2[a,b,c,e]	0.03	22.28[a,b,c,e]	0.39[a,c,e]	11.3	18.0[g]	2.1[g]	9.2
SD	6.4	0.14	0.89	102.9	0.01	7.92	0.27	2.7	7.2	1.4	1.7

[a] Versus group II, $P < 0.05$.
[b] Versus group III, $P < 0.05$.
[c] Versus group IV, $P < 0.05$.
[d] Versus group V, $P < 0.05$.
[e] Versus group I, $P < 0.05$.
[f] Interdialytic period.
[g] Three subjects were anuric; therefore, $n = 3$ for these parameters.

ceftibuten administration. Each subject was given three 100-mg capsules of ceftibuten-*cis* (lot FMR 87677DOZ; Schering-Plough Corporation, Kenilworth, N.J.) with 120 ml of water at approximately 8 a.m. The subjects remained ambulatory for 2 h after drug administration and remained fasting for 4 h after the dose, when a standardized lunch was served.

Subjects in groups I to IV were confined to the research facility for 48 h after drug administration, to facilitate the collection of blood and urine samples. These subjects also returned to the research facility at 72, 96, and 120 h after drug administration to return urine collections. The final blood sample was obtained at the 72-h visit. Subjects in group V received the drug on two separate occasions, an

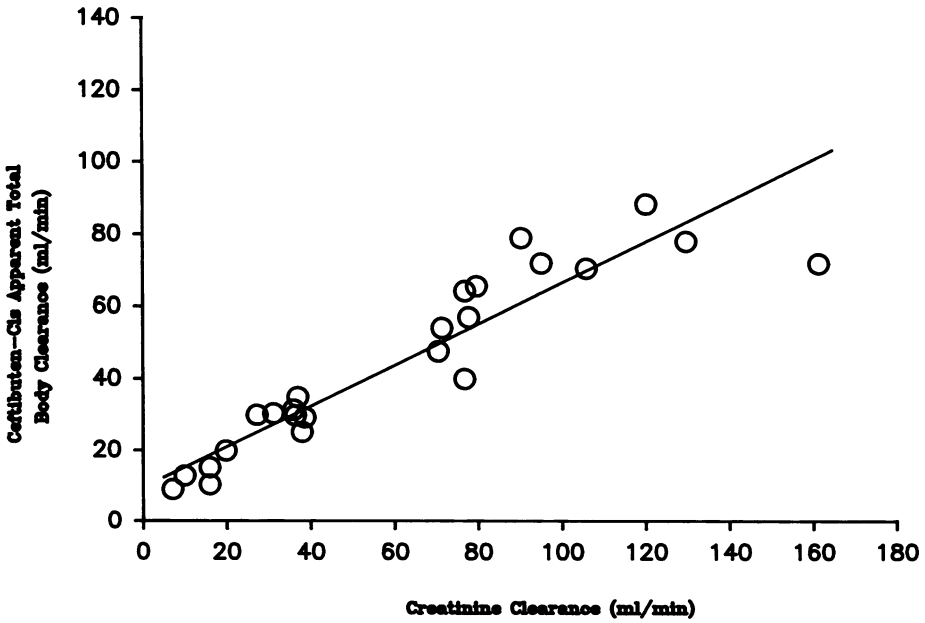

FIG. 3. Relationship of the ceftibuten-*cis* CL_P/F versus CL_{CR} (in millimeters per minute); $CL_P/F = (0.569 \cdot CL_{CR}) + 0.957$ ($n = 24$; for groups I to IV, $r^2 = 0.855$, $P < 0.05$).

interdialytic day and a hemodialysis day. On the interdialytic day, they followed the same procedures as those subjects in study groups I to IV. At least 2 weeks after receiving their first dose, subjects in group V returned to the unit the evening before they were to receive the second dose. They fasted for 10 h, with the exception of water and their required concomitant medications. At 4 h before their regularly scheduled hemodialysis procedure, each patient received three 100-mg capsules of ceftibuten-*cis* orally with 120 ml of water. A high-efficiency dialyzer was used for all of the hemodialysis procedure. Five of the six subjects were dialyzed with a Travenol CA-210 hollow-fiber dialysis filter (Travenol Laboratories, Deerfield, Ill.). The membrane is made of cellulose acetate with 15-μm wall thickness and 2.1-m^2 surface area. One patient was dialyzed with a Travenol CA-170 filter, which has a membrane surface area of 1.7 m^2. All other characteristics of the Travenol CA-170 and Travenol CA-210 filters were comparable. The electrolyte and glucose concentrations of the dialysate content were standardized, with the exception of potassium content, which varied according to the patient's clinical status.

