tissue specific drug delivery, chemotherapy, and treatment of inflammatory and infectious diseases of the liver and biliary system.

NOTATIONS

$AUC = \int_0^\infty c\,dt$
B = drug depot compartment
c = blood cimetidine concentration
D = dose
$D_B = X_B + (1 - F_{G1})D$
$D_T = F_{G1}D + F_BD_B$, the apparent amount of the dose absorbed
$F = (F_{G1}D + F_BD_B)/D$, the apparent fraction of the dose absorbed
F_B = fraction of drug cumulated in B that is released to G at time $t = T_B$
F_{G1} = fraction of D absorbed by first-order absorption into the central compartment
$1 - F_{G1}$ = fraction of D transferred from G to B
G = compartment from which absorption takes place
K_{xx} = first-order transfer rate constants
$-\lambda_1, -\lambda_2$ = eigenvalues of the linear system
t = time
T_L = lag time
T_B = time when a part (F_BD_B) of the drug cumulated in B is released to G
V = volume of distribution
X_B = amount of drug transferred from compartment 1 to compartment B at time $t = T_B$

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ACKNOWLEDGMENTS

Supported in part by the South African Medical Research Council.

Human Pharmacokinetics of a New Broad-Spectrum Parenteral Cephalosporin Antibiotic, Ceforanide

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Received July 14, 1977, from the *Department of Drug Metabolism and Pharmacokinetics, Bristol Laboratories, Syracuse, NY 13201.* Accepted for publication October 26, 1979.

Abstract □ The pharmacokinetics of the *l*-lysine salt of ceforanide were studied after intravenous administration of 1132 and 2264 mg as 30-min constant-rate infusions and after intramuscular administration of 556 and 1132 mg. The peak intravenous plasma concentrations were 136 and 222 μg/ml at termination of infusion, and 12-hr trough concentrations were 5.9 and 9.0 μg/ml, respectively. The peak intramuscular plasma concentrations were 38 and 74 μg/ml at 1.0–1.3 hr after dosing, and 12-hr trough concentrations were 3.9 and 6.7 μg/ml, respectively. When 19 successive intravenous and intramuscular doses at these levels were administered at 12-hr intervals, there was no tendency toward drug accumulation. The major drug elimination route was urinary excretion; 85% of the dose was excreted unchanged in the urine within 12 hr, and no metabolites with antibiotic activity were observed in urine. The mean terminal plasma half-life was 2.98 hr, the mean plasma protein binding was 80.6%, the steady-state volume of distribution was 12 liters, the plasma clearance was 45.9 ml/min/1.73 m^2, and the renal clearance was 34.9 ml/min/1.73 m^2. The pharmacokinetic properties and antibacterial activity spectrum indicate that this antibiotic should be effective in treating human bacterial infections when administered at 12-hr intervals. It is presently under clinical investigation.

Keyphrases □ Ceforanide—pharmacokinetics, humans □ Antibiotics, cephalosporins—ceforanide, pharmacokinetics, humans □ Pharmacokinetics, humans—ceforanide

The *in vitro* antimicrobial activity and *in vivo* properties in rodents of ceforanide, 7-[*o*-(aminomethyl)phenylacetamido]-3-[[[1-(carboxymethyl)-1*H*-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid, a new parenterally

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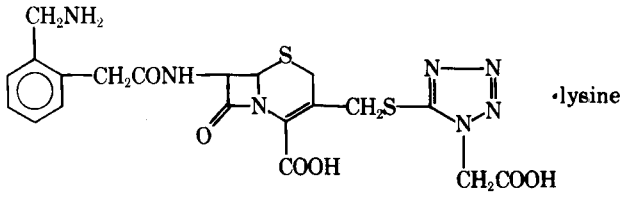


I

administered cephalosporin antibiotic, have been described in detail and compared with those of cephalothin, cephaloridine, and cefazolin (1). With few exceptions, ceforanide was more active than these reference antibiotics against major Gram-negative pathogens, and it inhibited their growth at plasma and urinary concentrations readily achievable in humans.

This report describes the pharmacokinetics of the lysine salt (I) of this cephalosporin antibiotic in normal subjects following single and multiple intravenous and intramuscular doses.

EXPERIMENTAL

Drug Doses and Administration Routes—All doses are expressed in terms of free acid equivalents of ceforanide. The drug was prepared immediately before administration as sterile solutions in vials containing 283 mg of drug. For intramuscular injection, the vial contents were reconstituted with sterile water USP to yield concentrations of 283 mg/ml. The intramuscular injections were administered in the outer quadrant of the gluteal muscle as 2 ml of solution for the 566-mg dose and as 4 ml of solution for the 1132-mg dose. For intravenous administration, the antibiotic was reconstituted in sterile physiological saline solution USP to give a final concentration of 1132 or 2264 mg in 50 ml of solution. Fifty milliliters of either solution was administered into an antecubital vein by 30-min constant-rate infusion using a compact infusion pump[1].

