Comparative Human Oral Clinical Pharmacology of Cefadroxil, Cephalexin, and Cephadrine

MORRIS PFEFFER¹*, ANDRE JACKSON, JOSE XIMENES, AND JAIRO PERCHE DE MENEZES

Bristol-Myers Co., Inc., New York, New York 10022

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At equivalent oral doses, cefadroxil has a longer serum half-life, slower urinary excretion rate, greater area under the serum level versus time curve than cephalexin or cephradine, and peak serum concentrations that are 75 to 80% those of cephalexin. The calculated, apparent in vivo volume of distribution of cefadroxil is greater than that of cephalexin. These properties infer greater persistence of cefadroxil in serum and urine and more prolonged in vivo bacterial exposure to cefadroxil than to cephalexin or cephradine. Neither cefadroxil nor cephalexin demonstrates drug accumulation on repeated administration. The serum levels achieved by cefadroxil are unaffected by food. The pharmacokinetic properties of cefadroxil are supportive of the development of clinical efficacy data which could indicate that cefadroxil could be administered at 12-h intervals.

The studies reported here were undertaken to compare the pharmacokinetic properties in humans of the orally administered cephalosporin antibiotics cefadroxil, cephalexin, and cephradine (structures presented in Fig. 1) and to determine the factors which control their disposition in vivo. A companion paper presents data on the antibacterial activity of cefadroxil (1). The inhibitory activity of cefadroxil on clinical isolates was similar to that of cephalexin and cephradine. Cefadroxil was more effective than cephalexin against *Streptococcus pyogenes* and comparably as effective as cephalexin against *Streptococcus pneumoniae*, *Staphylococcus aureus*, and several gram-negative species in oral treatment of experimental infections in mice.

MATERIALS AND METHODS

Bioassays for antibiotic activity in serum and urine were carried out by standard cup plate assay methodology (4) using *Sarcina lutea* ATCC 9341 as the bioassay organism versus analytical standards of each of the cephalosporin antibiotics employed. All antibiotic doses administered are reported in terms of antibiotic content as established by bioassay.

In all three studies all subjects gave informed consent to their participation. All subjects were between the ages of 23 and 59 years and weighed between 51 and 83 kg. Additional criteria for entrance into the studies included lack of penicillin allergy or sensitivity, a normal routine physical examination, and determinations of hemoglobin, hematocrit, white blood cell and differential count,

blood area nitrogen, serum glutamic pyruvic transaminase, bilirubin, urinalysis (including protein test, sugar and microscopy for casts and cells), and stool parasitological examination. Subjects with abnormal values or findings were not admitted into these studies. None of the subjects were to have taken any medication for 3 weeks prior to the study in which they participated.

All subjects were fasted overnight before each study. Oral doses of drugs were always administered at 8:00 a.m. with 250 ml of water, and a further 250 ml of water was ingested every succeeding 2 h for the duration of the study. Except for portions of a study on the effect of food on drug bioavailability, the subjects maintained their fast for 2 h after drug administration.

All studies were designed as balanced, randomized complete crossovers. There was a 6-day washout period between crossover legs.

Study HL-74-41. The first study was a three-period crossover pharmacokinetic and bioavailability comparison between cephalexin and the monohydrate and trihydrate of cefadroxil. The drugs administered were: cefadroxil monohydrate capsules, 300 mg; cefadroxil trihydrate capsules, 300 mg; and commercial cephalexin monohydrate capsules, 250 mg. There were 16 volunteers (13 males, 3 females). Blood samples for the preparation of serum were taken at zero time (before dosage) and at 0.5, 1, 1.5, 3, 6, and 8 h after dosing. Total urine collections were made during the 0- to 4- and 4- to 8-h intervals after dosing.

Study HL-75-47. Study HL-75-47 was a three-period crossover comparison between cefadroxil monohydrate capsules, commercial cephalexin monohydrate capsules, and commercial cephradine capsules. The doses of all three antibiotics were a constant 500 mg. There were 12 volunteers (11 males and 1 female). Blood samples were collected at zero time and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h after

¹ Address reprint requests to: P.O. Box 657, Syracuse, NY 13201.

FIG. 1. Structures.

dosing. Total urine collections were made over the 0- to 3-, 3- to 6-, and 6- to 12-h intervals after dosing.