Sample collection. Blood samples (7 ml) were obtained from subjects in groups I to IV and group V (interdialytic dose) immediately prior to drug administration and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 h after dosing.

All blood samples were drawn into heparinized Vacutainer tubes. Plasma was harvested within 15 min of each sample collection. The plasma was pipetted into appropriately labeled polypropylene tubes, frozen, and maintained at −70°C until analysis.

The total urine outputs of subjects in groups I to IV were collected during the following time intervals: before (−12 to 0 h) and 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 h after drug administration. Urine volumes were quantified, and an aliquot was saved at −70°C until analysis.

During the hemodialysis phase for group V subjects, blood samples were obtained immediately before and at 0.5, 1, 2, and 3 h after drug administration. Paired arterial (predialysis filter) and venous (postdialysis filter) blood samples were obtained prior to and 0.5, 1, 2, and 3 h after the start of hemodialysis. Additional blood samples were obtained immediately at the cessation of hemodialysis and at 0.16, 0.33, 0.5, 0.75, 1, 2, 12, 24, 36, and 48 h after the end of hemodialysis.

For those subjects in group V who were not anuric, urine was collected during the following time intervals after each drug administration: 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, and 24 to 48 h. Urine volumes were quantified, and an aliquot sample was saved at −70°C until analysis.

During the hemodialysis procedure, quantitated dialysate collections were performed over the following intervals after the initiation of hemodialysis: 0 to 0.5, 0.5 to 1, 1 to 2, and 2 to 3 h and 3 h to the end of hemodialysis. The total volume was measured, and an aliquot was frozen at −70°C until analysis.

Analytic procedures. The plasma, urine, and dialysate samples were analyzed for ceftibuten-*cis* and ceftibuten-*trans* by a high-performance liquid chromatography method at Schering-Plough Corporation (1). The high-performance liquid chromatography method involves the addition of an internal standard (acyclovir) and 100 μl of 0.2 M sodium phosphate buffer (pH 7) to a 100-μl sample. A 5-μl sample of the resulting solution was then injected into a high-performance liquid chromatograph consisting of a μBondapak C18

TABLE 3. Dialyzer characteristics and ceftibuten-*cis* pharmacokinetic parameters during and after hemodialysis[a]

Intradialytic dose no. in group V subjects	Type of dialyzer filter	Hemodialysis time (min)	Q_D (ml/min)	Q_P (ml/min)	CL_{CR} (ml/min)	CL_{BUN} (ml/min)	CL_{HD} (ml/min)	k_{HD} (h^{-1})	$t_{1/2HD}$ (h)	% of ceftibuten dose recovered in dialysate	Prefilter C_p at the end of HD (mg/liter)	T_{max} (h)	C_p at T_{max} (mg/liter)	Max change in C_p at T_{max} (%)	$t_{1/2\beta}$ after redistribution (h)
25	CA 170	180	748	330	213.0	214.5	69.0	0.312	2.22	36	5.70	0.5	6.20	8.8	17.8
26	CA 210	180	774	204	190.5	233.3	94.3	0.334	2.07	50	4.71	0.75	8.59	81.3	13.1
27	CA 210	240	718	292	210.1	333.1	75.0	0.476	1.46	38	2.49	1.0	5.32	113.0	26.9
28	CA 210	122	742	259	177.6	255.5	54.2	0.553	1.25	25	5.99	0.75	7.39	23.4	17.3
29	CA 210	180	735	228	170.4	245.2	101.9	0.344	2.01	45	7.57	0.16	9.05	19.6	11.5
30	CA 210	174	713	226	155.5	235.5	66.8	0.246	2.82	36	5.43	0.33	7.02	29.3	46.2
Mean		179.3	730	256	186.2	252.9	76.9	0.378	1.97	39	5.32	0.58	7.26	45.9[b]	22.5
SD		37.4	22	40	22.7	41.6	18.0	0.114	0.56	9	1.68	0.31	1.41	41.5	13.1

[a] Q_D, dialysate flow rate; Q_P, plasma flow rate through dialyzer; CL_{CR}, average dialyzer creatinine clearance during hemodialysis procedure; CL_{BUN}, average dialyzer urea nitrogen clearance during hemodialysis procedure; CL_{HD}, average dialyzer ceftibuten-cis clearance during hemodialysis; k_{HD}, apparent elimination rate constant of ceftibuten-*cis* during hemodialysis; $t_{1/2HD}$, half-life during hemodialysis; C_p, ceftibuten concentration in plasma; T_{max}, time of maximal increase in ceftibuten concentration in plasma after cessation of hemodialysis.