Volunteers and Study Design—The drug was administered to 24 normal adult males, 22–40 years old, with an average weight ($\pm SE$) of 72.5 ± 1.3 kg and an average body surface area ($\pm SE$) of 1.90 ± 0.02 m^2.

Six randomly selected subjects were given 556 and 1132 mg im and 1132 and 2264 mg iv twice daily at 12-hr intervals for a total of 19 successive doses over 10 dosing days (a second dose was not administered on the last dosing day). The morning dose was given before breakfast.

Sample Collection—Plasma and urine specimens were collected after the first, ninth, and 19th doses. Plasma samples were collected from the intravenous subjects immediately before dosing (zero time), at 15 and 30 min during the infusion (the 30-min sample was collected at the end of the infusion and also constituted the zero-time postinfusion sample), and then at 0.25, 0.50, 1.0, 2.0, 4.0, 6.0. 8.0, and 11.5 hr after infusion termination. Plasma samples were collected from the intramuscular subjects immediately before dosing (zero time) and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.5, 4.0, 6.0, 9.0, and 12 hr after dosing.

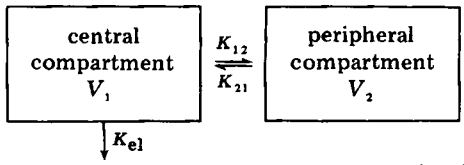
Complete urine samples were collected from all subjects over the 0–2-, 2–4-, 4–6-, 6–9-, and 9–12-hr intervals after the start of dosing. After the 19th dose, a 12–24-hr urine sample also was collected.

Heparinized blood samples, 10 ml, were collected by venipuncture[2]. The contents of the tubes were mixed gently and then immediately placed in a chipped ice bath where they were kept until plasma was separated by centrifugation at 4°. At least 3 ml of plasma was withdrawn and placed in polypropylene tubes with caps.

The urine samples were refrigerated at 4° while being collected. The subjects were instructed to empty their bladders at the end of each collection interval. The total volume and pH of each urine sample were measured and recorded. Immediately thereafter, 10-ml aliquots of each urine sample were transferred to polypropylene bottles.

The plasma and urine samples were flash frozen by immersion in an ethanol–dry ice bath and stored at or below −20° until they were thawed for assay.

Antibiotic Assay—Plasma and urine concentrations of ceforanide were determined by standard cup-plate bioassay techniques (2) using *Klebsiella pneumoniae* (Bristol A9977)[3] as the bioassay organism. Other microorganisms cannot be expected to yield equivalent, valid results for the bioassay of ceforanide. All bioassay results are expressed in terms of free acid equivalent concentrations.



Scheme I—Open, first-order, two-compartment model of drug distribution

The lower sensitivity limit of the assay was equivalent to a plasma concentration of 2.0 μg/ml. The linear concentration ranges for the cup-plate assay were 0.5–5.0 μg/ml for plasma and 1–10 μg/ml for urine. The mean coefficient of variation [(standard deviation of zone diameter/mean zone diameter) × 100] of replicate cup-plate assays of the standards was 3.10%.

Determination of Plasma Protein Binding—Ceforanide was added to fresh, pooled, heparinized 90% human plasma at concentrations of 27, 53, 99, and 200 μg/ml, and the samples were incubated at 37° for 15 min with gentle shaking. Replicate solutions were prepared in aqueous pH 7.40 buffer containing 0.05 *M* NaCl and 0.10 *M* *N*-tris(hydroxymethyl)-methyl-2-aminoethanesulfonic acid[4] and were treated similarly. These samples were subjected to centrifugal ultrafiltration[5].

The drug concentrations in the filtrates were determined by the same cup-plate assay technique used for plasma and urine analyses. The concentration in the plasma filtrate as a percentage of the total concentration in the unfiltered plasma sample was subtracted from 100% to determine the percentage bound to plasma protein. Ceforanide did not bind to the ultrafiltration membrane.

Bioautographic Analysis for Urinary Metabolites with Antibiotic Activity—Urine samples were diluted with 0.1 *M* potassium phosphate buffer (pH 7.0) and spotted on 1.2 × 57-cm strips of filter paper[6]. The strips were developed overnight in the descending mode using *n*-butanol–acetic acid–water (60:15:25). Then they were air dried, overlaid on seed agar inoculated with *Bacillus subtilis* (A9506A), and incubated overnight at 28°. Inhibition zones were visualized by spraying with 1.2% triphenyltetrazolium chloride in 1.25% dextrose solution. The R_f value of ceforanide was 0.3.

Pharmacokinetic Analysis—Mean plasma concentrations during and after intravenous infusion of the first doses were fitted to an open, first-order, two-compartment model of drug distribution (Scheme I) (3). The fitting was performed according to Marquardt's algorithm (4) using a digital computer program. The best-fit parameters found by this procedure were corrected by the Loo–Riegelman procedure (5) to obtain the equivalent parameters that could be found on instantaneous bolus intravenous administration of the same drug doses. This procedure yielded an equation of the form $C = A \exp(-\alpha t) + B \exp(-\beta t)$, where C is the plasma concentration, t is time, A and B are coefficients, and α and β are exponents. The A, B, α, and β parameters and the urinary excretion data were processed further, allowing the various pharmacokinetic parameters to be calculated by standard procedures (6).

