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Human Intravenous Pharmacokinetics and Absolute Oral Bioavailability of Cefatrizine

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Cefatrizine was administered intravenously and orally at dose levels of 250, 500, and 1,000 mg to normal male volunteers in a crossover study. Intravenous pharmacokinetics were dose linear over this range; mean peak plasma concentrations at the end of 30-min infusions were, respectively, 18, 37, and 75 μg/ml, total body clearance was 218 ml/min per 1.73 m^2, renal clearance was 176 ml/min per 1.73 m^2, and mean retention time in the body was 1.11 h. Cumulative urinary excretion of intact cefatrizine was 80% of the dose, and half-lives ranged from 1 to 1.4 h. Steady-state volume of distribution was 0.22 liters/kg. On oral administration, the absolute bioavailabilities of cefatrizine were 75% at 250 and 500 mg and 50% at 1,000 mg. The mean peak plasma concentrations and peak times were, respectively, 4.9, 8.6, and 10.2 μg/ml at 1.4, 1.6, and 2.0 h, mean residence times were 2.4, 2.6, and 3.1 h, and mean absorption times were 1.3, 1.6, and 1.9 h. Oral renal clearance and half-life values corresponded well to the intravenous values. Cumulative urinary excretion of intact cefatrizine (as percentage of dose) was 60 at 250 mg, 56 at 500 mg, and 42 at 1,000 mg. It is hypothesized that the lack of oral dose linearity between the 500- and 1,000-mg doses is due to a component of cefatrizine absorption by a saturable transport process. Relative absorption at the high dose would be sufficiently slow that an absorption "window" would be passed before maximum bioavailability could be attained. It is not expected that the observed bioavailability decrease at doses exceeding 500 mg will have any therapeutic significance, since clinical studies are establishing efficacy for a recommended unit dosage regimen of 500 mg.

Cefatrizine, 7-[R-(-)-2-amino-(*p*-hydroxyphenyl)acetamido-]-3-[1H-1,2,3-triazole-4(5)-ylthiomethyl]3-cephem-4-carboxylic acid, is an orally active semisynthetic cephalosporin antibiotic that exhibits a broad spectrum of antibacterial activity against most strains of clinically important gram-positive and gram-negative bacteria (7, 8, 9, 11, 12). The purpose of this study was to investigate the intravenous (i.v.) pharmacokinetics and absolute oral bioavailability of cefatrizine after administration to normal human volunteers at dose levels of 250, 500, and 1,000 mg.

MATERIALS AND METHODS

Cefatrizine for i.v. administration was supplied in vials by Bristol Laboratories (Syracuse, N.Y.) as the sterile, lyophilized propylene glycol solvate. The contents of a vial were reconstituted in such a manner as to obtain a 600 mg/120 ml (i.e., 5 mg/ml) solution. A portion of the solution in each vial was set aside, frozen, and assayed by the same method used for plasma and urine samples to determine the exact doses administered. Cefatrizine for oral administration was supplied as formulated 250-mg capsules. Analysis of 10 samples from the capsule lot used indicated that capsule cefatrizine content ± standard deviation (SD) was 252.5 ± 1.4 mg.

Cefatrizine was administered to 18 male volunteers, 20 to 45 years of age, each of whom provided informed consent. None had a known sensitivity to penicillin or cephalosporin antibiotics. All were judged healthy on the basis of physical and clinical examination (hemoglobin, erythrocyte sedimentation rate, leukocyte count, eosinophil count, and measurements of bilirubin, creatinine, urea nitrogen, alkaline phosphate, lactic dehydrogenase, aspartate aminotransferase, alanine aminotransferase, serum iron, iron-binding capacity, cholesterol, and total protein in serum).