[b] $P < 0.05$ compared with the ceftibuten concentration in plasma at the end of hemodialysis.

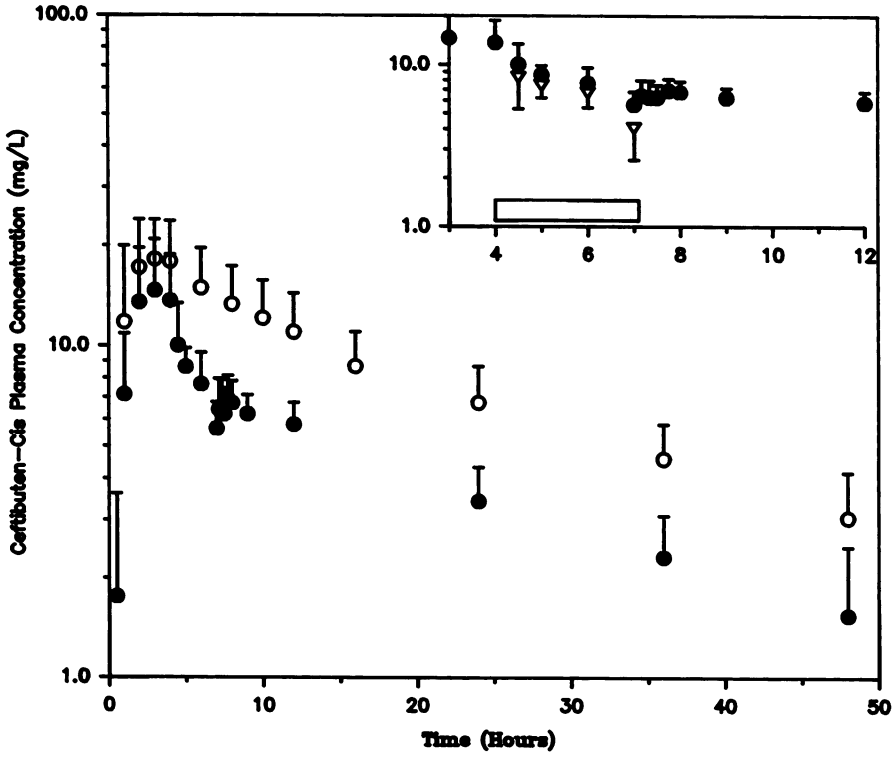

FIG. 4. Ceftibuten-*cis* concentrations (mean ± SD) in plasma following the interdialytic (○) and intradialytic (●) doses of ceftibuten-*cis* for group V subjects. (Inset) Ceftibuten-*cis* predialysis filter (●) and postdialysis filter (▽) concentration in plasma during the 3- to 12-hour time frame after the 300-mg intradialytic oral dose of ceftibuten-*cis*. Hemodialysis was from 4 to 7 h (□).

column and a Waters model 440 absorbance detector with a fixed wavelength of 254 mm. The mobile phase consisted of acetonitrile and 0.05 M ammonium acetate (2:98; vol/vol) delivered at a flow rate of 1 ml/min. The assay was linear over a concentration range of 0.1 to 50 μg/ml. The high-performance liquid chromatography technique was precise and accurate down to 0.1 μg of ceftibuten-*cis* and ceftibuten-*trans* per ml in plasma and dialysate and 0.5 μg/ml in urine. The intra- and interassay coefficients of variation were less than 5% in plasma, urine, and dialysate at concentrations of 5, 10, and 20 μg/ml (12).