The individual subject's observed peak plasma concentrations, C_{max}, and the time to peak plasma concentrations, t_{max}, by both dosing routes and at all dose levels were tabulated, and the mean values and standard errors were calculated. The individual area under the plasma concentration–time curves from $t = 0$ to $t = \infty$ (AUC) were calculated for the first dose by the trapezoidal rule:

$$AUC = \sum_{i=1}^{n-1} (C_{i+1} + C_i)(t_{i+1} - t_i)/2 + C_n/\beta \qquad \text{(Eq. 1)}$$

where $C_1 = 0$ at $t_1 = 0$. The β term is the slope of a plot of the natural logarithms of the 3–12-hr plasma concentrations *versus* time as determined by linear regression analysis. The AUC values for the ninth and 19th doses were calculated between 0 and 12 hr. The observed terminal plasma half-life, $t_{1/2}$, was calculated from β by:

$$t_{1/2} = 0.693/\beta \qquad \text{(Eq. 2)}$$

for all subjects. The individual AUC and $t_{1/2}$ values also were tabulated, and their means and standard errors were calculated.

[1] Model 975, Harvard Apparatus Co., Millis, Mass.
[2] Vacutainer tubes, Becton-Dickinson, Rutherford, N.J.
[3] This microorganism is a mutant strain of *K. pneumoniae* (A9977) specifically selected by the Department of Microbiological Research, Bristol Laboratories.
[4] Calbiochem, Los Angeles, Calif.
[5] DF50A Centriflo membrane cones, Amicon, Lexington, Mass.
[6] Whatman No. 1.

Table I—Ceforanide Binding to Human Plasma Proteins

Plasma Concentration, μg/ml	Percent Bound[a]
27	83.0 (0.0)
53	82.8 (0.2)
99	80.7 (0.0)
200	76.0 (1.1)

[a] Mean (±*SE*) of triplicate determinations.

The absorption profile following intramuscular administration was determined from the mean plasma concentration data using the Loo–Riegelman method (7).

The absolute percentage bioavailability following intramuscular administration was determined by linear regression analysis of a plot of *AUC versus* dose for the intravenous and intramuscular data and by:

$$100F = (U_{im}/U_{iv}) \times 100 \qquad \text{(Eq. 3)}$$

where $100F$ is the absolute percentage bioavailability and U is the fraction of the dose excreted in the urine in 12 hr.

Statistical Analysis—The various observed and calculated pharmacokinetic parameters by each dosing route and at each dose level were compared between dosing groups by the *t* test for group comparisons. The statistical tests (both the *t* test and linear regression analyses) were analyzed for significance at $p = 0.05$. All references to significant or nonsignificant results refer to the tests for statistical significance.

When comparisons were performed between study days within a given dosing group, a *t* test for paired comparisons was used, except in one case. Since there were data for only four subjects for the first 1132-mg iv infusion dose but there were data for all six subjects for the ninth and 19th doses, these data sets also were compared by a *t* test for group comparisons so that two subjects did not have to be omitted at the ninth and 19th doses. These *t* tests for group comparisons yielded the same results as the *t* tests for paired comparisons.

The results of the absolute bioavailability analyses of urinary excretion data were subjected to a *t* test of the null hypothesis that the true mean bioavailability was 100%. These tests also were analyzed for significance at $p = 0.05$.

RESULTS

Plasma Protein Binding—These results are summarized in Table I. The binding over the 27–200-μg/ml range was essentially constant at 80.6%. Investigations of the binding of other cephalosporin antibiotics, using the same technique and the same pooled plasma sample as for ceforanide, indicated 89.7% protein binding for cefazolin between 25 and 205 μg/ml, 50.0% for cefoxitin between 11 and 88 μg/ml, 44.7% for cefuroxime between 9 and 75 μg/ml, and 82.7% for cefamandole (either as the sodium salt or as cefamandole nafate) between 8 and 88 μg/ml.

Bioautographic Analysis—No evidence was found for the presence of any ceforanide metabolite(s) with antibiotic activity in urine.

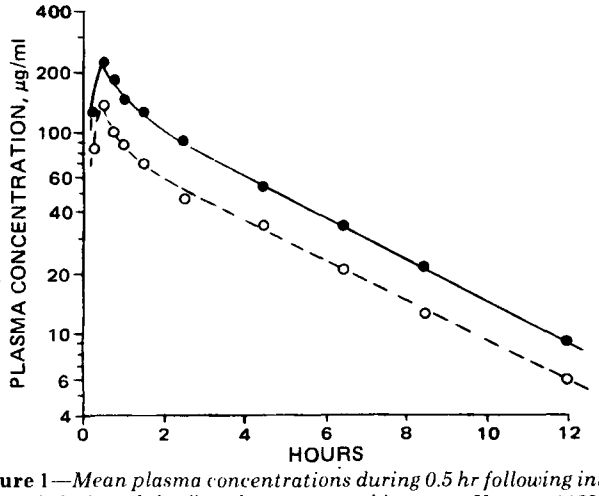


Figure 1—*Mean plasma concentrations during 0.5 hr following intravenous infusion of the first dose to normal humans. Key:* ○, *1132-mg dose; and* ●, *2264-mg dose.*

