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Human Pharmacology of Cefotaxime (HR 756), a New Cephalosporin

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Cefotaxime (HR 756) is a new semisynthetic parenteral cephalosporin with exceptional activity against gram-negative organisms and considerable stability against their β-lactamases. To study its pharmacokinetic properties, 0.5-, 1-, and 2-g doses were administered to each of six volunteers intravenously over 15 min, followed by a sustaining infusions of 0.5, 1, and 2 g/h, respectively, for 3 consecutive hours. The loading doses produced mean peak levels of 41, 93, and 160 μg/ml, and mean steady-state serum concentrations were 27, 64, and 138 μg/ml, respectively. The mean terminal half-life was 75 ± 7 min. The total volume of distribution averaged 0.22 ± 0.03 liters/kg of body weight. Total body and renal clearances were 232 ± 30 and 145 ± 24 ml/min per 1.73 m^2, respectively; 63 ± 9% of the administered dose was excreted through the kidneys in 24 h. To determine the effect of cefotaxime on the renal tubules, urinary alanine aminopeptidase excretion was measured before, during, and after the infusions. It remained within the normal range in all instances; however, 48 ± 14% of the total daily alanine aminopeptidase output was recovered during the infusion period. Side effects were dose related and included fatigue, loose stools, and night sweats. No significant changes in hematology, serum chemistry, or urinalysis were recorded.

Cefotaxime {proposed generic name of 3-acetoxymethyl-7-[(2-(2-amino-4 thiazolyl)-2-methoxy-iminoacetyl)amino]-ceph-3-eme-4-carboxylic acid, sodium salt} is a novel parenteral cephalosporin with remarkable activity against gram-negative organisms, including indole-positive *Proteus* species, *Serratia*, and, to some extent, *Pseudomonas aeruginosa* (5, 11, 12, 28, 29). Its resistance to hydrolysis by gram-negative β-lactamase Richmond types I, III, IV, and V is of the same order as that of cefoxitin and cefuroxime (8). In experimental animal infections, cefotaxime appeared to be superior to cefazolin (12).

We conducted a pharmacokinetic study with this compound to evaluate the following aspects of this new cephalosporin: (i) determination of the pharmacokinetic parameters during steady-state infusions at three different dose levels; (ii) effect of cefotaxime on the urinary excretion of alanine aminopeptidase (AAP) as a possible indicator of tubular toxicity; and (iii) evaluation of the local and systemic tolerances of high doses.

(These results were presented in part at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., 1-4 October 1978.)

MATERIALS AND METHODS

Six healthy, young male volunteers took part in the study. Informed consent was obtained from each participant. At intervals of 1 week 0.5-, 1-, and 2-g doses of cefotaxime were administered to each volunteer over 15 min, followed by sustaining infusions of 0.5, 1, and 2 g/h, respectively, for 3 consecutive hours (Fig. 1). The infusion rate was controlled with an infusion pump (Perfusor E+2; Braun Melsungen, West Germany).

A total of 28 serum samples were drawn from the contralateral forearms at 0, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, 195, 200, 205, 210, 215, 220, 225, 240, 270, 300, 360, 420, 480, 540, 600 and 660 min to document the serum concentration time curves during the loading and sustaining infusions and the following 8 hours after the infusions were stopped. Blood specimens were centrifuged at 4°C after clotting at room temperature. Urine specimens were collected quantitatively during five time intervals (0 to 120, 120 to 195, 195 to 360, 360 to 660, and 660 to 1,440 min) over the 24-h study period. Serum and urine specimens were immediately frozen in liquid nitrogen and assayed within 1 week by the large plate agar diffusion method described by Bennett et al. (3). Concentrations between 256 and 2 μg/ml were assayed with the multiresistant Minnesota strain of *Klebsiella pneumoniae* (ATCC 27799); for concentrations between 4 and 0.03 μg/ml a strain of *Escherichia coli* was used. (The assay strain