Data analysis. The maximum ceftibuten-*cis* and ceftibuten-*trans* concentrations in plasma (C_{max}s) and time to C_{max} (T_{max}) were determined by visual inspection of the plasma concentration-time curves. The terminal elimination rate constant (β) was estimated by nonlinear regression analysis (PCNONLIN, version 3.0; Statistical Consultants, Inc., Lexington, Ky.) (10) of the terminal segment of the postabsorptive or postformation plasma concentration-time curve. In all cases, regressions were carried out from the 8-h postdose sample through the last measured concentration in plasma. $t_{1/2\beta}$ was calculated as $t_{1/2\beta} = 0.693/\beta$. The area under the plasma concentration-time curve from zero to the last time point (AUC_{0-t}) was calculated by the linear trapezoidal method. The residual AUC beyond the last datum point ($AUC_{t-\infty}$) was calculated as the product of the last ceftibuten concentration in plasma and 1/β. The apparent total body clearance (CL_P/F) of ceftibuten-*cis* was determined as CL_P/F = dose/$AUC_{0-\infty}$, where F is the absolute bioavailability of the oral capsule. The apparent volume of distribution (V_β/F) of ceftibuten-*cis* was calculated as $V_\beta/F = (CL_P/F)/\beta$. The renal clearance ($CL_R$) of ceftibuten-*cis* and ceftibuten-*trans* was calculated as $CL_R = A_e^{t_1-t_2}/AUC^{t_1-t_2}$, where $A_e^{t_1-t_2}$ is the amount of ceftibuten-*cis* or ceftibuten-*trans* recovered in the urine within a specific time interval (t_1–t_2), and $AUC^{t_1-t_2}$ is the AUC during the same interval. The apparent nonrenal clearance of ceftibuten-*cis* (CL_{NR}/F) was calculated as the difference between CL_P/F and CL_R.

The hemodialysis clearance (CL_{HD}) of ceftibuten-*cis*, the clearance of blood urea nitrogen (BUN), and CL_{CR} were calculated by the equation $CL_{HD} = AR/AUC_{HD}$, where AR is the total amount of ceftibuten-*cis* recovered in the dialysate, and AUC_{HD} is the area under the arterial (predialysis filter) plasma concentration-time curve during hemodialysis. The apparent elimination rate constant of ceftibuten-*cis* during hemodialysis (k_{HD}) was estimated by nonlinear regression analysis of all arterial (predialysis filter) plasma concentrations obtained during hemodialysis.

In vivo interconversion of ceftibuten-*cis* and ceftibuten-*trans* was not accounted for in the data analysis.

Statistical analysis. Differences in pharmacokinetic parameters between the five groups were evaluated by one-way analysis of variance and the Duncan procedure post hoc test for significance (SPSS/PC + V2.0; SPSS, Inc.). The relationships between CL_{CR} and CL_P/F, CL_{CR} and CL_R, CL_{CR} and β, CL_{CR} and CL_{NR}/F, and CL_{CR} and V_β/F were assessed by orthogonal regression analysis (9, 11). The relationship between CL_{CR} and CL_P/F was used to project the dosage modifications of ceftibuten-*cis* for subjects with renal insufficiency.

Statistical significance was assessed at the $P < 0.05$ level. Data are expressed as mean ± standard deviation (SD).

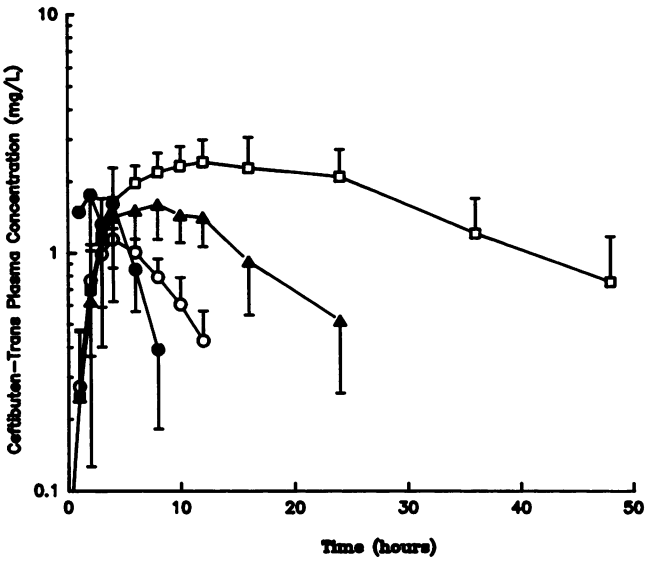

FIG. 5. Ceftibuten-*trans* plasma concentration-versus-time profiles (mean ± SD) for group I (●), group II (○), group III (▲), and group IV (□) subjects following a 300-mg oral dose of ceftibuten-*cis*.

