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Pharmacokinetics of Intravenous Cefetamet (Ro 15-8074) and Oral Cefetamet Pivoxil (Ro 15-8075) in Young and Elderly Subjects

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The purpose of this investigation was to evaluate the effect of advanced age on the pharmacokinetics of cefetamet and its prodrug, cefetamet pivoxil. A secondary objective of this study was to assess the effect of food on the absorption of cefetamet pivoxil in the elderly. Twenty-four healthy subjects (twelve young and twelve elderly) received (in a Latin square design) a single-dose, 515-mg infusion of cefetamet, a single 1,000-mg oral dose of cefetamet pivoxil during fasted conditions, and a single 1,000-mg oral dose of cefetamet pivoxil 10 min after a standardized low-fat breakfast. Serial blood and urine samples were collected over a 36-h period and analyzed by high-performance liquid chromatography. Intravenous and oral pharmacokinetic parameters were obtained by using model-independent techniques. The systemic clearance and renal clearance of cefetamet were significantly lower ($P < 0.05$) in elderly subjects compared with in young controls after intravenous administration. No significant difference was observed in the apparent volumes of distribution at steady state between the two groups. Consequently, half-life and mean residence time were prolonged. A trend toward a lower renal clearance/creatinine clearance ratio was observed in our elderly population. Oral clearance of cefetamet was only slightly reduced in our elderly subjects, consistent with an increase in plasma half-life. Otherwise, oral pharmacokinetic parameters were comparable between elderly and young subjects. Additionally, the same effects of food were observed on the absorption characteristics of cefetamet (no change in maximum concentration of drug in plasma and an increase in both time to maximum concentration of drug in plasma and bioavailability) in our elderly subjects as in our young volunteers. Age did not appear to alter the deesterification and bioavailability of cefetamet pivoxil. We conclude that the small reduction in the elimination of cefetamet in the elderly would not require dose adjustment for this population.

Cefetamet pivoxil (Ro 15-8075) is a new oral cephalosporin antibiotic which requires deesterification on its first pass through the intestinal mucosa or liver or both to form the microbiologically active drug cefetamet (4). Cefetamet possesses broad-spectrum antimicrobial activity against many aerobic gram-positive and -negative bacteria (10). It shows particular promise against members of the family *Enterobacteriaceae* and *Proteus mirabilis* (10).

The pharmacokinetics of both intravenous (i.v.) cefetamet and oral cefetamet pivoxil have been well described for healthy adult male volunteers (4). Briefly, cefetamet is eliminated predominantly unchanged in urine via glomerular filtration and is shown to have systemic clearance (CL_S) and renal clearance (CL_R) values of 140.3 and 130.1 ml/min, respectively (4). Cefetamet has a relatively small distribution volume (volume of distribution at steady state [V_{ss}] = 0.29 liter/kg), consistent with other cephalosporin antibiotics (1). Cefetamet is only modestly bound (~22%) to human plasma proteins (4). An important finding after oral administration of cefetamet pivoxil was the presence of a food effect (4; Y. K. Tam et al., manuscript in preparation).

The elderly population has been shown to have reductions in glomerular filtration rate (8) and achlorhydria (2). Therefore, we investigated the effect of age on the absolute oral bioavailability (F) of cefetamet pivoxil under fed and fasted conditions as well as the distribution and elimination of i.v. cefetamet.

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MATERIALS AND METHODS

Subjects. Twelve healthy young (ages, 20 to 39 years) and 12 healthy elderly (ages, 65 to 78 years) normal male subjects within 20% of their ideal body weight (6) were included in the study. All subjects received a complete medical history, physical examination, 12-lead electrocardiogram, and laboratory tests (hematology, urinalysis, and blood chemistry) within 14 days of the start of the study. Subjects presenting abnormal results were excluded from the study. Additional exclusion criteria included having any history of gastrointestinal, renal, hematologic, hepatic, endocrine, or cardiovascular disease. Subjects who had a febrile illness within 14 days prior to the study, ingested prescription medication within 14 days of the study, or consumed over-the-counter medications within 3 days of the study initiation were also excluded from participation. Subjects were instructed to refrain from alcohol ingestion from 72 h before initiation of the study and through the follow-up period.