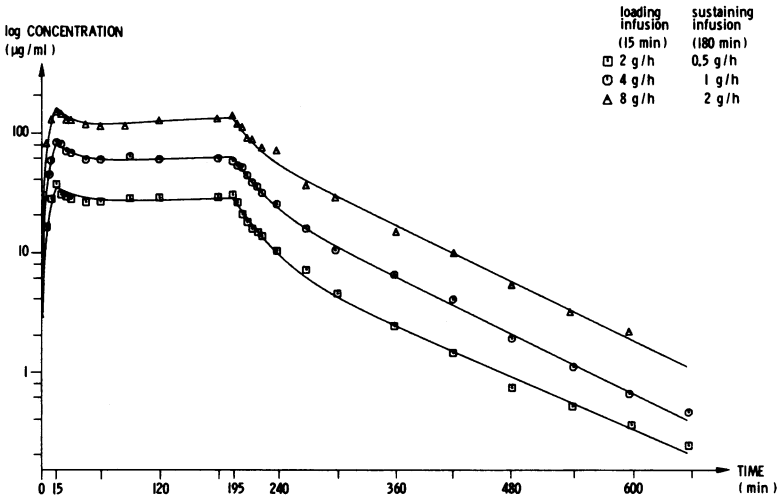

FIG. 1. *Serum concentration time curves during and after the administration of three different doses of cefotaxime to one volunteer.*

designated V 6311/65 was obtained from Hoechst AG, Frankfurt, West Germany, and is available on request.) Both of these strains measure total microbiological activity and do not discriminate between the original compound and its metabolite(s), which was to be anticipated since studies with liver homogenates suggested a deacetylation of cefotaxime in vivo. However, in vitro the compound appears to be relatively stable, with less than 10% loss of activity over 16 h at various pH values and temperatures (13). The accuracy of the bioassay was estimated by the method of Bennett et al. (3). For all concentrations within the measured range (0.03 to 256 µg/ml), the 95% confidence limits do not exceed ±12% of the determined value. Serum and urine standards in the range of expected concentrations were prepared on the day of each study from pooled, antibiotic-free human serum and 0.0 5 M phosphate buffer, pH 7, respectively. The total amount of antibiotic administered to each volunteer was calculated by weighing the syringes before and after the infusion and by determining the antibiotic concentration in the infusate. The actual total doses which were administered averaged 1,989 ± 104, 4,166 ± 445, and 7,767 ± 131 mg for the low, medium, and high doses, respectively.

Before, during, and after each study, the following tests were performed: complete blood count, prothrombin time, Coomb's test, serum and urine creatinine, urea, bilirubin, transaminases, alkaline phosphatase, and urinalysis.

In addition to these parameters, a specific attempt was made to evaluate the effect of cefotaxime on the proximal tubules of the kidney. AAP is an enzyme located primarily on the brush border membranes of the renal tubules, and several authors have demonstrated that damage to the proximal tubules (either drug induced or due to an inflammatory process) is reproducibly associated with an increased urinary AAP output (4, 18–21, 25). AAP activity was determined by a spectrophotometric method using alanine-*p*-nitranilide (Roche Reagents; catalog no. 1402) as substrate. The reaction was followed at 25°C and 405 nm (19). Normal values at our institution range between 1.7 and 13.0 mU/ml. Before and after each study, AAP excretion, defined as the ratio of enzymatic activity to urine volume, was measured in a pooled specimen of the 24-h urine. Samples of urine specimens collected during the five time periods on the study days and of five equally timed urine samples collected several weeks after the last infusion were immediately refrigerated at −20°C and analyzed for AAP activity within 1 week. Pooled samples were handled identically.

Pharmacokinetic calculations. For pharmacokinetic calculations, a two-compartment open model was used. The mathematical description of this model, incorporating a loading and a sustaining infusion, can be realized by the linear superposition of two solutions corresponding to two different temporal patterns of intravenous infusions (9). The pharmacokinetic parameters of the model (volume of distribution of the central compartment [V_1], rate constant of transfer between the two compartments [k_{12} and k_{21}], and rate constant of elimination [k_e]) were adapted to the experimental serum concentration time curve with a nonlinear fitting program (16). Calculations were performed with a CDC 6400/6500 computer at the Federal Institute of Technology, Zürich. The exponential terms α and β and the corresponding half-lives were subsequently defined by these parameters (9). The total volume of distribution ($V_{D_{ss}}$) and total body clearance (Cl_B) were defined by the following equations: $V_{D_{ss}} = V_1 \times (1 + k_{12}/k_{21}$ and $Cl_B = V_1 \times k_e$. Renal clearance (Cl_R) was computed by two independent methods: (i) by using the definition of renal clearance, $Cl_{R_{ss}} = (c_U \times V_U)/c_{ss}$, where c_U is the urine concentration of a specimen collected between 120 and 195 min, V_U is the corresponding urine volume, and c_{ss} is the steady-state serum concentration during that time; and (ii) by using the model-dependent formula,

$Cl_R = Cl_B \times feU$, where feU is the excreted urinary fraction of the administered dose. All clearance values were corrected for body surface area. Statistical differences were calculated with the paired t test.