RESULTS

The five groups were not significantly different in sex distribution or height (Table 1). However, subjects in group V weighed significantly less than subjects in groups I, II, and III. Thus, the dose of ceftibuten, in milligrams per kilogram of body weight, was larger in group V subjects ($P < 0.05$). In addition, subjects in group II were significantly older than subjects in group I. The single-dose ceftibuten-*cis* administration was well tolerated in all subjects.

The mean ceftibuten-*cis* plasma concentration-time curves are presented in Fig. 2. The C_{max} of ceftibuten-*cis* was significantly higher in group IV subjects than it was group I and III subjects (Table 2). In addition, C_{max} in group V subjects was higher than that in group I subjects. When C_{max} was adjusted for body weight, group IV and V subjects had significantly larger C_{max} values compared with those in group I, II, and III subjects. The mean T_{max} of ceftibuten-*cis* was significantly longer in group IV subjects compared with that in subjects in all other groups (Table 2).

A significant decline in the CL_P/F of ceftibuten-*cis* was observed as renal function declined. The mean CL_P/F values were 76.7 ± 6.8, 54.7 ± 9.8, 30.2 ± 3.2, 16.2 ± 7.7, and 11.3 ± 2.7 ml/min for subjects in groups I, II, III, IV, and V, respectively. The CL_R of ceftibuten-*cis* also progressively declined as renal function declined (Table 2). Furthermore, the CL_{NR}/F of ceftibuten-*cis* significantly declined as a function of renal insufficiency. The V_β/F of ceftibuten-*cis* was not significantly different between subjects in groups I, II, III, and IV. However, V_β/F was significantly greater in group V subjects than it was in group I, II, and IV subjects; 0.39 ± 0.27 versus 0.21 ± 0.03, 0.22 ± 0.05, and 0.22 ± 0.5 liter/kg, respectively. The $t_{1/2\beta}$ of ceftibuten-*cis* was significantly prolonged in group V subjects compared with that in group I, II, III, and IV subjects. Additionally, the $t_{1/2\beta}$ of ceftibuten-*cis* for subjects in group IV was significantly prolonged compared with that in subjects in groups I, II, and III.

The ceftibuten-*cis* CL_P/F [$CL_P/F = (0.569 \cdot CL_{CR}) + 9.57$; $r^2 = 0.855$] (Fig. 3), the ceftibuten-*cis* CL_R [$CL_R = (0.410 \cdot CL_{CR}) - 1.82$; $r^2 = 0.922$, forced through zero], the ceftibuten-*cis* β [$\beta = (0.0019 \cdot CL_{CR}) + 0.042$; $r^2 = 0.743$], and the ceftibuten-*cis* CL_{NR}/F [$CL_{NR}/F = (0.133 \cdot CL_{CR}) + 11.3$; $r^2 = 0.409$] were all significantly correlated with CL_{CR}. However, changes in the V_β/F of ceftibuten-*cis* did not correlate with the decline in CL_{CR} ($r^2 = 0.059$).

Characteristics of the hemodialysis procedures and ceftibuten-*cis* pharmacokinetic parameters during and after hemodialysis are outlined in Table 3. The time for a dialysis procedure was 179.3 ± 37.4 min. The dialyzer clearance of ceftibuten-*cis* was 76.9 ± 18.0 ml/min, and the percentage of the administered dose of ceftibuten-*cis* recovered in the dialysate during hemodialysis was 39 ± 9%. The CL_{HD} of ceftibuten-*cis* was 25.6% of the CL_{HD} of BUN and 34.8% of the CL_{HD} of creatinine. The average elimination rate constant of ceftibuten-*cis* for all subjects during hemodialysis was 0.378 ± 0.114 h^{-1}, and the corresponding $t_{1/2\beta}$ of ceftibuten-*cis* during hemodialysis was 1.97 ± 0.56 h.