Study design and treatment assignment. This was an open-labeled study in which young and elderly subjects were assigned in a random fashion to one of six possible treatment sequences forming eight three-by-three Latin squares. Each subject received each of the following treatments. Treatment A was i.v. infusion of 545 mg of cefetamet monosodium salt (equivalent to 515 mg of cefetamet free acid) in a total volume of 20 ml over a period of 20 min; treatment B was oral administration of 1,000 mg (two tablets) of cefetamet pivoxil as the hydrochloride salt (equivalent to 705 mg of cefetamet free acid) with 200 ml of water on an empty stomach after a 10-h fast; treatment C was oral administra-

tion of 1,000 mg (two tablets) of cefetamet pivoxil as the hydrochloride salt (equivalent to 705 mg of cefetamet free acid with 200 ml of water) 10 min after a standard breakfast. All subjects completed all three treatments. A 1-week washout separated each treatment period.

Drug administration. Subjects entered the study facility by 10 p.m. the night before drug administration during each treatment period. Subjects fasted from 10 p.m. the evening before drug administration through 3 h after drug administration (except for subjects in treatment group C, who completed a standard breakfast 10 min before oral cefetamet pivoxil administration). The standard breakfast consisted of the following: two rolls with a small amount of butter (5 g) and jam (20 g), one cup of black coffee or tea (100 ml), one cup of milk (150 ml), one orange or banana, and 50 g of cheese. Water was taken at a rate of approximately 100 ml every 2 h for the first 6 h of each treatment period. Shortly before drug administration, an indwelling Longdwel catheter (64 mm long) with corresponding obturator was inserted into an antecubital vein. Prior to i.v. administration of cefetamet, an additional indwelling Longdwel catheter was inserted into an antecubital vein in the opposite arm from that of blood collection. A total dose of 515 mg of cefetamet (in a concentration of 25.8 mg/ml) was administered to each subject over a 20-min period. During all three treatment periods, the time of drug administration was 8 a.m.

Sample collection. (i) i.v. administration. Samples (5 ml) of venous blood were collected into VACUTAINER tubes containing sodium fluoride and potassium oxalate as anticoagulants at the following times: preadministration; 5, 10, and 15 min after the start of the drug infusion; and exactly at the end of the infusion (20 min). Additional samples were collected 25, 30, 40, and 50 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 36 h after the start of the infusion. The samples were collected during the first 12 h via the indwelling catheter. The later samples were obtained via venipuncture. Urine samples were obtained from each subject during the following time intervals: preadministration, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 24, and 24 to 36 h after drug administration.

(ii) Oral administration. Samples (5 ml) of venous blood were collected into the above-mentioned VACUTAINER tubes at the following times: preadministration; 10, 20, 30 min after drug administration; and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 36 h after drug administration. The samples during the first 12 h after administration were collected via the indwelling catheter. The later samples were obtained via venipuncture. Urine samples were obtained from each subject at the following time intervals: preadministration, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 24, and 24 to 36 h after drug administration.

(iii) CL_{CR}. A 24-h urine creatinine clearance (CL_{CR}) measurement (from a 24-h urine collection and a plasma sample collected at the midpoint of the urine sampling) was obtained during the screen and at intervals of 12 to 24 and 24 to 36 h during the three treatment periods. Values reported in Table 1 and used in Table 2 were obtained during treatment A.

Sample preparation and analysis. After blood sample collection, the VACUTAINER tube was slowly tilted backwards and forwards to bring the anticoagulant into solution. Within 30 min after collection, the blood sample was centrifuged at 1,000 × *g* for 15 min and the plasma was transferred into polyethylene-stoppered glass tubes. Both plasma and urine samples were stored in the dark at −20°C until analysis. Cefetamet was determined in plasma and urine according to the validated high-performance liquid chromatography method of Wyss and Bucheli (11). The method used reversed-phase (C_{18}) chromatography with UV detection. The mobile phase was 4 mM $HClO_4$–acetonitrile 83:17 (vol/vol). Urine samples were diluted with 0.01 N hydrochloric acid, and the mobile phase was adjusted to an 85:15 (vol/vol) composition. The detection limits for this assay were 0.2 and 20 μg/ml in plasma and urine, respectively. Quality control plasma specimens at concentrations of 1, 20, and 40 μg/ml (coefficients of variation of 5.5, 4.1, and 4.0%, respectively) and urine specimens at concentrations of 30, 300, and 500 μg/ml (coefficients of variation of 6.0, 3.4, and 4.8%, respectively) were analyzed in duplicate with each assay batch, which consisted of all plasma or urine samples from a given subject treatment period.

