ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1982, p. 320–322
0066-4804/82/020320-03$02.00/0

Vol. 21, No. 2

Pharmacokinetics of Cefadroxil After Oral Administration in Humans

FRANCESCO LA ROSA,[1]* SANDRO RIPA,[1] MANUELA PRENNA,[1] ALBERTO GHEZZI,[1] AND MORRIS PFEFFER[2]

Institute of Microbiology, University of Camerino, Camerino, Italy,[1] and Bristol Laboratories, Syracuse, New York 13201[2]

Received 29 May 1981/Accepted 6 November 1981

The human oral pharmacokinetics of cefadroxil were studied in parallel at doses of 250, 500, and 1,000 mg in three groups of 10 healthy young male volunteers. Renal excretion of intact cefadroxil, accounted for 82, 79, and 77% of the above doses. Mean peak serum levels were dose linear: 9, 18, and 35 μg/ml at 250, 500, and 1,000 mg, respectively. However, overall pharmacokinetics were linear only in the 250- to 500-mg dose range; apparent serum clearances were 10 liters/h, and true renal clearances were 9 and 8 liters/h at 250 and 500 mg. At 1,000 mg, apparent serum clearance dropped to about 7 liters/h, true renal clearance, dropped to 6 liters/h, and the area under the curve increased disproportionately. At 250 and 500 mg, mean half-life was about 1.2 h; at 1,000 mg, however, it was 1.6 h. The nonlinear decrease in clearance could be related to saturation of active renal tubular secretion of cefadroxil between the 500- and 1,000-mg doses. Previous results indicating that cefadroxil has greater persistence than other oral cephalosporins such as cephalexin, cephradrine, cefaclor were confirmed.

Cefadroxil monohydrate, 7-[[D-2-amino-2-(4-hydroxyphenyl) acetyl]amino]- 3-methyl-8-oxo-5-thia-l-azabicyclo[4.2.0]oct-2-ene -2-carboxylic acid monohydrate, is a semisynthetic cephalosporin intended for oral administration. In vitro, it exhibits activity against most strains of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella* sp., and both penicillin-susceptible and resistant *Staphylococcus aureus* (2, 7). The objective of this study was to characterize the pharmacokinetic properties of cefadroxil administered orally in doses of 250, 500, and 1,000 mg to healthy male volunteers.

MATERIALS AND METHODS

Cefadroxil monohydrate was supplied as formulated 250-mg capsules (Bristol Italiana Sud-Spa). Doses of 250, 500, and 1,000 mg were administered orally to 30 male volunteers, 20 to 29 years of age. None had known sensitivity to β-lactam antibiotics. All were judged healthy on the basis of clinical examination, urinalysis, and serum chemistry analyses (i.e., hemoglobin, erythrocyte sedimentation rate, leukocyte count, eosinophil count, differential count, bilirubin, serum creatinine, blood urea nitrogen, alkaline phosphatase, lactic acid dehydrogenase, aspartate aminotransferase, alanine aminotransferase, serum iron, total iron-binding capacity, cholesterol, and total protein). Each provided informed consent.

Experimental procedure. The 30 volunteers were divided into three groups of 10. In a parallel study, each member of the group received oral cefadroxil doses of 250, 500, or 1,000 mg after overnight fasting. Blood samples were collected at 0.5, 1, 2, 4, 6, and 7 h after dosing. Serum samples were prepared and stored at −20°C until assayed. A total 0 to 7 h urine collection was made.

Assay procedure. Cefadroxil concentrations were estimated by bioassay, using a disk plate method (3). Antibiotic assay base agar (210 ml) was seeded with a static culture of *Sarcina lutea* ATCC 9341 in Trypticase soy broth (4 ml; BBL Microbiology Systems) after overnight incubation of the culture at 37°C. The seeded base agar was placed into 23-cm^2 assay plates. A maximum of 49 filter paper antibiotic assay disks, 6 mm in diameter, were placed on each plate. For serum and urine assays, standard lines were prepared by plotting log dose-response data, using pH 6.0 phosphate buffer diluents. Plates were incubated for 20 h at 37°C. Zones of inhibition were measured to the nearest 0.1 cm by using either calipers or an overhead projection device.

Pharmacokinetic analysis. The peak serum cefadroxil level (C_{max}) and 0- to 7-h urinary excretion for each volunteer were tabulated, and the means and standard errors (SE) were calculated. C_{max} is presented in micrograms per milliliter, and urinary excretion is given as the percentage of the dose excreted in 7 h [U_7(%)]. Since data were collected from three parallel groups of subjects rather than according to a crossover design, further analyses were carried out on mean serum level and urinary excretion data rather than on individual subject data.