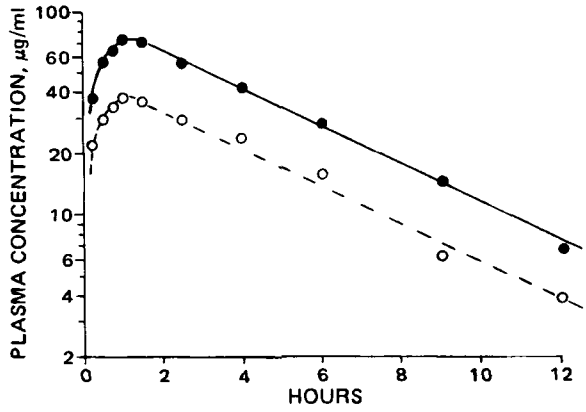


Figure 2—*Mean plasma concentrations following intramuscular administration of the first dose to normal humans. Key:* ○, *566-mg dose; and* ●, *1132-mg dose.*

Plasma and Urine Levels—Figures 1 and 2 are semilogarithmic plots of the mean concentration *versus* time data for the first intravenous and intramuscular doses. There were data from six subjects for each dosage route and dosage level on all dosing days, except for the first 1132-mg iv dose where there were only four subjects. At that time, one infusion pump developed a minor mechanical problem. Therefore, the starting time and exact dose administered to two of the subjects were unknown, although it was estimated that they received ~85% of the dose. Neither plasma nor urine samples were collected from these two subjects on the 1st day. The mechanical problem was resolved immediately, and there were no other difficulties with dosing throughout the study.

The various observed mean plasma parameters after intravenous and intramuscular administration are listed in Table II. The mean peak concentrations did not change significantly over the 19 drug doses by either route or at any given dose level, indicating that there was no tendency toward accumulation of ceforanide when administered every 12 hr, even though there was an appreciably detectable trough plasma concentration immediately before the next dose was given. The mean time of peak concentrations after intramuscular dosing did not change significantly over the duration of the study, indicating that the absorption profile of ceforanide did not change on repeated administration.

The terminal plasma half-lives (2.7–3.2 hr) remained essentially constant throughout the study by both routes and dose levels. Figure 3 is a rectilinear plot of the mean area under the plasma concentration–time curve *versus* dose for the intravenous and intramuscular data from the first, ninth, and 19th doses. Linear regression analysis indicated that the areas by the two dosage routes were on the same statistically significant straight line and that the *y* intercept was not significantly different from zero ($p = 0.05$). Therefore, the absolute bioavailability was 100% following intramuscular administration. The reciprocal of the slope of this line was the plasma clearance, Cl_p, of the drug, 50.2 ml/min/1.73 m^2.

The mean urinary recoveries are listed in Table III. The compound was excreted through the kidneys at high concentrations. On the average, 85% of the administered dose was recovered in the urine within 12 hr of the start of injection. There were no statistically significant differences in total excretion after intramuscular or intravenous administration, which

Table II—Mean Observed Plasma Parameters for Ceforanide[a]

Route	Dose, mg	Dose Number	Peak Concentration, μg/ml	Peak Time, hr	Plasma Half-Life, hr
Intravenous	1132	1	136 (14)	0.5	3.06 (0.16)
		9	128 (4)	0.5	2.83 (0.15)
		19	125 (2)	0.5	2.65 (0.11)
	2264	1	222 (10)	0.5	2.88 (0.09)
		9	240 (4)	0.5	2.80 (0.28)
		19	240 (4)	0.5	2.70 (0.08)
Intramuscular	566	1	38.0 (1.9)	1.04 (0.10)	3.25 (0.23)
		9	40.7 (2.7)	1.12 (0.12)	2.84 (0.31)
		19	39.8 (1.8)	1.08 (0.14)	3.04 (0.40)
	1132	1	74.3 (2.8)	1.33 (0.10)	3.24 (0.26)
		9	76.0 (1.8)	1.00 (0.11)	3.11 (0.34)
		19	75.7 (2.0)	0.92 (0.05)	2.78 (0.14)

[a] Standard errors in parentheses.