A rise in the ceftibuten-*cis* concentration in plasma was observed in all hemodialysis subjects within 10 min after the cessation of hemodialysis. The maximum increase in the concentration of ceftibuten-*cis* in plasma occurred at 0.58 ± 0.31 h after the cessation of hemodialysis and represented an increase of 45.9 ± 41.5% above the concentration in plasma measured at the cessation of hemodialysis. Thereafter, the ceftibuten-*cis* concentrations in plasma declined monoexponentially (Fig. 4). The $t_{1/2\beta}$ of ceftibuten-*cis* after the redistribution period was 22.5 ± 13.1 h and was not significantly different from the $t_{1/2\beta}$ observed after the interdialytic dose of ceftibuten-*cis*.

Interfering substances were detected in the plasma, urine, and dialysate with the ceftibuten-*trans* analytical procedure in two subjects in group IV and all subjects in group V. This interference was not present in any biologic specimens from the other subjects for which data are reported.

The C_{max} values of ceftibuten-*trans* in plasma ranged from 1.18 to 2.68 mg/liter at 1.75 to 11.33 h following ceftibuten-*cis* administration (Fig. 5 and Table 4). The C_{max} of ceftibuten-*trans* was significantly higher when it was normalized for body weight in group IV subjects in comparison with that in group II and III subjects, and the T_{max} was significantly prolonged in group IV subjects in comparison with that in group I, II, and III subjects. The $AUC_{0-\infty}$ of ceftibuten-*trans* significantly increased as CL_{CR} declined. The $t_{1/2\beta}$ of ceftibuten-*trans* was significantly shorter in group I and II subjects than it was in group III and IV subjects. The $t_{1/2\beta}$ of ceftibuten-*trans* was not significantly different than the $t_{1/2\beta}$ of ceftibuten-*cis* in any of the groups. Although the CL_R of ceftibuten-*trans* was approximately 10 times lower in group IV subjects compared with that in group I subjects, the difference did not achieve statistical significance. One subject from group I and one subject from group II had extremely high CL_R values of ceftibuten-*trans* (group I subject, CL_R = 170 ml/min; group II subject, CL_R = 141 ml/min). If these data are excluded from the analysis, the CL_R of ceftibuten-*trans* remains not significantly changed as CL_{CR} declines (25.8 ± 13.9, 23.5 ± 12.0, 15.1 ± 7.6, and 6.5 ± 7.2 ml/min in group I, II, III, and IV subjects, respectively).

CL_{CR} correlated significantly with ceftibuten-*trans* β [$\beta = (0.0021 \cdot CL_{CR}) + 0.011$; $r^2 = 0.755$]. The ratio of the $AUC_{0-\infty}$ of ceftibuten-*trans* to ceftibuten-*cis* averaged 0.22, 0.20, 0.31, and 0.33 for subjects in groups I, II, III, and IV, respectively, and were not significantly different.

TABLE 4. Ceftibuten-*trans* pharmacokinetic parameters

Subject group	C_{max} (mg/liter)	C_{max} (mg/liter/kg)	T_{max} (h)	$AUC_{0-\infty}$ (mg · h/liter)	β (h^{-1})	$t_{1/2\beta}$ (h)	CL_R (ml/min)	% of total dose recovered in urine as *trans*	Ratio of $AUC_{0-\infty}$
Group I									
Mean	2.12[a]	0.027	3.50	14.12	0.295[a,b,c]	2.63[b,c]	49.89	9.8	0.22
SD	1.38	0.021	1.75	4.88	0.102	1.02	60.31	6.5	0.08
Group II									
Mean	1.18	0.015	4.33	19.62	0.143[c]	5.37[b,c]	43.03	15.3	0.20
SD	0.11	0.003	1.39	6.76	0.051	1.93	49.05	14.5	0.03
Group III									
Mean	1.71	0.022	6.67	52.20[a,d]	0.072	14.29	15.06	14.7	0.31
SD	0.37	0.005	2.40	16.49	0.045	10.84	7.57	7.3	0.10
Group IV									
Mean	2.68[a,b]	0.037[a,b]	11.33[a,b,d]	111.68[a,b,d]	0.045	19.46	6.51[e]	8.7[e]	0.23
SD	0.32	0.008	4.64	44.90	0.024	9.69	7.23	3.9	0.14

[a] Versus group II, $P < 0.05$.
[b] Versus group III, $P < 0.05$.
[c] Versus group IV, $P < 0.05$.
[d] Versus group I, $P < 0.05$.
[e] There were only four subjects because of assay interference in the other two subjects.