Study HL-75-51. Study HL-75-51 was a four-period crossover comparison directed toward the effect of food on the bioavailabilities of cefadroxil monohydrate and cephalixin monohydrate. Cefadroxil monohydrate capsules, 500 mg, and commercial cephalixin monohydrate capsules, 500 mg, were administered. Sixteen volunteers (10 male and 6 female) were employed. Each volunteer received three consecutive doses of each drug with and without food. There were 24-h intervals between the successive doses. All volunteers took both cefadroxil and cephalixin with and without food. On the test days when drug was administered with food, the volunteers ingested 50 g of bacon, one fried egg, one slice of bread, and one cup of coffee with the drug.

On test day 1, blood samples were taken at zero time and at 0.5, 1, 1.5, 3, 6 and 8 h after dosing. On test days 2 and 3, blood samples were taken at 2 and 8 h after dosing. The 8-h blood collections were omitted when the test drug was cephalixin. Total urine collections were made over the 0- to 4- and 4- to 8-h intervals after dosing.

Pharmacokinetic bioavailability and statistical analyses. Serum concentration versus time data for each individual subject were fitted to the following biexponential equation:

$$C = -A_1 \exp(-K_a t) + B_1 \exp(K_{el} t) \quad (1)$$

which describes an open, one-compartment model of drug disposition when drug absorption from the gastrointestinal tract into the systemic circulation occurs by passive diffusion (7). A_1 and B_1 are coefficients; K_a is a first-order rate constant for drug absorption, and K_{el} is a rate constant for drug elimination by first-order processes. The fitting was performed via nonlinear regression analysis using the

digital computer program NLIN which employs Marquardt's algorithm (5).

The lag time between drug administration and the onset of absorption, t_0 , was found by setting equation 1 equal to zero and rearranging it:

$$t_0 = \ln(A_1/B_1)/(K_a - K_{el}) \quad (2)$$

The time at which peak serum level occurs, $t_{\max}$, was calculated by setting the differential of equation 1 equal to zero and solving for $t_{\max}$:

$$t_{\max} = \ln(A_1 K_a / B_1 K_{el}) / (K_a - K_{el}) \quad (3)$$

$C_{\max}$, the peak serum level, was calculated by substituting $t_{\max}$ into equation 1. The area under the serum concentration versus time curve (AUC) from $t = 0$ to infinity was calculated by integrating equation 1 between these time limits:

$$\text{AUC} = -A_1/K_a + B_1/K_{el} \quad (4)$$

The renal clearances (Cl_r) of the drugs were found by plotting the renal excretion rates of the drug ($\Delta M_u / \Delta t$) versus serum concentrations at the midpoint times of the urine collection intervals (9). The total amount of drug in milligrams, M_u , excreted in any given time interval in hours, t_1 to t_2 , was divided by the length of the interval to get the renal excretion rate in milligrams per hour:

$$\Delta M_u / \Delta t = M_u / (t_2 - t_1) \quad (5)$$

This was plotted versus serum concentration at time $(t_1 + t_2)/2$. If the serum concentration at a given time had not been experimentally determined, it was estimated by interpolation from a semilogarithmic plot of serum concentration versus time data.

This paper reports the mean results by drug and subject groups rather than the results for each subject. In these three studies there were 44 subjects and 12 different treatments for a total of 528 sets of serum-urine data.

The goodness of fit between the estimates of serum concentration ($\hat{C}_i$) provided by equation 1 and the measured serum concentrations (C_i) was evaluated by F , the sums of squares of the deviations:

$$F = \sum_{i=1}^n (C_i - \hat{C}_i)^2 \quad (6)$$

and r^2 :

$$r^2 = \left[\sum_{i=1}^n C_i^2 - \frac{\left(\sum_{i=1}^n C_i \right)^2}{n} - F \right] / \left[\sum_{i=1}^n C_i^2 - \frac{\left(\sum_{i=1}^n C_i \right)^2}{n} \right] \quad (7)$$

The serum concentration and urinary excretion data for each subject in each of the studies presented here were each evaluated, using the method presented above, separately. This paper reports the mean data by drug and subject groups, but the results reported for the bioavailability analyses are from the individual subject analyses.