Area under the curve (AUC) was calculated by using the trapezoidal rule,

$$\mathrm{AUC} = \sum_{i=2}^{n}(C_i + C_{i-1})(t_i - t_{i-1})/2 + C_n/K_{el} \qquad (1)$$

where C is serum concentration and t is time. The cefadroxil elimination rate constant, K_{el}, was estimated by least-squares linear regression analysis of ln$C$ versus t between 1.5 and 7 h. K_{el} is the absolute value of the best-fit slope. Equation 1 represents the AUC to infinite time (AUC_∞). The 0- to 7-h AUC was estimated by omitting the C_n/K_{el} term in equation 1. Serum half-life, $t_{1/2}$, was estimated by:

$$t_{1/2} = 0.693/K_{el} \quad (2)$$

Serum clearance (Cl_s) was assumed to conform to the relationship

$$Cl_s = FD/AUC_\infty \quad (3)$$

where F is the overall fraction bioavailability of oral cefadroxil and D is the oral dose in milligrams. Since F is unknown, only the apparent serum clearance (Cl_s/F) can be estimated:

$$Cl_s/F = D/AUC_\infty \quad (4)$$

The true renal clearance (Cl_r) was estimated as

$$Cl_r = U_7(\%)/(100\ AUC_7) \quad (5)$$

By combining the relationship

$$Cl_s = K_{el}\ V \quad (6)$$

Where V is cefadroxil volume of distribution, and equation 3, an apparent volume of distribution (V/F) can be estimated:

$$V/F = D/(K_{el}\ AUC_\infty) \quad (7)$$

RESULTS AND DISCUSSION

Table 1 contains the mean serum cefadroxil concentrations and SE. Peak serum levels and 0- to 7-h urinary excretion and SE and the estimated parameters K_{el}, $t_{1/2}$, AUC_∞, AUC_7, Cl_s/F, V/F, and Cl_r are listed in Table 2.

The various values for the pharmacokinetic parameters found for oral doses up to 500 mg agreed quite well with the results reported by Pfeffer et al. (6) and seemed to indicate a linear pharmacokinetic response over this range. However, when the oral dose was doubled to 1,000 mg, mean AUC_∞ increased almost threefold, rather than twofold as might be expected, and mean half-life increased from 1.20 to 1.61 h. As a result, there were substantial decreases in apparent serum clearance and apparent volume of distribution. Renal clearance, which was estimated solely from measured quantities, also decreased substantially at the 1,000-mg dose.

When the method of Pfeffer et al. (6) was used to estimate the possible range of cefadroxil volumes of distribution at the various doses administered, the results were 14.0 to 17.1 liters at 250 mg, 13.5 to 17.1 liters at 500 mg, and 12.2 to 15.9 liters at 1,000 mg.

Table 3 compares some of the essential pharmacokinetic parameters found at the 1-g oral dose in this study with the results in the four other 1-g oral studies in normal volunteers (1, 4, 5, 8). Peak levels, elimination rate constants, half-lives, and apparent serum clearances compared quite closely, except for the Adam and Gierschick study (1), even though different subject panels are represented. Given that Adam and Gierschick reported a low 0 to 24-h renal excretion of cefadroxil (68% of the dose), it seems likely that they had lower than normal oral bioavailability of cefadroxil. This comparison emphasizes the likely validity of the present results at the 1-g dose. Despite this apparent pharmacokinetic change, renal excretion of intact drug remained the major route of cefadroxil elimination.

This is the first single study incorporating oral cefadroxil administration throughout the 250- to 1,000-mg range. It has produced reasonable evidence indicating that, as previously reported, oral cefadroxil pharmacokinetics are dose proportional up to at least 500 mg but that somewhere between 500 and 1,000 mg oral cefadroxil pharmacokinetics become dose superproportional. This phenomenon is unlikely to be due to

TABLE 1. Observed serum cefadroxil concentrations

Dose (mg)	Serum concn (mean μg/ml ± SE) at:						
	0.5 h	1 h	1.5 h	2 h	4 h	6 h	7 h
250	3.3 ± 0.4	7.5 ± 0.6	9.0 ± 0.5	6.8 ± 0.5	2.1 ± 0.2	0.7 ± 0.1	0.3 ± 0.0
500	6.5 ± 1.2	14.7 ± 1.6	17.9 ± 1.0	13.2 ± 0.9	5.3 ± 0.5	1.9 ± 0.1	0.6 ± 0.1
1,000	9.9 ± 0.4	29.4 ± 0.8	35.2 ± 0.6	32.4 ± 0.6	25.2 ± 0.9	5.6 ± 0.4	3.5 ± 0.3