Experimental procedure. The study was designed as a two-way crossover between i.v. and oral dosing of cefatrizine at nominal dose levels of 250, 500, and 1,000 mg. Six subjects were randomly assigned to each of the dose level groups. i.v. doses of cefatrizine were administered as 30-min infusions of the cefatrizine solution using compact infusion pumps (Harvard Instrument Co., Millis, Mass.). The contents of one, two, or four capsules were emptied into 75 ml of water and stirred thoroughly before oral dosing. On oral dosing the subjects drank the 75 ml of water containing the capsule contents and a further 75 ml of water used to rinse the dosing containers. The capsule shells were swallowed with a final 30-ml rinse. There was a 3-week

TABLE 1. Subject data and cefatrizine doses

Subject no.	Mean ± SD					
	Dose (mg)		Age (yr)	Ht (cm)	Wt (kg)	Body surface area (m^2)
	i.v.	Oral				
1–6	260.0 ± 8.0	252.5	28 ± 11	170 ± 7	69 ± 10	1.79 ± 0.13
7–12	527.5 ± 24.6	505.0	28 ± 9	170 ± 5	67 ± 7	1.78 ± 0.08
13–18	1,037.5 ± 35.6	1,010.0	32 ± 7	170 ± 3	67 ± 7	1.78 ± 0.08

interval between successive doses to any given subject. All subjects fasted overnight before both oral and i.v. dosing. Table 1 presents the doses administered and the mean subject physical characteristics. Subject body surface areas, in square meters, were calculated from height and weight by the Du Bois formula (3). All subject serum creatinine concentrations were 1.1 mg/100 ml or lower.

Heparinized whole blood samples and complete urine collections were taken according to the schedules in Tables 2 and 3. The blood samples were kept in a water ice bath until centrifuged for plasma collection at 3°C. Urine collection bottles were refrigerated during each collection interval. Urine volumes and pH were recorded immediately at the end of each collection interval, and a portion was taken and saved for analysis. The plasma and urine samples were immediately flash-frozen in an alcohol-dry ice bath and maintained at −20°C until thawed for analysis. All plasma, urine, and i.v. dosing solution samples were assayed within 2 weeks of their collection. The mean percentage of original cefatrizine concentration remaining in plasma was 96.0% after 1 week, 99.8% after 2 weeks, and 89.6% after 4 weeks of storage at −15°C. Storage stability at −15°C in urine was 99% remaining after 1 week, 95.1% after 2 weeks, and 90.3% after 4 weeks when pH was preadjusted to 4.0. With no pH adjustment (urine pH 6.8) storage stability was 97.2% after 1 week, 91.8% after 2 weeks, and 81.0% after 4 weeks. The pH of the urine samples collected in this study was not adjusted to pH 4.0 before storage, so there could have been a loss of up to 9% of cefatrizine activity before assay.

Assay procedure. Cefatrizine concentrations were estimated by using a cylinder plate bioassay method according to the Code of Federal Regulations (1). The bioassay organism used was *Sarcina lutea* ATCC 9341, and the assay concentration range was 0.06 to 0.20 μg/ml. All plasma samples were given a preliminary 1:2 dilution with an equal mixture of acetone and 1% pH 6.0 potassium phosphate buffer before further dilution to bring them within the assay concentration range; the minimum detectable plasma concentration was therefore 0.12 μg/ml. All urine samples were given a preliminary 1:5 dilution in 1% pH 6.0 potassium phosphate buffer before further dilution to bring them within the assay concentration range; the minimum detectable urine concentration was therefore 0.30 μg/ml. The mean coefficient of variation (SD of zone diameter/mean zone diameter) of replicate assays of standards was 3.10%.