Cefadroxil, cephalexin, and cephradine are each distinctive chemical entities, and it could not be assumed that their *in vivo* dispositions were identical. For that reason it was inappropriate to consistently test statistical hypotheses regarding bioavailability within each study by a single multiway analysis of variance (ANOVA). Such an ANOVA was appropriate when testing "treatment" effects on bioavailability for a given antibiotic within a single study. Thus, when comparing cefadroxil monohydrate and trihydrate in study HL-74-41 and the effect of food and fasting on cefadroxil monohydrate or cephalexin monohydrate in study HL-75-51, such an ANOVA could be used. A two-period crossover design ANOVA (3) served in these cases. When comparing different antibiotics in a single study or performing interstudy comparisons, the more appropriate one-way ANOVA (6) was used. All hypotheses were tested at the $P = 0.05$ level of significance.

Bioavailability comparisons on a given antibiotic were performed using K_a , $t_{\max}$ and $C_{\max}$ to characterize rate of availability and AUC to characterize total extent of availability once statistical equivalence of K_{el} values in the crossover had been established (10).

The urine concentrations of the antibiotics have been calculated and compared at their modes (the concentration values corresponding to the greatest concentration frequencies) rather than their means, since the distributions of urine concentrations were skewed and apparently not normal distributions.

RESULTS AND DISCUSSION

Serum concentrations. Tables 1 and 2, 3 and 4, and 5 and 6 contain the mean serum concentrations and pharmacokinetic parameters $\pm$ standard error (SE) for studies HL-74-41, HL-75-47, and HL-75-51, respectively. Up to concentrations of 25 $\mu\text{g/ml}$, the serum protein bindings of cefadroxil and cephalexin were very similar: cefadroxil was 20% bound, and cephalixin was 17% bound (1).

The monohydrate and trihydrate of cefadroxil are fully equivalent to each other. Statistical analyses indicated no significant differ-

ences between their rate or total extent of bioavailability.

The data from all three studies indicate that cephalexin is more rapidly absorbed than cefadroxil: K_a for cephalexin was always greater than K_a for cefadroxil. This led to the later $t_{\max}$ for cefadroxil than for cephalexin. This later $t_{\max}$ for cefadroxil was not due to delayed absorption of the drug; the overall absorption lag times for the two drugs were almost identical at 24 min for cefadroxil and 20 min for cephalexin. At doses of 500 mg, the mean $C_{\max}$ for cefadroxil (16 $\mu\text{g/ml}$) was about 80% of that for cephalexin (21 $\mu\text{g/ml}$). The overall mean half-life of cefadroxil (1.2 h) was twofold greater than the overall mean half-life of cephalexin (0.6 h); the AUC for cefadroxil (47.4 $\mu\text{gh/ml}$) was 1.6-fold greater than the AUC for cephalexin (29.0 $\mu\text{gh/ml}$), indicating that although the peak serum level of cefadroxil is lower than that of cephalexin, cefadroxil persists in the body an appreciably longer time than does cephalexin. At equivalent doses the cefadroxil serum level was higher than the cephalexin serum level by 1.5 h after dose and remained consistently higher thereafter. At the 500-mg dose, cephalexin concentration dropped to 1 $\mu\text{g/ml}$ at about 4 h, and

TABLE 1. Mean serum antibiotic concentrations for study HL-74-41

Time (h)	Mean serum antibiotic concn ($\mu\text{g/ml} \pm \text{SE}$)		
	Cefadroxil monohydrate (300 mg)	Cefadroxil trihydrate (300 mg)	Cephalexin monohydrate (250 mg)
0	0	0	0
0.5	2.52 ± 0.8	3.38 ± 0.65	4.28 ± 0.79
1	9.19 ± 0.38	9.59 ± 0.55	8.58 ± 0.65
1.5	9.43 ± 0.36	9.29 ± 0.41	5.19 ± 0.39
3	4.13 ± 0.23	3.90 ± 0.19	1.20 ± 0.09
6	0.74 ± 0.06	0.67 ± 0.04	<0.04
8	0.34 ± 0.04	0.28 ± 0.03	<0.04