TABLE 1. Demographic data

Age group and subject no.	Age (yr)	Wt (kg)	Ht (cm)	CL_{CR} (ml/min)
Young				
1	27	67.4	177	167
2	23	64.7	177	144
3	28	72.3	176	95
4	20	83.5	185	206
5	32	66.7	176	152
6	39	72.4	174	138
7	34	67.8	170	65
8	35	76.1	179	134
9	26	71.7	170	116
10	26	58.3	166	101
11	28	78.8	175	156
12	27	63.8	165	70
Mean (SD)	29 (5)[a]	70.3 (7.0)	174 (6)	129 (41)
Elderly				
13	73	75.4	171	85
14	72	80.8	178	123
15	69	77.0	177	109
16	66	71.3	174	125
17	78	62.8	163	94
18	70	90.9	183	97
19	69	85.2	173	102
20	65	73.5	186	96
21	72	89.2	172	87
22	66	77.7	170	152
23	66	71.5	173	151
24	67	68.6	163	88
Mean (SD)	69 (4)	77.0 (8.4)	174 (7)	109 (24)

[a] $P < 0.05$ (elderly compared with young).

Pharmacokinetic analysis. Plasma concentration data were analyzed by standard model-independent pharmacokinetic techniques. Terminal elimination rate constants (β) were estimated for all curves by performing standard unweighted linear least-squares regression analysis of the natural log of concentration versus time. The slope of this line is equal to −β. The area under the plasma concentration-versus-time curve (AUC) was estimated by using a combination of the linear and log trapezoidal rules (3). The log trapezoidal rule was employed when concentration data were in an exponentially declining phase. The AUC from the last point to infinity ($AUC_{t,\infty}$) was estimated by dividing this last concentration by β. The half-life ($t_{1/2}$) was estimated by dividing 0.693 by β. Systemic clearance (CL_S) after i.v. doses was estimated by dividing the dose by the $AUC_{0-\infty}$. Renal clearance (CL_R) after i.v. administration was calculated by dividing the amount of drug excreted unchanged in the urine by the AUC over the urine collection interval. Nonrenal

TABLE 2. Pharmacokinetic parameters of cefetamet in young and elderly subjects after i.v. infusion (20 min) of 545 mg of cefetamet monosodium salt

Age group and subject no.	CL_S (ml/min)	V_{ss} (liter/kg)	$t_{1/2}$ (h)[a]	Mean residence time (h)	CL_R (ml/min)	CL_{NR} (ml/min)	CL_R/CL_{CR}	CL_R/CL_S
Young								
1	168	0.35	1.85	2.36	96.4	71.6	0.58	0.57
2	134	0.35	2.11	2.82	97.2	36.8	0.67	0.73
3	127	0.33	2.34	3.12	101	26.0	1.07	0.80
4	182	0.36	2.19	2.71	145	37.0	0.71	0.80
5	173	0.35	1.93	2.24	133	40.0	0.87	0.77
6	176	0.27	1.58	1.87	142	34.0	1.03	0.81
7	144	0.30	1.91	2.32	115	29.0	1.77	0.80
8	144	0.33	2.29	2.94	112	32.0	0.84	0.78
9	149	0.31	1.96	2.52	121	28.0	1.04	0.81
10	134	0.34	1.98	2.48	124	10.0	1.23	0.93
11	169	0.29	1.80	2.22	122	47.0	0.78	0.72
12	157	0.35	1.86	2.34	115	42.0	1.64	0.73
Mean (SD)	155 (18.6)[b]	0.33 (0.03)	1.96 (0.22)[b]	2.49 (0.35)[b]	119 (16.0)[b]	36.1 (14.6)	1.02 (0.37)	0.77 (0.08)
Elderly								
13	97.1	0.29	2.92	3.78	62.2	34.9	0.73	0.64
14	126	0.30	2.56	3.20	98.7	27.3	0.80	0.78
15	117	0.31	2.71	3.37	87.9	29.1	0.81	0.75
16	137	0.45	2.70	3.85	96.6	40.4	0.77	0.71
17	82.0	0.33	3.20	4.20	68.3	13.7	0.73	0.83
18	147	0.25	1.91	2.60	102	45.0	1.05	0.69
19	117	0.25	2.23	3.03	101	16.0	0.99	0.86
20	109	0.29	2.61	3.27	91.2	17.8	0.95	0.84
21	112	0.30	3.14	4.00	71.2	40.8	0.82	0.64
22	142	0.34	2.48	3.11	112	30.0	0.74	0.79
23	133	0.34	2.46	3.04	104	29.0	0.69	0.78
24	109	0.29	2.56	3.08	65.0	44.0	0.74	0.60
Mean (SD)	119 (19.0)	0.31 (0.05)	2.58 (0.38)	3.38 (0.48)	88.3 (17.2)	30.7 (10.8)	0.82 (0.12)	0.74 (0.09)