TABLE 2. Pharmacokinetic parameters after oral administration of 250, 500, and 1,000 mg of cefadroxil

Dose (mg)	Parameter								
	C_{max} (μg/ml)	K_{el} (h^{-1})	$t_{1/2}$ (h)	AUC_∞ (μg/h per ml)	Cl_s/F (liters/h)	V/F (liters)	U_7 (% of dose)	AUC_7 (μg/h per ml)	Cl_r (liters/h)
250	9.0 ± 0.5	0.603	1.15	24.3	10.3	17.1	81.9 ± 22	23.8	8.6
500	17.9 ± 1.0	0.575	1.20	50.8	9.8	17.1	78.8 ± 2.3	49.8	7.9
1,000	35.2 ± 0.6	0.430	1.61	146	6.8	15.9	76.9 ± 1.8	138	5.6

TABLE 3. Comparison of pharmacokinetic results for 1-g oral doses of cefadroxil

Study	Parameter					
	C_{max} (μg/ml)	K_{el} (h^{-1})	$t_{1/2}$ (h)	AUC (μg/h per ml)	Cl_s/F	U_{24} (%)[a]
This report	35	0.43	1.47	146	10.3	
Lode et al. (5)	33	0.43	1.63	108	9.3	90
Adam and Gierschick (1)	30	0.66	1.05	115	8.7	68
Simon (8)	28	0.47	1.50	96	10.4	
Humbert et al. (4)	26	0.50	1.39	83	12.1	93

a reduction in serum protein binding of the antibiotic because, in this case, a subproportional reduction in AUC_∞ and, to some extent, a half-life decrease would be expected. A reduction in degree of binding would result in an increase in renal clearance because there would be more unbound cefadroxil immediately subject to elimination by glomerular filtration. An increase in extent of fractional oral bioavailability at the 1,000-mg dose is unlikely because there is no sensible increase in the percentage of renal excretion of intact cefadroxil. The likeliest explanation, that most amenable to experimental investigation, is that active renal tubular secretion of cefadroxil starts to approach its saturation level between the 500- and 1,000-mg oral doses and, therefore, the observed rate of renal clearance decreases. An experimental design to investigate this possibility would preferably be a crossover study incorporating determination of subject glomerular filtration rate (either by creatinine or inulin clearance) and relatively short-term determinations (over 1- to 2-h intervals) of cefadroxil clearance at 250-, 500-, and 1,000-mg oral doses.

LITERATURE CITED

1. **Adam, D., and P. Gierschik.** 1980. Vergleichende Untersuchungen zur Pharmakokinetik von Cefadroxil und Amoxicillin nach Oraler Nuchterngable. Infection **8**(Suppl. 5):S561–S572.
2. **Buck, R. D., and K. E. Price.** 1976. Cefadroxil, a new broad-spectrum cephalosporin. Antimicrob. Agents Chemother. **11**:324–330.
3. **Grove, D. C., and W. A. Randall.** 1955. Assay methods of antibiotics. A laboratory manual. Medical Encyclopedia, New York.
4. **Humbert, G., A. Leroy, J. P. Filastre, and M. Godin.** 1979. Pharmacokinetics of cefadroxil in normal subjects and in patients with renal insufficiency. Chemotherapy **25**:189–195.
5. **Lode, H., R. Stahlmann, G. Dzevillo, and P. Koeppe.** 1980. Vergleichende Pharmakokinetik Oraler Cephalosporine: Cephalexin, Cefaclor und Cefadroxil. Arzneim. Forsch. **30I**:505–509.
6. **Pfeffer, M., A. Jackson, J. Ximenes, and J. Perche de Menezes.** 1977. Comparative human oral clinical pharmacology of cefadroxil, cephalexin and cephradine. Antimicrob. Agents Chemother. **11**:331–338.
7. **Ripa, S., and M. Prenna.** 1979. Laboratory studies with BL-S578 (cefadroxil), a new broad spectrum orally active cephalosporin. Chemotherapy **25**:9–13.
8. **Simon, C.** 1980. Zur Pharmakokinetik von Cefadroxil, Einem Neven Oralcephalosporin. Arzneim. Forsch. **30(I)**:502–504.