TABLE 2. Pharmacokinetic parameters for study HL-74-41

Parameter	Value $\pm$ SE		
	Cefadroxil monohydrate (300 mg)	Cefadroxil trihydrate (300 mg)	Cephalexin monohydrate (250 mg)
AUC ($\mu\text{gh per ml}$)	26.8 ± 0.8	26.3 ± 0.8	14.0 ± 0.6
K_a (h^{-1})	2.82 ± 0.36	2.97 ± 0.40	4.28 ± 0.42
K_{el} (h^{-1})	0.659 ± 0.028	0.666 ± 0.029	1.35 ± 0.10
$t_{\max}$ (h)	1.19 ± 0.05	1.12 ± 0.05	0.86 ± 0.05
$C_{\max}$ ($\mu\text{g/ml}$)	9.82 ± 0.31	10.3 ± 0.5	9.93 ± 0.76
$t_{1/2}$ (h)	1.05 ± 0.05	1.04 ± 0.05	0.51 ± 0.04
t_o (min)	26 ± 8	23 ± 2	24 ± 1
F	0.193	0.494	1.365
r^2	0.998	0.994	0.951

cefadroxil concentration dropped to 1 $\mu\text{g/ml}$ at about 7 h.

Figures 2 and 3 contain plots of AUC and C_{max} versus dose for all three studies. Linear

TABLE 3. Mean serum antibiotic concentrations for study HL-75-47

Time (h)	Mean serum antibiotic concn ($\mu\text{g/ml} \pm \text{SE}$)		
	Cefadroxil monohydrate (500 mg)	Cephalexin monohydrate (500 mg)	Cephadrine (500 mg)
0	0	0	0
0.5	5.61 ± 0.78	14.0 ± 2.2	11.3 ± 2.1
1	14.9 ± 1.7	17.9 ± 1.3	15.2 ± 1.3
1.5	15.0 ± 1.1	10.7 ± 1.1	10.6 ± 1.0
2	12.5 ± 0.8	6.02 ± 0.66	6.33 ± 0.77
4	4.63 ± 0.33	1.05 ± 0.16	0.96 ± 0.13
6	1.84 ± 0.14	0.10 ± 0.04	0.13 ± 0.04
8	0.65 ± 0.07	<0.04	<0.04
12	0.11 ± 0.03	<0.04	<0.04

regression analysis of AUC and C_{max} versus dose for cefadroxil and cephalixin was performed using individual subject data (each analysis had 42 degrees of freedom). In each case the slope of the curve was significantly greater than zero ($P < 0.005$ for all four analyses) and the y axis intercept was never significantly greater than zero ($P > 0.4$ for all four analyses). The linearity of these plots indicates essential pharmacokinetic linearity for serum level data for cefadroxil and cephalixin up to a 500-mg oral dose. The linearity of cefadroxil and cephalixin indicates that we can calculate serum levels for these antibiotics, at any unknown dose over this range, from serum levels at a known dose by multiplying the known serum levels by the ratio of unknown to known dose (7). We can then calculate the mean serum levels and AUC which would be yielded by a 250-mg dose of cefadroxil. A 250-mg dose of

TABLE 4. Pharmacokinetic parameters for study HL-75-47

Parameter	Value $\pm$ SE		
	Cefadroxil monohydrate (500 mg)	Cephalexin monohydrate (500 mg)	Cephadrine (500 mg)
AUC ($\mu\text{gh per ml}$)	47.4 ± 2.1	29.0 ± 2.5	27.5 ± 2.2
K_a (h^{-1})	2.44 ± 0.38	4.78 ± 0.59	3.73 ± 0.33
K_{el} (h^{-1})	0.545 ± 0.034	1.21 ± 0.11	1.14 ± 0.09
t_{max} (h)	1.29 ± 0.09	0.71 ± 0.06	0.80 ± 0.08
C_{max} ($\mu\text{g/ml}$)	16.2 ± 1.4	20.7 ± 1.5	17.7 ± 1.2
$t_{1/2}$ (h)	1.27 ± 0.08	0.57 ± 0.05	0.61 ± 0.05
t_o (min)	22 ± 2	18 ± 4	18 ± 4
F	1.135	5.497	1.430
r^2	0.996	0.978	0.992