Table III—Mean Urinary Recovery of Ceforanide [a]

Route	Dose, mg	Dose Number	Percent Recovery during Collection Intervals after Start of Injection						
			0–2 hr	2–4 hr	4–6 hr	6–9 hr	9–12 hr	12–24 hr	Cumulative
Intravenous	1132	1	34.5 (2.5)	24.5 (0.8)	13.9 (1.1)	11.3 (0.5)	5.9 (0.6)	—[b]	91.2 (3.6)
		9	34.3 (7.3)	18.1 (3.3)	11.7 (1.1)	9.2 (1.0)	4.9 (0.7)	—	78.3 (9.3)
		19	30.2 (2.0)	34.8 (4.0)	12.7 (2.3)	8.6 (1.1)	4.8 (0.6)	3.5 (0.7)	83.9 (4.6)
	2264	1	33.3 (3.8)	26.8 (4.0)	11.1 (2.5)	9.4 (1.3)	4.5 (0.6)	—	85.1 (5.4)
		9	29.7 (4.9)	23.7 (2.7)	14.9 (1.6)	9.1 (1.1)	4.9 (0.6)	—	83.7 (17.8)
		19	32.6 (2.7)	32.7 (4.4)	15.8 (1.0)	9.1 (0.6)	4.3 (0.5)	4.0 (0.6)	98.6 (3.0)
Intramuscular	566	1	19.6 (1.5)	26.1 (0.7)	16.7 (0.8)	11.7 (1.0)	5.7 (0.2)	—	79.8 (1.7)
		9	23.7 (3.7)	30.1 (2.2)	14.4 (1.3)	15.0 (3.4)	6.4 (4.2)	—	89.5 (2.8)
		19	23.8 (6.6)	25.3 (1.7)	13.0 (2.4)	13.0 (0.5)	5.4 (1.0)	4.7 (1.9)	90.5 (1.2)
	1132	1	18.1 (2.5)	26.1 (0.6)	15.5 (2.3)	11.2 (1.2)	7.1 (0.9)	—	78.1 (3.3)
		9	23.2 (1.3)	28.2 (0.8)	14.9 (1.8)	11.4 (1.2)	6.1 (0.5)	—	83.9 (2.5)
		19	23.8 (2.6)	28.8 (1.9)	18.1 (1.3)	10.5 (1.4)	6.0 (1.1)	5.0 (0.6)	92.3 (2.2)

[a] Standard errors in parentheses. [b] Sample not collected.

also is indicative of 100% bioavailability of ceforanide on intramuscular administration.

The data in Table III were converted to urinary excretion rates during each urine collection interval and plotted *versus* the plasma concentrations at the midpoints of the collection intervals (Fig. 4). The data yielded a statistically significant straight line by linear regression analysis. The y intercept was not significantly different from zero. Therefore, urinary excretion of ceforanide may be treated as a reaction following apparent first-order kinetics. The slope of the plot was equivalent to the renal clearance, Cl_r, of ceforanide, 34.9 ml/min/1.73 m^2.

The mean plasma concentrations for the first intravenous doses of ceforanide were analyzed using the open, two-compartment model of drug distribution (Scheme I). The central compartment, with a volume of distribution of V_1, is comprised of well-perfused tissues and includes the blood plasma. The peripheral compartment, with a volume of distribution of V_2, is comprised of more poorly perfused tissues. Both K_{12} and K_{21} are first-order rate constants for drug transfer between the central and peripheral compartments; K_{el} is the first-order rate constant for drug elimination, which occurs only from the central compartment. The total volume of the drug distribution in the body is V_{dss} (the volume of distribution at steady state). If it is assumed that drug clearances from the central to the peripheral compartments and from the peripheral to the central compartments are equal (*i.e.*, $V_1K_{12} = V_2K_{21}$), then $V_2 = K_{12}V_1/K_{21}$ and V_{dss} can be calculated as $V_{dss} = V_1 + V_2$. According to this model, the plasma clearance can be calculated as $Cl_p = V_1K_{el}$.

The best-fit values for the pharmacokinetic parameters are listed in Table IV. The results for the 1132- and 2264-mg iv doses were essentially identical; the differences between doses were attributed to normal intersubject differences between two panels of subjects. The half-lives (3.08 and 2.89 hr) were almost identical to those found by direct linear regression analysis of the data of individual subjects (3.06 and 2.88 hr, Table II). The overall Cl_p found by direct pharmacokinetic analysis of the mean intravenous infusion data, 45.9 ml/min/1.73 m^2, was close to the Cl_p of 50.2 ml/min/1.73 m^2 found by plotting the area under the curve *versus* dose for all subjects for both the intravenous and intramuscular data.

The most important, but not exclusive, factor controlling the terminal half-life of ceforanide was the elimination rate constant, K_{el}. The rate constant for drug transfer from the peripheral to the central compartment, K_{21}, was about three times larger than K_{el} and, therefore, cannot be process limiting.

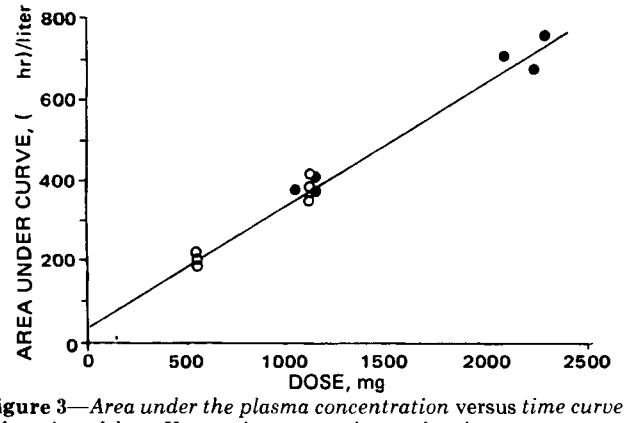


Figure 3—*Area under the plasma concentration* versus *time curve as a function of dose. Key:* ○, *intramuscular; and* ●, *intravenous.*