[a] Harmonic mean.
[b] $P < 0.05$ (elderly compared with young).

clearance (CL_{NR}) was determined by $CL_{NR} = CL_s - CL_R$. The volume of distribution at steady state (V_{ss}) and mean residence time (i.v.) were obtained by using standard statistical moments theory, correcting for i.v. infusion time (5). After oral dose administration, the maximum concentration (C_{max}) and the time to maximum concentrations in plasma (T_{max}) were read directly from the plasma concentration-versus-time curves. AUC was estimated as described above. F of the tablets was estimated as follows:

$$F = \frac{AUC_{0-\infty}\ (oral)}{AUC_{0-\infty}\ (i.v.)} \times \frac{Dose\ (i.v.)}{Dose\ (oral)}$$

Statistical analysis. Demographic data and kinetic parameters after i.v. administration were compared between young and elderly subjects by using the Mann-Whitney test for unpaired samples with equal dispersion. The influence of food and age on the pharmacokinetic parameters after oral administration (C_{max}, T_{max}, F, CL_o, and $t_{1/2}$) was examined by a two-way analysis of variance (RS/1; BBN Products Corp., Cambridge, Mass.). The criterion for statistical significance was $P < 0.05$.

RESULTS

i.v. infusion. Table 1 summarizes the demographic data on each of the subjects studied. As expected, a significant difference in age was prominent between elderly (69 ± 4 years) and young (29 ± 5 years) subjects. Although there was a trend toward higher body weights and lower CL_{CR} values in our elderly subjects, these differences were not

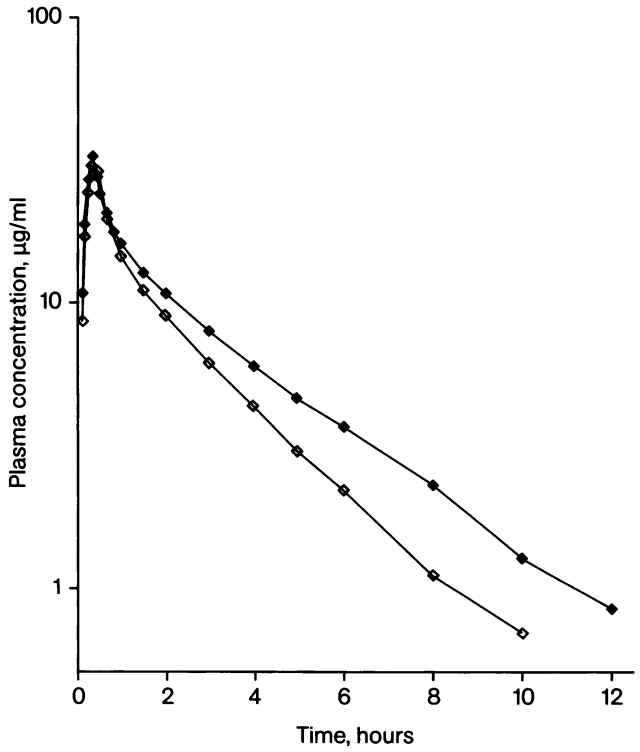

FIG. 1. Mean plasma concentration-versus-time profiles of cefetamet after i.v. infusion (20 min) of 545 mg of cefetamet monosodium salt in young (◇) and elderly (◆) subjects.