TABLE 5. Mean serum antibiotic concentrations for study HL-75-51^a

Drug	Time (h)	Mean serum antibiotic concn ($\mu\text{g/ml} \pm \text{SE}$)					
		With food			Without food		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Cefadroxil monohydrate	0	0	0	0	0	0	0
	0.5	7.31 ± 1.16	ND ^b	ND	6.03 ± 0.69	ND	ND
	1	15.5 ± 1.5	ND	ND	14.3 ± 1.2	ND	ND
	1.5	14.4 ± 1.2	ND	ND	14.7 ± 0.7	ND	ND
	2	ND	13.1 ± 0.7	13.9 ± 0.8	ND	14.4 ± 0.7	14.6 ± 1.2
	3	6.84 ± 0.61	ND	ND	7.68 ± 0.54	ND	ND
	6	1.57 ± 0.16	ND	ND	1.58 ± 0.17	ND	ND
	8	0.50 ± 0.05	0.51 ± 0.06	0.64 ± 0.05	0.55 ± 1.01	0.58 ± 0.08	0.57 ± 0.07
Cephalexin monohydrate	0	0	0	0	0	0	0
	0.5	11.5 ± 1.7	ND	ND	14.0 ± 1.7	ND	ND
	1	15.5 ± 1.2	ND	ND	20.7 ± 1.6	ND	ND
	1.5	12.2 ± 0.9	ND	ND	12.7 ± 0.8	ND	ND
	2	ND	8.17 ± 0.77	8.76 ± 1.00	ND	8.51 ± 0.84	7.90 ± 0.73
	3	3.09 ± 0.33	ND	ND	2.92 ± 0.25	ND	ND
	6	0.25 ± 0.05	ND	ND	0.12 ± 0.05	ND	ND

^a All doses 500 mg.

^b ND, Not determined.

TABLE 6. Pharmacokinetic parameters for study HL-75-51^a

Parameter	Value $\pm$ SE			
	Cefadroxil monohydrate		Cephalexin monohydrate	
	With food	Without food	With food	Without food
AUC ($\mu\text{gh per ml}$)	45.1 $\pm$ 2.4	43.3 $\pm$ 2.4	31.3 $\pm$ 1.8	32.8 $\pm$ 1.8
K_a (h^{-1})	3.21 $\pm$ 0.48	2.47 $\pm$ 0.32	5.31 $\pm$ 1.67	6.92 $\pm$ 2.23
K_{el} (h^{-1})	0.550 $\pm$ 0.052	0.546 $\pm$ 0.017	0.867 $\pm$ 0.085	0.960 $\pm$ 0.049
$t_{\max}$ (h)	1.17 $\pm$ 0.10	1.20 $\pm$ 0.06	0.82 $\pm$ 0.08	0.74 $\pm$ 0.22
$C_{\max}$ ($\mu\text{g/ml}$)	16.3 $\pm$ 0.8	14.7 $\pm$ 0.8	18.5 $\pm$ 1.9	21.4 $\pm$ 1.5
$t_{1/2}$ (h)	1.26 $\pm$ 0.12	1.27 $\pm$ 0.04	0.80 $\pm$ 0.08	0.72 $\pm$ 0.04
t_o (min)	24 $\pm$ 3	20 $\pm$ 2	17 $\pm$ 3	18 $\pm$ 2
F	0.169	2.230	0.666	1.440
r^2	0.999	0.988	0.996	0.995

^a All doses 500 mg.

FIG. 2. Area under curve as a function of dose.

cefadroxil would yield a $C_{\max}$ 80% as great and an AUC 1.6-fold greater than those produced by the 250-mg dose of cephalexin.

The pharmacokinetic parameters found for cefadroxil and cephalexin show no more than normal variation between studies. $C_{\max}$, $t_{\max}$, K_a , and AUC values under fasting conditions are very consistent. Cefadroxil half-life varied between 1.05 h in study HL-74-41 and 1.27 h in studies HL-75-47 and HL-75-51. Cephalexin half-life varied between 0.51 and 0.57 h in studies HL-74-41 and HL-75-47 and 0.8 h in study HL-75-51. These half-lives remain in the range of expectable biological variability. Cephalexin half-lives ranging from 0.6 to 1.2 h have been reported in the literature (8). In this series of three studies, cefadroxil consistently had a

FIG. 3. Peak serum levels as a function of dose.

longer half-life than cephalexin in each of the 44 subjects. We might expect to continue to see consistently longer half-lives for cefadroxil than for cephalexin in humans.