DISCUSSION

The pharmacokinetics of ceftibuten in subjects with renal insufficiency are markedly altered from those observed in subjects with normal renal function. This was expected since approximately 70% of ceftibuten-cis is recovered unchanged in urine in subjects with normal renal function. Ceftibuten-*cis* CL_P/F and CL_{NR}/F strongly correlated with CL_{CR}. The fact that the age of the subjects ranged from 27 to 70 years should not influence the data from this study, since age alone has no effect on ceftibuten disposition (1).

The significant increase in the C_{max} of ceftibuten-*cis* in the subjects with severe renal insufficiency may be due to a combination of increased F and/or decreased β of the drug. Renal insufficiency has been shown to reduce the F of some drugs, while it increases the F of others (2, 5). When the ceftibuten-*cis* C_{max} was adjusted for body weight (i.e., milligrams per liter per kilogram), the resulting mean C_{max} was larger in group IV subjects than it was in group I subjects. There was also a delay in the absorption of ceftibuten-*cis* in subjects with severe renal insufficiency (group IV). However, this small change in ceftibuten-*cis* C_{max} and T_{max} may not be clinically significant.

The C_{max}, T_{max}, $AUC_{0-\infty}$, and $t_{1/2\beta}$ values of ceftibuten-*trans* were significantly larger in the subjects with severe renal impairment not undergoing hemodialysis. Although the ratio of ceftibuten-*trans* to ceftibuten-*cis* $AUC_{0-\infty}$ was not significantly different between subjects in the four groups, the P value was 0.078. Given these changes and the fact that ceftibuten-*cis* β decreased as a function of CL_{CR}, it can be suggested that more drug may be metabolized to ceftibuten-*trans* in these severely impaired subjects. There was not a statistically significant difference in the CL_R of ceftibuten-*trans*; however, this may have been due to insufficient statistical power. The $t_{1/2\beta}$ of ceftibuten-*trans* was not different from the $t_{1/2\beta}$ of ceftibuten-*cis*, therefore suggesting that the β of ceftibuten-*trans* is formation rate limited. The percentage of the administered dose of ceftibuten recovered in urine as ceftibuten-*cis* plus ceftibuten-*trans* was significantly greater in group I and II subjects than it was in subjects in groups III and IV (77.6 ± 13.5, 67.8 ± 10.7, 55.7 ± 17.5, and 46.5 ± 15.3%, respectively).

Several methods for modification of the antibiotic dosage recommendation in subjects with reduced renal function have been suggested (4, 13). To achieve the same average concentration in plasma in subjects with impaired renal function as that in normal subjects, the dose can be kept constant and the dosing interval can be changed. Alternatively, the dosing interval can be kept constant and the dose can be altered. Both of these methods give similar average steady-state concentrations, but they yield vastly different effects on the maximum and minimum drug concentrations.

Ceftibuten, as with most other cephalosporins, has not been associated with any concentration-dependent toxicity. Consequently, ceftibuten dose adjustments may not be necessary from a toxicity standpoint. However, dosage adjustments could yield a significant cost savings by reducing the amount of drug required to achieve and maintain therapeutic concentrations. The MIC for 90% of most ceftibuten-susceptible organisms ranges between 0.025 to 0.4 mg/liter. However, clinical response has been demonstrated with once-daily administration of ceftibuten, in which the concentrations in plasma may not exceed the MIC for the entire dosing interval (3). In randomized, single-blind trials, ceftibuten administered once daily at doses of 400 mg (or 6 mg/kg in children) demonstrated a response rate of 92 and 94% against streptococcal pharyngitis and otis media infections, respectively (8). In patients with bronchitis treated with 400 mg of ceftibuten once daily, the infecting pathogens were eliminated from 85% of cases and the clinical response rate was 91% (8). Similar response data for the treatment of urinary tract infections, pneumonia, and sinusitis infections with ceftibuten given at 400 mg once daily also have been defined (12). On the basis of a dose of 400 mg of ceftibuten given orally every 24 h, the dose of ceftibuten should not need alteration until the CL_{CR} drops below 49 ml/min. Table 5 lists dosage adjustments and projected C_{max} and trough concentrations in plasma for ceftibuten on the basis of

TABLE 5. Ceftibuten dosage regimen interval[a]

Subject group	CL_{CR} (ml/min)	Dose (mg)	C_{max} (mg/liter)	Trough ceftibuten concn (mg/liter)
Group I	>80	400	10.1	0.04
Group II	50–79	400	14.0	0.2
Group III	30–49	200	7.8	0.9
Group IV	5–29	100	7.1	1.7
Group V		300[a]	20.0	1.5

[a] Ceftibuten was given to subjects in groups I to IV once every 24 h; hemodialysis patients received ceftibuten at 300 mg three times weekly, after hemodialysis.