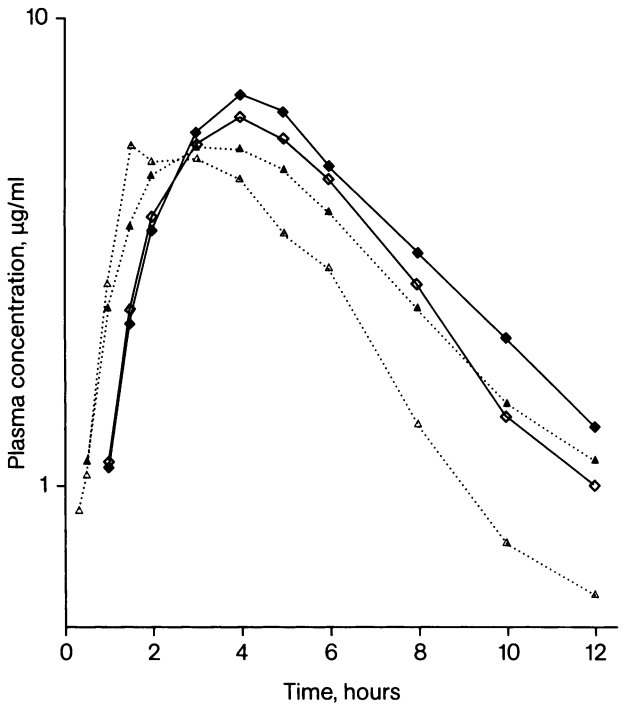

FIG. 2. Mean cefetamet concentrations in plasma at various times after oral administration of 1,000 mg (2 tablets) of cefetamet pivoxil in young (◇) and elderly (◆) subjects under fed conditions and in young (△) and elderly (▲) subjects under fasted conditions.

statistically significant. Figure 1 shows a semilogarithmic plot of mean cefetamet plasma concentration-versus-time data after the i.v. administration of 545 mg of cefetamet monosodium salt (equivalent to 515 mg of cefetamet free acid) over a 20-min period to elderly and young subjects. Table 2 summarizes the pharmacokinetic parameters obtained in the elderly and young subjects after i.v. administration. The CL_S (119 versus 155 ml/min) and CL_R (88.3 versus 119 ml/min) were significantly lower in the elderly subjects than in young controls. No significant changes between age groups were observed for the V_{ss} parameter (0.31 liter/kg [elderly] versus 0.33 liter/kg [young]). Consequently, both $t_{1/2}$ and mean residence time were prolonged in the elderly population. Although there were no differences in CL_{NR} between the two groups, the percentage of cefetamet excreted nonrenally (26% [elderly] and 23% [young]) was considerably higher than previously reported (4). A trend toward a lower CL_R/CL_{CR} ratio was observed within our elderly population (0.82 ± 0.11 [elderly] versus 1.02 ± 0.37 [young]). No adverse effects or side effects were reported or attributed to i.v. drug administration.

Oral administration. Figure 2 shows semilogarithmic plots of mean plasma concentration-versus-time profiles for oral administration of 1,000 mg of cefetamet pivoxil (equivalent to 715 mg of cefetamet free acid) in elderly and young subjects in the fasted and fed conditions. Table 3 provides a summary of the pharmacokinetic data obtained from these profiles. No significant differences were observed between elderly and young subjects in either the fasted or fed condition for the parameters C_{max}, T_{max}, and F. Elderly subjects did show a tendency toward a lower oral clearance (CL_o) and significant prolongation of plasma $t_{1/2}$ consistent with a reduction in renal function. However, both elderly and young subjects demonstrated similar effects of food administration on oral pharmacokinetic parameters. In young subjects, food significantly increased T_{max} (2.8 versus 4.0 h) and F (41.0 versus 51.2%) values. Similarly, elderly subjects had significantly higher T_{max} (3.2 versus 4.2 h) and F (40.1 versus 46.5%) values as a consequence of food ingestion. Neither young nor elderly subjects appeared to have significant alterations in C_{max} values. No adverse effects or side effects were reported or attributed to oral drug administration.