Cephalexin is normally administered every 6 h. At approximately 45 min after dosing, a 250-mg dose of cephalexin yields a mean $C_{\max}$ of 10 $\mu\text{g/ml}$, and at a 500-mg dose it yields a mean $C_{\max}$ of 20 $\mu\text{g/ml}$. By 6 h, at 250 mg, there is no detectable cephalexin present in serum. At a 500-mg dose, the mean 6-h serum level is 0.13 $\mu\text{g/ml}$. Cefadroxil is more persistent. At a dose of 250 mg it will achieve a mean peak serum level of 8 $\mu\text{g/ml}$ at approximately 70 min and the mean serum concentration will be 0.33 $\mu\text{g/ml}$ at 8 h and 0.06 $\mu\text{g/ml}$ at 12 h. At a dose of 500 mg, cefadroxil has a mean peak serum level of 16 $\mu\text{g/ml}$ at approximately 70 min and the mean serum concentrations will be 0.65 $\mu\text{g/ml}$

at 8 h and 0.11 $\mu\text{g/ml}$ at 12 h. Cefadroxil would have analogous persistence in urine at these doses. It would seem reasonable to develop clinical efficacy data which, supported by these pharmacokinetic properties, could indicate a 12-h dosing interval for cefadroxil.

The disposition of cephradine seems very similar to that of cephalixin. Their serum level curves and the values for their pharmacokinetic parameters are very similar (see Tables 3 and 4).

Concurrent ingestion of food with either cefadroxil or cephalixin on study day 1 (study HL-75-51, Tables 5 and 6) had no statistically significant effect on their bioavailability relative to fasting conditions. Neither rates of availability nor total availability were affected. Continued concurrent administration of food did not markedly affect cefadroxil or cephalixin bioavailability.

The predose, zero-time serum samples on days 2 or 3 did not contain detectable levels of antibiotics. Neither cefadroxil nor cephalixin demonstrated either accumulation of drug or induction of elimination on repeated administration.

Urinary excretion. Plotting $\Delta M_u/\Delta t$ versus serum concentrations for cefadroxil and cephalixin gave the results shown in Fig. 4. These data came from all three studies. Cephradine was excluded for lack of sufficient data. Linear regression analysis indicated that the apparent

straight-line portions of these plots were significantly linear. These results enable assignment of specific renal excretion phenomena to glomerular filtration and tubular secretion.

Net renal excretion of antibiotic can be represented as renal excretion rate = glomerular filtration rate + tubular secretion rate, i.e.:

$$dM_u/dt = VK_uC + T_mC/(K_m + C) \quad (8)$$

$\Delta M_u/\Delta t$ is the numerical approximation to dM_u/dt ; V is the apparent volume of distribution of drug in the body; K_u is the net first-order rate constant for glomerular filtration; C is the serum concentration of drug; T_m is the maximum transport rate for tubular secretion, and K_m is the Michaelis constant. The term $T_mC/(K_m + C)$ describes the capacity-limited process and is exactly analogous to the Michaelis-Menten equation for enzyme activity. When $C \gg K_m$ this reduces to T_m and equation 5 becomes:

$$dM_u/dt = VK_uC + T_m \quad (9)$$

Equation 9 is the best overall description of the curves seen in Fig. 4. At relatively low serum concentrations, less than 0.3 $\mu\text{g/ml}$ for cephalixin and at about 1 $\mu\text{g/ml}$ for cefadroxil, the tubular secretion mechanism has become saturated (i.e., $C \gg K_m$) and tubular secretion proceeds at its maximum rate, T_m . This constant rate is about 30 mg/h for cephalixin and 15 mg/h for cefadroxil. It appears that cephalixin has a greater affinity for the tubular secretion mechanism than does cefadroxil; cephalixin has a higher T_m and a smaller K_m . This is the primary reason for the shorter half-life of cephalixin—it is more readily excreted in the urine.

The slopes of the linear portions of the plots in Fig. 4 are equivalent to the term VK_u , which is the renal clearance rate due to glomerular filtration. This rate is 112 ml/min for cephalixin and 90.1 ml/min for cefadroxil. These rates are statistically equivalent to the commonly accepted value for creatinine clearance rate (glomerular filtration rate) in humans, 95.5 ml/min (2).