CL_{CR}, assuming a 90% F (1) and utilizing the average pharmacokinetic parameters for the CL_{CR} group.

Ceftibuten is a low-molecular-weight compound that is soluble in water and has a relatively low extent of protein binding (although that was not assessed in the subjects in this study); therefore, as anticipated, much of it was removed by hemodialysis. The fraction of the ceftibuten dose removed during the 3-h hemodialysis procedure was 39%, and the CL_{HD} of ceftibuten-*cis* was 25.6 and 34.8% of the simultaneous CL_{HD} of BUN and creatinine, respectively. Therefore, in order to maintain effective concentrations of ceftibuten in plasma, a 300-mg dose of ceftibuten given three times weekly after hemodialysis should achieve effective concentrations in plasma (C_{max} of 20 mg/liter and a trough concentration after hemodialysis of 1.5 mg/liter). These proposed dosage regimens need to be validated for their efficacy in infected patients.

ACKNOWLEDGMENTS

We acknowledge the secretarial assistance of Dee Lunzer, the statistical assistance of Mark Macres, and the technical assistance of the staff of The Drug Evaluation Unit, Clinical Research Unit.

This study was supported by the Schering-Plough Corporation.

REFERENCES

1. **Barr, W. H., C.-C. Lin, E. Radwanski, J. Lim, S. Symchowicz, and M. Affrime.** 1991. The pharmacokinetics of ceftibuten in humans. Diagn. Microbiol. Infect. Dis. **14**:93–100.
2. **Bianchetti, G., G. Graziani, and D. Brancaccio.** 1976. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. Clin. Pharmacokinet. **1**:373–384.
3. **Drusano, G. L.** 1988. Role of pharmacokinetics in the outcome of infections. Antimicrob. Agents Chemother. **32**:289–297.
4. **Gibson, T. P.** 1983. Principles of drug dose adjustment during hemodialysis. Am. J. Kidney Dis. **3**:111–113.
5. **Gibson, T. P., K. M. Giacomini, and W. A. Briggs.** 1980. Propoxyphene and norpropoxyphene plasma concentrations in the anephric patients. Clin. Pharmacol. Ther. **27**:665–670.
6. **Jones, R. N., and A. L. Barry.** 1988. Ceftibuten (7432-5), SCH 39720: comparative antimicrobial activity against 4735 clinical isolates, beta-lactamase stability and broth dilution quality control guidelines. Eur. J. Clin. Microbiol. Infect. Dis. **7**:802–807.
7. **Jones, R. N., and A. L. Barry.** 1988. In-vitro antimicrobial activity of 7432-5 (Sch 39720) against commonly isolated respiratory tract pathogens. J. Antimicrob. Chemother. **22**:387–389.
8. **Kammer, R. L., and T. Jackson.** 1991. Once-daily ceftibuten in the treatment of respiratory tract infections. Abstr. 17th Int. Congr. Chemother., 1991, abstr. 364.
9. **Lentner, C.** 1982. Geigy scientific tables, vol. 2, 8th ed., p. 217. CIBA-GEIGY, Basel, Switzerland.
10. **Metzler, C. M., G. L. Elfring, and A. J. McEwen.** 1974. A package of computer programs for pharmacokinetic modeling. Biometrics **30**:562–571.
11. **Riggs, D. S., J. A. Guarnieri, and S. Addelman.** 1978. Fitting straight lines when both variables are subject to error. Life Sci. **22**:1305–1360.
12. **Schering-Plough Corporation.** Data on file.
13. **Tozer, T. N.** 1974. Nomogram for modification of dosage regimens in subjects with chronic renal function impairment. J. Pharmacokinet. Biopharm. **2**:13–28.