Plasma protein binding. Aliquots of fresh, pooled plasma from normal human volunteers were spiked with cefatrizine to yield final concentrations of up to 50 μg/ml. These were incubated with gentle shaking for 15 min. Protein binding was determined by the centrifugal ultrafiltration method (13) using DF50A Centriflo membrane cones (Amicon Corp., Lexington,

TABLE 2. Mean plasma concentrations of cefatrizine

Time	Mean plasma concn (μg/ml) ± SD at the following doses (mg) and routes of administration:					
	260, i.v.	252.5, oral	527.5, i.v.	505, oral	1,037.5, i.v.	1,010, oral
0	0	0	0	0	0	0
5 min	6.1 ± 1.8		13 ± 3		26 ± 4	
10 min	11 ± 2		22 ± 6		44 ± 11	
15 min		0.58 ± 0.29		1.4 ± 0.6		0.60 ± 0.12
20 min	18 ± 4		30 ± 7		65 ± 10	
30 min	18 ± 3	2.1 ± 1.0	37 ± 7	3.7 ± 1.1	75 ± 14	3.2 ± 0.6
35 min	12 ± 3		26 ± 4		57 ± 10	
45 min		3.1 ± 1.0		5.2 ± 1.4		4.5 ± 0.8
50 min	7.9 ± 1.4		17 ± 3		34 ± 11	
1.0 h	6.6 ± 1.5	4.3 ± 13	13 ± 3	6.6 ± 0.6	28 ± 7	7.0 ± 1.6
1.5 h	3.7 ± 0.9	4.6 ± 1.0	7.0 ± 0.9	8.1 ± 1.0	18 ± 5	8.4 ± 2.4
2.0 h	2.4 ± 0.5	4.1 ± 0.8	5.0 ± 0.4	7.6 ± 1.5	11 ± 3	9.6 ± 2.4
3.0 h		2.7 ± 0.5		5.1 ± 0.7		7.8 ± 2.4
3.5 h	1.0 ± 0.3		1.8 ± 0.3		3.8 ± 0.7	
4.0 h		1.5 ± 0.4		3.1 ± 0.8		5.0 ± 1.6
4.5 h	0.35 ± 0.10		0.77 ± 0.27		2.0 ± 0.8	
6.0 h		0.23 ± 0.10		0.65 ± 0.37		1.7 ± 0.6
6.5 h	0.15 ± 0.09		0.26 ± 0.07		1.0 ± 0.4	
12.0 h		0		0		0
12.5 h	0		0		0	

TABLE 3. Urinary excretion of intact cefatrizine

Time (h)	Mean excretion (mg) ± SD at the following doses (mg) and routes of administration:					
	260, i.v.	252.5, oral	527.5, i.v.	505, oral	1,037.5, i.v.	1,010, oral
0–1	79.2 ± 42.9	13.7 ± 13.6	191 ± 104	14.6 ± 9.7	278 ± 77	6.2 ± 5.6
1–2	91.1 ± 37.0	44.6 ± 24.3	125 ± 31	89.2 ± 35.4	326 ± 124	84.2 ± 61.4
2–3	21.9 ± 7.9	41.6 ± 12.3	37.2 ± 15.2	84.0 ± 52.8	100 ± 70	117 ± 23
3–4	10.1 ± 4.3	22.0 ± 7.9	22.2 ± 13.2	39.5 ± 10.0	80.3 ± 86.4	90.6 ± 49.6
4–6	8.7 ± 5.3	15.9 ± 4.6	14.1 ± 3.8	35.2 ± 9.6	38.4 ± 12.1	77.2 ± 33.5
6–9	5.8 ± 3.1	8.4 ± 3.8	6.6 ± 4.7	12.5 ± 7.6	17.7 ± 3.3	36.0 ± 15.1
9–12	2.0 ± 1.6	4.4 ± 7.1	2.5 ± 0.9	3.6 ± 2.1	4.2 ± 1.5	6.2 ± 1.9
12–24	1.2 ± 0.6	1.8 ± 0.6	2.6 ± 1.1	2.2 ± 0.9	3.0 ± 0.8	8.4 ± 10.1
0–24	220 ± 48	152 ± 37	401 ± 98	281 ± 85	848 ± 178	426 ± 140

Mass.). Control studies indicated that cefatrizine did not bind to the membranes.