DISCUSSION

i.v. pharmacokinetic data in our healthy young male control volunteers were similar to those which were previously reported. However, our CL_S values were slightly higher (155 versus 140.3 ml/min) and our CL_R determinations were slightly lower (119 versus 130.3 ml/min), resulting in a higher percentage of CL_{NR} (23 versus 6%) in our study compared with the corresponding percentage in previous investigations (4). CL_R/CL_{CR} ratios approached unity in our young control population. Since cefetamet is negligibly protein bound, this data suggests that glomerular filtration represents the major mechanism of renal elimination. Volume of distribution (V_{ss}) and $t_{1/2}$ values for cefetamet compared favorably with previous reports (4).

Comparisons of the i.v. pharmacokinetic parameters between elderly and young volunteers are summarized in Table 2. It is important to emphasize that strict inclusion criteria were imposed throughout this study to ensure that the elderly subjects were free of disease(s) or condition(s) which might interfere with the interpretation of these results. Although a trend toward lower CL_{CR} values was present in the elderly group (109 versus 129 ml/min), this difference was not significant. Additionally, a CL_{CR} value of 109 ml/min is seemingly higher than expected for an elderly population with a mean age of 69 years. However, recent reports support the concept of near normal CL_{CR} values in physiologically healthy elderly people (9).

We did observe a significant reduction in CL_S and CL_R in our elderly population despite our inability to detect statistically significant reductions in CL_{CR}. This discrepancy can be explained by the fact that larger variability in our CL_{CR} determinations was present, making it difficult to detect differences of only 15 to 20%. Despite this inconsistency, the majority of the reduction in the CL_S and CL_R of cefetamet could be accounted for by the apparent reduction in glomerular filtration rate. No significant differences in V_{ss} were observed between elderly and young subjects. Consequently, both $t_{1/2}$ and mean residence time were prolonged secondary to a reduction in CL_S and CL_R.

The CL_R/CL_{CR} ratio has frequently been used as an indicator for xenobiotic renal clearance mechanisms. Assuming that cefetamet is bound only 22% to plasma proteins in both young and elderly subjects, we would observe CL_R/CL_{CR} ratios corrected for protein binding of 1.31 and 1.05 in young and elderly subjects, respectively. This data would then suggest that the CL_R of cefetamet in young subjects may include a minor component of tubular secretion. In contrast, elderly subjects appear to have lower CL_R/CL_{CR} ratios, suggestive of a disproportionate reduction in tubular versus glomerular function. This concept of preferential reduction in tubular function in the elderly was previously suggested by Reidenberg et al. (7). They observed a similar reduction in the ratio of procainamide CL_R to CL_{CR} with advancing age. If these findings are substantiated, application of CL_{CR} measurements as a tool in adjust-

TABLE 3. Pharmacokinetic parameters of cefetamet in young and elderly subjects after oral administration of 1,000 mg (2 tablets) of cefetamet pivoxil under fasted and fed conditions