The mean values listed for the pharmacokinetic parameters in Table IV were used to determine the intrinsic intramuscular absorption profile according to the Loo–Riegelman procedure (7). The results are presented in Fig. 5 as a semilogarithmic plot of the percentage of dose unabsorbed *versus* time. The values for the 566- and 1132-mg doses essentially were superimposable and formed a straight line. Intramuscular absorption of the drug can be considered to be a passive process proceeding by apparent first-order kinetics. The first-order intramuscular absorption rate constant, K_a, was 1.19 hr^{-1}, yielding an absorption half-time of 35 min. Intramuscular absorption of ceforanide had no dose-dependent features.

DISCUSSION

Ceforanide has linear, dose-independent pharmacokinetic properties in humans. These properties are compared to those of several other parenteral cephalosporin antibiotics in Table V. Its plasma half-life, 2.9 hr, is the longest of any of these antibiotics; cefazolin, at 1.8 hr, has the next longest plasma half-life. Concomitant with its extended half-life, ceforanide has the lowest rates of plasma and renal clearance. These factors result in the prolonged *in vivo* duration of ceforanide. Peak plasma levels of ceforanide following intramuscular administration would be higher than those reported for equivalent doses of cephalothin, cephaloridine, cefoxitin, cefuroxime, and cefamandole and should be similar to peak plasma concentrations following the intramuscular administration of cefazolin. Volumes of distribution are in the range of the values of the two-compartment model reported for cephalothin and cefoxitin and are 1.4- to 1.8-fold higher than these volumes of distribution for cefazolin. These relatively high volumes of distribution, coupled with high peak plasma concentrations and prolonged duration, suggest favorable distribution of the drug to tissue sites. Ceforanide was excreted in the urine in 12 hr, suggesting little or no contribution of biliary excretion or metabolism to drug elimination.

The linear, dose-independent kinetics of ceforanide permit prediction of plasma concentrations that would result from different dosage regimens. For instance, the predicted mean peak plasma concentrations after intramuscular injection of 500 and 1000 mg should be about 34 and 66 μg/ml, respectively. The peak plasma concentration and time to peak on intravenous administration can be controlled by controlling the size and

Table IV—Pharmacokinetic Parameters for Ceforanide from Mean Plasma Concentration Data for First Intravenous Doses

Parameter	Dose, mg		Mean (*SE*)
	1132	2264	
A, μg/ml	75.5	11	—
α, hr^{-1}	1.89	1.80	1.84 (0.06)
B, μg/ml	81.7	151	—
β, hr^{-1}	0.225	0.240	0.232 (0.011)
K_{12}, hr^{-1}	0.638	0.523	0.580 (0.04)
K_{21}, hr^{-1}	0.387	0.377	0.382 (0.007)
$t_{1/2}$, hr	3.08	2.89	2.98 (0.13)
V_1, liters	7.20	8.64	7.92 (1.02)
V_{dss}, liters	11.4	12.6	12.0 (0.8)
Cl_p, ml/min/1.73 m^2	42.3	49.5	45.9 (5.1)

Table V—Comparison of Pharmacokinetic Parameters for Various Parenteral Cephalosporin Antibiotics [a]

Parameter	Ceforanide	Cephalothin	Cephaloridine	Cefazolin	Cefoxitin	Cefuroxime	Cefamandole
Cl_p, ml/min/1.73 m^2	45.9	472	167	62	331	150	241
Cl_r, ml/min/1.73 m^2	34.9	274	125	64	298–331	139	—
Renal excretion, % of dose	85	52	75	100	90–100	95	100
$t_{1/2}$, hr	2.98	0.56	0.6–1.5	1.80	0.666	1.17	0.90
Percent protein bound	81	65	8–31	90	50	45	83
Peak levels, μg/ml							
500 mg im	34	6–8	30	11–70	11	26	15
1000 mg im	66	15–20	40	38–75	22	40	36
V_1, liters	7.92	7.76	—	4.44	6.88	—	—
V_{dss}, liters	12.0	14.3	—	8.48	13.3	—	—

[a] Protein binding values for ceforanide, cefazolin, cefoxitin, cefuroxime, and cefamandole were obtained in this laboratory. All other cefuroxime values are from Ref. 8. All other cefamandole values are from Refs. 9 and 10. All other values for cephalothin, cephaloridine, cefazolin, and cefoxitin are from Ref. 11.