Pharmacokinetic analysis. Plasma concentration (C) versus time (t) data were analyzed by noncompartmental methods (5, 10). All concentrations <0.12 μg/ml were treated as equivalent to zero.

Peak plasma concentrations on i.v. dosing (C_T) always occurred at the end of infusion, 30 min. Observed peak plasma concentrations on oral dosing (C_{max}) and the time at which they occurred (t_{max}) were tabulated. The absolute value of the terminal slope of the C versus t data (β) was determined by least-squares, linear regression analysis (14) of the post-peak plasma concentration data; the regression of the natural logarithm of C versus t was determined starting with a minimum of the last three data points for which $C > 0$. The value of β chosen was that based on the number of points which gave the largest correlation coefficient. Half-life ($t_{1/2}$) was then calculated from β by

$$t_{1/2} = \ln 2/\beta \quad (1)$$

The area under the C versus t curve (AUC_∞) and the area under the first moment of the C versus t curve ($AUMC_\infty$) were calculated by the trapezoidal rule:

$$AUC_\infty = \Sigma (C_i + C_{i-1})(t_i - t_{i-1})/2 + C_n/\beta \quad (2)$$

AUC_∞ was reported as the geometric mean because AUC_∞ is log normally distributed (17).

$$AUMC_\infty = \Sigma (C_i t_i + C_{i-1} t_{i-1})(t_i - t_{i-1})/2 + (C_n/\beta)(1/\beta + t_n) \quad (3)$$

where n was the number of data points (n = 18 for i.v. dosing and n = 11 for oral dosing). Mean residence time in the body (MRT) for both oral and i.v. dosing were estimated by

$$MRT = AUMC_\infty/AUC_\infty \quad (4)$$

Using equation 4 with i.v. infusion data gives an MRT_{inf} value which must be corrected to the true MRT_{iv} by correcting for the infusion time, T:

$$MRT_{iv} = MRT_{inf} - T/2 \quad (5)$$

Infusion time was held constant at 0.5 h; therefore, $T/2$ was a constant 0.25 h. Since MRT on oral dosing includes the absorption time, the mean absorption time (MAT) could be found by difference:

$$MAT = MRT_{po} - MRT_{iv} \quad (6)$$

Total body clearance (Cl_{TB}) for i.v. dosing was determined by

$$Cl_{TB} = D_{iv}/AUC_\infty \quad (7)$$

where D_{iv} was the i.v. dose administered. Renal clearance (Cl_r) for both i.v. and oral dosing was determined by

$$Cl_r = U/AUC_\infty \quad (8)$$

where U was the cumulative urinary excretion of intact cefatrizine in milligrams. Clearances were converted to terms of milliliters per minute and normalized to 1.73 m^2 body surface area. The volumes of distribution obtained for i.v. dosing were

$$V_{area} = D_{iv}/(AUC_\infty \beta) \quad (9)$$

and

$$V_{ss} = Cl_{TB}\, MRT_{iv} \quad (10)$$

Percent bioavailability (F) in each subject was estimated from both plasma concentration and urinary excretion data:

$$F = 100(AUC_{po} D_{iv}/AUC_{iv} D_{po}) \quad (11)$$

$$F = 100(U_{po} D_{iv}/U_{iv} D_{po}) \quad (12)$$

RESULTS

Percentage binding of cefatrizine was, respectively, 62.7, 60.9, 62.4, and 63.9 at plasma concentrations of 5, 10, 25, and 50 μg/ml. Appar-