Human renal excretion of these two cephalosporin antibiotics does not proceed by a completely linear, first-order process. As cefadroxil or cephalixin dose increases, it would take a longer time to excrete any given percentage of the dose. Since the tubular secretion rate for cefadroxil is less than the tubular secretion rate for cephalixin, the urinary excretion of cefadroxil is of longer duration. Cefadroxil yields initially lower urine concentrations than an equal dose of cephalixin, but

FIG. 4. Renal excretion rates as a function of serum concentration.

cefadroxil maintains higher urine concentrations at the later times (see Tables 7 and 8). Within each given experiment the ranges and means of urine volumes remain reasonably constant. The 0- to 3- or 0- to 4-h modal urine concentrations of cefadroxil are lower than the 0- to 3- or 0- to 4-h modal urine concentrations of cephalexin or cephradine. At the 4- to 8- and 3- to 6- or 6- to 12-h intervals, cefadroxil maintains the highest modal urine levels. In study HL-75-47, urine concentrations of cefadroxil were maintained at a relative constant modal level through 0 to 3 and 3 to 6 h and remained at least twice as high as cephalexin and cephradine modal concentrations from 3 through 12 h.

Figure 5 contains cumulative urinary excretion plots drawn from the three studies being reported here. The total cumulative urinary excretion of active cefadroxil and cephalexin are statistically equivalent with an overall mean of approximately 88% of dose. They are almost completely absorbed; there may be small components of their elimination by biliary excretion or metabolism. All of a dose of cephradine appears to be excreted in the urine; presumably, cephradine is completely absorbed and eliminated completely by renal excretion. The total assayed cumulative urinary excretion of antibiotic in some subjects was greater than 100% of the dose, but the range of these recoveries did not exceed the 10 to 15% variability normally expected from cup-plate assays.

Since cefadroxil is eliminated more slowly than cephalexin or cephradine, it has a longer residence time in the body, time in which it could distribute more extensively. The range of the apparent volumes of distribution can be estimated from the relationship, creatinine clearance rate = G.F.R. = VK_u . Elimination rate constants may be described as $K_{el} = K_u + K_{nr}$ where K_{nr} is a first-order rate constant for drug elimination via nonrenal routes.

If renal excretion is the only elimination route, then $K_{nr} = 0$ and $K_u = K_{el}$. This presumes that the active antibiotic excreted in

FIG. 5. Cumulative urinary excretion.

TABLE 7. Time course of antibiotic concentrations in urine for studies HL-74-41, HL-75-51

Drug	Dose (mg)	0-4 h				4-8 h			
		Urine vol (ml)		Urine concn (μg/ml)		Urine vol (ml)		Urine concn (μg/ml)	
		Range	Mean	Range	Mode	Range	Mean	Range	Mode
Cefadroxil	300	100-900	396	203-1,960	497	90-560	262	84-450	243
	500	80-800	348	308-3,500	1,003	100-560	298	84-1,099	293
Cephalexin	250	130-770	361	332-1,697	573	180-470	277	38-270	108
	500	110-950	374	326-3,350	1,140	120-700	327	37-745	201

TABLE 8. Time course of antibiotic concentration in urine for study HL-75-47^a

Drug	0-3 h				3-6 h				6-12 h			
	Urine vol (ml)		Urine concn (μg/ml)		Urine vol (ml)		Urine concn (μg/ml)		Urine vol (ml)		Urine concn (μg/ml)	
	Range	Mean	Range	Mode	Range	Mean	Range	Mode	Range	Mean	Range	Mode
Cefadroxil	70-320	156	730-2360	1211	65-420	184	368-3110	1113	100-320	203	83-263	167
Cephalexin	65-420	172	830-5720	1783	20-430	165	264-1360	607	90-380	210	31-287	78
Cephradine	85-400	170	1068-3805	2136	35-780	231	281-1339	582	85-360	179	9-202	61

^a All doses 500 mg.

urine represents all of the drug absorbed. If the drug was completely bioavailable, then the difference between the total dose and the cumulative fraction excreted in the urine (F_e) represents the amount eliminated by nonrenal routes and:

$$K_u = K_{el} - K_{nr} = F_e K_{el} \quad (10)$$

since $K_{nr} = (1 - F_e)K_{el}$. Thus, the value of K_u must lie between K_{el} and $F_e K_{el}$. Applying these limits to the relationship $V = G.F.R./K_u$ we can calculate that the possible range of apparent volumes of distribution for cefadroxil is 9.7 to 11.6 liters (i.e., 14 to 17% of body weight) and for cephalixin it is 5.2 to 5.8 liters (i.e., 7.4 to 8.3% of body weight). The longer duration and more extensive distribution of cefadroxil in vivo are interrelated factors.

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