Table VI—Estimated Mean Duration of Plasma Ceforanide Concentrations

Mode of Administration	Dose, mg	Duration (hr) at Plasma Concentrations Greater Than or Equal to 6.25 μg/ml	8.0 μg/ml	12.5 μg/ml
Intramuscular	500	9.6	8.2	6.2
	1000	12.8	11.6	9.4
Intravenous bolus	1000	10.4	9.3	7.4
	2000	13.3	12.3	10.4
Constant rate intravenous infusion for 30 min	1000	10.5	9.5	7.6
	2000	13.5	12.5	10.5
Constant rate intravenous infusion for 60 min	1000	10.8	9.7	7.8
	2000	13.8	12.7	10.8

mode of the intravenous injection. The predicted mean peak plasma concentrations resulting from a 0.5-hr constant-rate infusion would occur at 0.5 hr and would be 103 μg/ml for a 1000-mg dose and 205 μg/ml for a 2000-mg dose. If the doses remain the same and are infused over 1 hr, the peak concentrations at 1 hr should be 88 μg/ml for 1000 mg and 176 μg/ml for 2000 mg. If these doses are given by true bolus intravenous injection, the immediate peak plasma concentrations should be 126 μg/ml at 1000 mg and 252 μg/ml at 2000 mg.

The varying modes of administration also would affect the periods over which observed plasma concentrations would exceed the given minimum

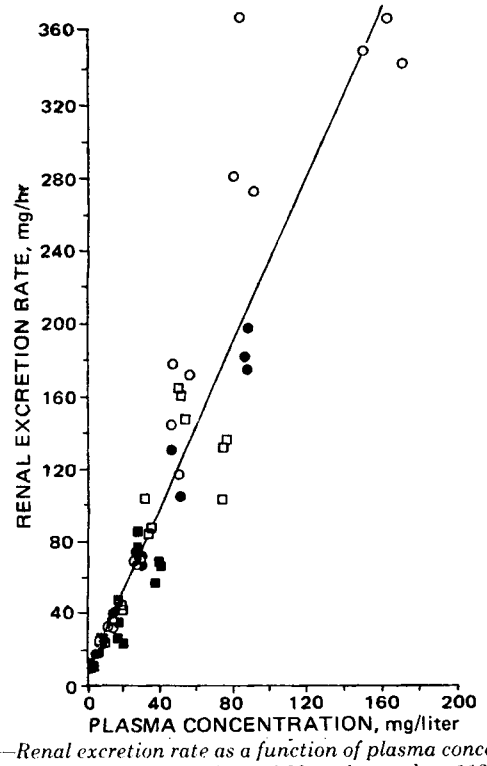


Figure 4—*Renal excretion rate as a function of plasma concentration. Key:* ●, *1132 mg iv;* ○, *2264 mg iv;* ■, *566 mg im; and* □, *1132 mg im.*

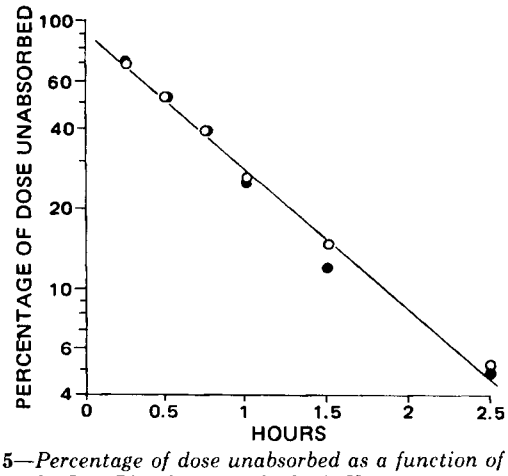


Figure 5—*Percentage of dose unabsorbed as a function of time according to the Loo–Riegelman method (7). Key:* ○, *566-mg dose; and* ●, *1132-mg dose.*

plasma concentrations. Table VI lists the estimated periods that plasma concentrations would exceed 6.25, 8.0, and 12.5 μg/ml (standard concentrations in a geometrically diluted minimum inhibitory concentration series) using these modes of parenteral administration. If ceforanide is dosed at 12-hr intervals, a 500-mg im dose would exceed 6.25 μg/ml for about 80% of that period and would exceed 12.5 μg/ml for about 52% of that period. If the intramuscular dose is increased to 1000 mg, the plasma concentration would exceed 6.25 μg/ml for the entire 12-hr period and would exceed 12.5 μg/ml for about 78% of that period. From the point of view of maintaining a proper peak-to-trough plasma concentration relationship, a 500-mg im dose every 12 hr is reasonable. The kinetic relationships pertaining to constant-rate intravenous infusion of ceforanide are such that increasing the infusion time for a given dose from 0.5 to 1 hr would lower the peak concentration without appreciably lengthening the duration of plasma concentrations above the given minimum levels.

Ceforanide demonstrated no tendency to accumulate. It yielded high and prolonged plasma concentrations and has useful distribution properties. These favorable properties, together with its good antibacterial activity, suggest that it could be effective in treating bacterial infections in humans when administered at 12-hr intervals. This regimen is undergoing clinical trials.

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ACKNOWLEDGMENTS

The authors thank Dr. John C. Godfrey, clinical monitor of the study. They are grateful to Katherine Casson for direction of the cup-plate bioassays and to Violet Z. Rossomano for direction of the bioautographic urine analysis.