TABLE 4. Pharmacokinetic parameters calculated from the i.v. dosing data

Parameter	Mean ± SD at the following doses (mg):		
	260	527.5	1,037.5
C_T (μg/ml)[a]	18 ± 3	37 ± 7	75 ± 14
$t_{1/2}$ (h)	1.08 ± 0.29	0.98 ± 0.12	1.41 ± 0.30
AUC_∞ (μg h/ml)[b]	19.1	37.8	82.9
MRT_{iv} (h)	1.09 ± 0.11	1.06 ± 0.08	1.19 ± 0.13
$V_{d\ area}$ (liters/kg)	0.36 ± 0.14	0.27 ± 0.07	0.38 ± 0.10
V_{ss} (liters/kg)	0.22 ± 0.05	0.22 ± 0.03	0.22 ± 0.04
Cl_{TB} (ml/min per 1.73 m^2)	221 ± 30	228 ± 25	206 ± 38
Cl_r (ml/min per 1.73 m^2)	186 ± 42	174 ± 46	170 ± 56

[a] C_T, Plasma concentration at 30 min (end of infusion).
[b] The geometric mean is given for AUC_∞.

ently, binding was constant over this range.

Table 2 contains the mean plasma cefatrizine concentrations on i.v. and oral dosing, and Table 3 contains the urinary excretion data. Urinary excretion on i.v. dosing remained relatively constant with dose. An overall mean of 80% of the cefatrizine dose was excreted intact in the urine. About 97% of all the cefatrizine excreted in the urine was excreted within 6 h of the start of i.v. dosing. Bioautographic examination has indicated that no antibiotically active metabolites of cefatrizine have been detected in fresh human urine (8). Renal excretion is the major route of cefatrizine clearance from the human body. A human oral balance study with ^{14}C-labeled cefatrizine (4) has established that approximately 10% of the dose is excreted in human urine as at least three antibiotically inactive materials. *P*-Hydroxyphenylglycine has been identified as present in human urine after cefatrizine dosing (8). The mean total percentage of dose excreted intact on oral dosing decreased from 60% at the 252.5-mg dose to 42% at the 1,010-mg dose.

The i.v. pharmacokinetics of cefatrizine (Table 4) remained dose linear. C_T and AUC_∞ were dose proportional. There were no significant differences between MRT_{iv}, Cl_{TB}, or Cl_r at the three dose levels. The overall mean values ± SD for these three parameters were 1.11 ± 0.12 h for MRT_{iv}, 218 ± 31 ml/min per 1.73 m^2 for Cl_{TB}, and 176 ± 46 ml/min per 1.73 m^2 for Cl_r. Since the Cl_r exceeded the accepted normal mean value for glomerular filtration rate in men, 131 ml/min per 1.73 m^2 (2), and it has been reported that probenecid elevates plasma cefatrizine concentrations (16), it is evident that cefatrizine is excreted by both glomerular filtration and tubular secretion.

There were no significant differences between V_{ss} or V_{area} at the three dose levels. Their respective overall means ± SD were 0.22 ± 0.04 and 0.34 ± 0.10 liters/kg. The mean V_{ss} value is quite close to the average value accepted for the body fraction occupied by extracellular water, 0.17 liters/kg (2).

On oral dosing, mean Cl_r values and mean $t_{1/2}$ values (Table 5) remained quite constant and quite close to those observed for i.v. dosing (no statistically significant difference). However, the other parameters showed some evidence of dose dependency, especially between 505 and 1,010 mg. Neither C_{max} nor AUC_∞ were linearly dose proportional over this range, although they were between 252.5 and 505 mg. Both mean t_{max} and MAT increased with increasing dosage. A two-way analysis of variance (dose *X* sequence) (14) indicated a significant difference between