Age group and subject no.	Fasted					Fed				
	C_{max} (μg/ml)	T_{max} (h)	F (%)	$t_{1/2}$ (h)[a]	CL_O (ml/min)	C_{max} (μg/ml)	T_{max} (h)	F (%)	$t_{1/2}$ (h)[a]	CL_O (ml/min)
Young										
1	5.50	3.0	41.6	2.16	404	5.72	5.0	51.9	2.11	323
2	3.73	2.0	24.1	2.22	555	5.69	4.0	49.0	2.19	273
3	14.7	1.5	26.2	2.81	486	7.07	4.0	58.5	3.62	218
4	4.83	3.0	52.9	2.71	344	4.34	4.0	44.9	2.68	406
5	5.40	2.0	35.8	1.93	483	5.12	4.0	40.5	1.94	428
6	4.32	3.0	40.3	1.93	457	5.45	4.0	50.0	2.02	352
7	6.44	2.0	44.0	2.07	328	5.77	3.0	47.4	2.23	304
8	5.20	4.0	44.2	2.42	325	5.61	4.0	49.3	2.97	291
9	5.82	2.0	39.1	2.17	382	8.98	4.0	71.4	2.38	209
10	4.44	3.0	28.9	2.37	464	7.77	5.0	59.0	2.23	227
11	7.18	6.0	64.0	1.85	264	5.87	3.0	44.2	1.95	382
12	6.84	2.0	51.4	2.17	305	6.77	4.0	47.8	1.69	328
Mean (SD)	6.20 (2.87)	2.8 (1.2)[b]	41.0 (11.6)[b]	2.20 (0.28)[c]	399 (89)	6.18 (1.26)	4.0 (0.6)	51.2 (8.3)	2.24 (0.43)[c]	312 (73)
Elderly										
13	4.55	4.0	32.2	3.35	301	9.41	4.0	54.6	3.21	178
14	4.23	3.0	32.3	2.75	391	6.33	5.0	53.6	3.26	235
15	5.53	4.0	39.3	2.68	298	7.92	4.0	51.5	2.66	227
16	1.87	4.0	18.1	3.39	759	5.51	4.0	41.1	2.37	334
17	10.5	4.0	59.5	3.52	138	9.47	5.0	61.6	4.44	133
18	5.06	2.0	36.7	2.42	400	5.55	4.0	39.9	2.32	368
19	6.66	4.0	45.7	2.72	257	8.73	4.0	52.3	2.44	224
20	7.24	3.0	48.9	2.80	224	5.42	4.0	33.8	3.08	324
21	4.57	3.0	43.8	4.69	257	4.61	5.0	36.6	3.42	307
22	5.70	4.0	56.5	3.48	251	7.43	4.0	60.9	2.66	233
23	4.17	2.0	32.8	2.95	407	9.83	4.0	58.4	2.14	229
24	5.97	1.0	35.9	2.71	303	1.90	3.0	13.8	3.42	788
Mean (SD)	5.50 (2.09)	3.2 (1.0)[b]	40.1 (11.5)[b]	3.03 (0.50)	332 (156)	6.84 (2.39)	4.2 (0.6)	46.5 (14.0)	2.83 (0.58)	298 (168)

[a] Harmonic mean.
[b] $P < 0.05$ (fasted compared with fed).
[c] $P < 0.05$ (elderly compared with young).

ing drug dosage regimens in the elderly could result in an overestimation of drug clearance for those drugs undergoing extensive renal tubular secretions. The clinical significance of this observation with cefetamet would be minimal.

The oral pharmacokinetic profile in our young control population was consistent with previous findings (4). Mean values for cefetamet (CL_O, C_{max}, T_{max}, and F) obtained during the fasted state were 399 ml/min, 6.2 μg/ml, 2.8 h, and 41%, respectively. Mean terminal elimination $t_{1/2}$ was 2.2 h. We did observe a significant food effect in our young population resulting in an increase in both the T_{max} (4.0 h) and F (51%) parameters for cefetamet. This finding is consistent with an earlier report (4). We observed no significant differences in the absorption parameter of C_{max}, T_{max}, and F between our elderly and young subjects. As expected, a trend toward a lower CL_O was observed, while $t_{1/2}$ was slightly prolonged as a consequence of reduced renal function. Additionally, we observed the same effect of food on the absorption characteristics of cefetamet (no change in C_{max} and increases in both T_{max} and F) in our elderly subjects as we did in our younger volunteers. Consequently, it does not appear that otherwise healthy elderly patients will have a significant effect in hydrolyzing the cefetamet pivoxil prodrug ester to cefetamet.

In summary, healthy elderly subjects exhibited modest 20 to 25% reductions in the elimination of cefetamet secondary to reductions in renal function. Otherwise, the pharmacokinetic behaviors of cefetamet pivoxil and cefetamet appear comparable between elderly and young subjects. Considering the good tolerability of the β-lactam antibiotics in general and that of cefetamet pivoxil and cefetamet in particular, the small reduction in the elimination of cefetamet in the elderly would not require any dose reduction in this population.

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