Influence of Viscosity on Absorption from Nitrofurantoin Suspensions

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Abstract □ Nitrofurantoin, 200 mg, was administered orally to 11 subjects in an aqueous reference dispersion and in five suspensions having the same rheogram. Algin, carbomer, guar gum, methylcellulose, and colloidal magnesium aluminum silicate were the five suspending agents employed. Complexation was demonstrated by dialysis between nitrofurantoin and methylcellulose and between nitrofurantoin and carbomer; however, physiological availability was not altered by the interaction. The viscosity increase slowed absorption and urinary excretion, thus delaying the time of the maximum excretion rate without a decrease in bioavailability. A clinically acceptable urinary nitrofurantoin concentration was maintained for at least 2 hr longer by a viscosity increase.

Keyphrases □ Nitrofurantoin—suspensions, effect of viscosity on absorption □ Suspensions—nitrofurantoin, effect of viscosity on absorption □ Bioavailability—nitrofurantoin suspensions, effect of viscosity on absorption □ Antibacterial agents—nitrofurantoin suspensions, effect of viscosity on absorption

Based on the few literature reports, it is difficult to generalize the effect of viscosity on the absorption and availability of medicinal compounds from oral liquids. Malone *et al.* (1) noted that increasing viscosity by increasing the concentration of sucrose in aqueous solutions of phenobarbital sodium progressively lengthened the induction time of narcosis in rats. Davison *et al.* (2) found that methylcellulose delayed the absorption from orally administered sodium salicylate solutions as demonstrated by the reduction of brain and plasma salicylate levels.

Levy and Jusko (3) concluded that the decrease in absorption by the ligated rat stomach of alcohol and salicylic acid from solutions containing methylcellulose was due to the slower movement of the drug molecule to the absorbing membrane. Harper and Wordan (4) reported that the LD_{50} values of isoniazid (isonicotinic acid hydrazide) in rats were 3300, 2650, and 2000 mg/kg in acacia solution, gelatin solution, and water, respectively, and they concluded that the apparent toxicity was influenced by the vehicle. Hewitt and Levy (5) reported that, contrary to expectation, the oral administration of thiamine and riboflavin in highly viscous methylcellulose solutions did not affect the rate and extent of absorption. Ashley and Levy (6) showed that the absorption of phenolsulfonphthalein was decreased during the 1st hr by the addition of algin (sodium alginate) to the solution but that the total amount absorbed was unchanged.

BACKGROUND

Suspending agents are added to suspensions to increase the viscosity so that the sedimentation rate is slowed and the measurement of a proper dose is simplified. Because a suspending agent improves the physical properties of a suspension, it may concomitantly affect the absorption of the medicinal compound by the increased viscosity or by complexation. It has been shown that the dissolution rate of a solid is inversely proportional to the viscosity of the dissolution medium (7).

Since the dissolution rate often is the limiting factor in availability of a relatively insoluble medicinal compound in an orally administered suspension, viscosity would be expected to affect absorption. Seager (8) found that methylcellulose affected the excretion after the oral administration of a nitrofurantoin suspension so that less nitrofurantoin was excreted and the time of maximum excretion was delayed by 1 hr.

This study was conducted to determine, by a urinary recovery technique, the effect of suspending agents (algin, carbomer, guar gum, methylcellulose, and colloidal magnesium aluminum silicate) on the absorption of nitrofurantoin. Because the main concern was to determine if the viscosity affected GI absorption, all formulations containing a suspending agent had the same viscosity.

EXPERIMENTAL

Suspension Preparation—Nitrofurantoin[1] was classified by a sonic sifter[2], and the 70–140-mesh fraction (157 μm) was used. Nitrofurantoin, 200 mg, was dispersed in 20 g of vehicle. Each vehicle was prepared by making dispersions of various concentrations of the suspending agent, and their viscosities were measured by a rotational viscometer[3]. Guided by these results, more appropriate concentrations then were prepared, and their viscosities were measured. For each suspending agent, a concentration was found experimentally that provided a rheogram similar to that of a 2% aqueous solution of methylcellulose, 4000 cps.

Dialysis—Dialysis was carried out at 37° in cellophane tubing[4] tied into a sac with distilled water as the dialysis medium. The nitrofurantoin dispersion, 50 ml, was placed in the cellophane sac, which was soaked previously for 24 hr to achieve hydration; then the open end was tied. The sac was immersed in 100 ml of distilled water, sealed in the container, and attached to a submersion rotator[5].

At 3, 6, 12, 24, and 36 hr, one dialysis sac of a series was removed, fluid volume inside and outside of the sac was measured, and the nitrofurantoin concentration in the fluid inside and outside of the sac was determined from spectrophotometric measurements at 367 nm. Equilibrium was always attained in <36 hr.

Protocol—All suspensions were coded and distributed according to the Latin square law (9) so that two of the initial 12 volunteers received

[1] Lot 43C-1550, Sigma.
[2] Allen-Bradley.
[3] Brookfield LVT.
[4] Fisher 8-667E dialyzer tubing, 2.74 cm i.d.
[5] Model SR-25V, Scientific Industries.

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