TABLE 5. Mean parameter values calculated from the oral dosing data

Parameter	Mean ± SD at the following doses (mg):		
	252.2	505	1,010
t_{max} (h)	1.4 ± 0.4	1.6 ± 0.2	2.0 ± 0.6
C_{max} (μg/ml)	4.9 ± 1.2	8.6 ± 1.0	10.2 ± 2.1
$t_{1/2}$ (h)	0.83 ± 0.16	0.98 ± 0.24	1.34 ± 0.21
AUC_∞ (μg h/ml)[a]	14.2	27.0	37.0
MRT_{po} (h)	2.43 ± 0.23	2.60 ± 0.26	3.06 ± 0.29
MAT (h)	1.34 ± 0.21	1.58 ± 0.25	1.87 ± 0.30
Cl_r (ml/min per 1.73 m^2)	170 ± 25	169 ± 49	190 ± 82
Percent absolute bioavailability			
From AUC_∞	76.8 ± 6.8	75.0 ± 10.2	46.8 ± 10.2
From urinary excretion	71.8 ± 12.1	76.8 ± 29.1	55.2 ± 19.4

[a] Geometric means are given.

the mean MAT values at the three doses (df = 2.12; $F = 9.21$; $p < 0.01$), but not between sequences, and a comparison between these means (Student-Newman-Keuls test [15]) indicated that each mean MAT was significantly different from the others. Apparently, cefatrizine absorption became slower as dose increased.

Mean percentage bioavailabilities (Table 5) estimated from plasma and urine data were in good agreement. The overall mean bioavailability was 75% at the 252.5- and 505-mg doses but decreased to about 50% at the 1,010-mg dose.

DISCUSSION

Since cefatrizine displayed linear pharmacokinetics over the entire dose range on i.v. administration and the i.v. and oral renal clearances were in close correspondence at all three doses, the decrease in oral bioavailability at the 1-g dose would not appear to have been due to any internal mechanism based on a change in drug disposition with dose. It would also seem to be unlikely to be due to formation of any absorbable degradation products in the gut or to portal metabolism because when 490 and 1,100 mg of ^{14}C-labeled cefatrizine were administered orally, the plasma levels of ^{14}C, expressed as cefatrizine equivalents, and the assayable cefatrizine concentrations were not significantly different from each other within the first 2 h after dosing (4).

It seems likely that the bioavailability decrease is connected with the observed decrease in speed of absorption with increasing dose. Although oral absorption was somewhat slower at the 0.5-g level than at the 0.25-g level, ultimately the same percentages of the dose were absorbed. At the 1-g level, absorption was slower still and a larger fraction of the total dose remained unabsorbed. This could be understood on the basis of an "absorption window" effect. Despite absorption differences at 0.25 and 0.5 g, cefatrizine remained in the window long enough that the doses were bioequivalent. Absorption at 1 g would then have been slow enough that the window was passed before the maximum possible bioavailability was attained. A possible explanation for such behavior exists. Kimura et al. (6), using rat in situ and in vitro models, have presented evidence to indicate that there is a saturable, energy-requiring, carrier-mediated transport mechanism for intestinal absorption of cefatrizine as well as cefadroxil, cephalexin, cephradine, cefroxadin, and SCE-100. Cefatrizine absorption in humans might therefore occur by a combination of passive diffusion and a saturable transport process. If this were the case and if the saturable mechanism were approaching its capacity limitation at the 1-g dose, we might expect to see an apparent decrease in the speed of cefatrizine absorption.

If the in vivo disposition of a drug conforms to a linear model (i.e., as in this case, MRT_{iv} remains constant with increasing dose), the overall absorption process, defined by the MAT, may involve any types of input and may not be definable by any given mathematical function (10). That is, since it has been shown that the in vivo disposition of cefatrizine can be described by linear processes over the dosage range employed, statistical moment theory can be used to demonstrate the oral dosing non-linearities in the input processes.

These observations on cefatrizine and their possible relationship to saturable absorption are of considerable theoretical interest. However, it is unlikely that the cefatrizine oral bioavailability decrease at a 1-g dose level will have any clinical significance. Clinical efficacy trials with a 500 mg every 12 h dosing regime are proceeding satisfactorily. At oral doses of up to 500 mg, at least, oral cefatrizine is 75% bioavailable and has a linear pharmacokinetic response.

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