Because of inappropriate administration of the drug, the data of one volunteer obtained in the 2-g/h study had to be excluded from the above calculations.

RESULTS

Table 1 represents the mean peak concentrations of cefotaxime which were recorded after the infusion of loading doses of 0.5, 1, and 2 g over 15 min. In 5 of 18 instances the maximum concentration was recorded at 20 min rather than at the end of the loading infusion.

The sustaining infusions of 0.5 and 1 g/h produced mean steady-state serum concentrations of 27 and 64 μg/ml, respectively, between 60 and 195 min, whereas with the high dose (2 g/h) cefotaxime levels rose continuously until the end of the 3-h infusion (Table 1). Since no steady state was achieved with the 2-g/h dose, serum concentrations between 60 and 195 min were fitted to an exponential curve, and the value of 138 μg/ml thus represents an extrapolated value at 195 min. Figure 1 shows the serum concentration time curves of one volunteer during the low-, medium-, and high-dose studies. With increasing doses, serum concentrations increased more than expected by a dose-proportional assumption. This increase was significant for the low and medium doses and for the low and high doses (Table 1).

Upon termination of the infusion, the serum concentration time curves followed a biexponential decline, with mean terminal half-lives of 78, 71, and 78 min for the low, medium, and high doses, respectively. Since there was no correlation with the administered dose, it appears justified to calculate an average half life of 75 min for all doses (Table 2).

After the infusions were stopped, a very uniform decline in the serum concentrations was observed at every dose level and in all volunteers, which is in contrast to the pronounced interindividual variability of the serum levels noted during the first hour of administration. This phenomenon is shown in Fig. 2 for the 0.5-g/h dose. Instead of depicting the absolute concentrations, each serum level of each of the six volunteers was normalized to the corresponding mean steady-state concentration for that particular volunteer. Mathematically the normalized concentration $[c_n(t)]$ of the concentration $c(t)$ is defined as: $c_n(t) = c(t)/c_{ss}$, where c_{ss} is the mean steady-state concentration in that individual volunteer between 60 and 195 min.

The total volume of distribution (V_{Dss}) averaged 0.22 ± 0.03 liters/kg of body weight or 14.8 ± 1.8 liters per 1.73 m^2 (Table 2). Total body clearance of cefotaxime decreased significantly with increasing doses from 255 to 214 ml/min per 1.73 m^2 (for low dose-medium dose and low dose-high dose comparisons, $2P < 0.02$; the difference between medium-dose and high-dose values was not significant). A similar tendency, which barely missed statistical significance, was observed with renal cefotaxime clearance (Cl_R), which decreased from 166 to 134 ml/min per 1.73 m^2. The two independent methods which were used to calculate renal cefotaxime clearance (Cl_R and Cl_{Rss}) yielded virtually identical values for corresponding doses (Table 2).

An intraindividual comparison between creatinine clearance determined on the day of the study and renal cefotaxime clearance (Cl_R) revealed that the latter was consistently higher than the former during the infusions with 0.5 g/h, as analyzed by the paired t test ($2P < 0.05$), whereas for the medium and high doses the difference between the two clearance rates was not significant (Table 2).

The 24-h urinary excretion averaged 63 ± 9% of the administered dose. No significant differences were found among low, medium, and high doses. Almost three-quarters of the total amount excreted through the kidneys appeared in the urine during the infusion period (Table 2).

AAP excretion on the day before and the day after infusion and a determination several weeks after the last dose (with equally timed urine collection periods as on the study day) remained

TABLE 1. *Mean peak serum concentrations of cefotaxime after infusion of a loading dose and mean steady-state serum concentrations between 60 and 195 min*[a]

Loading dose (15 min) (g/h)	Peak serum concn (μg/ml)	Sustaining infusion (180 min) (g/h)	Steady-state serum concn (μg/ml)
2	41 ± 4 (35–45)[b]	0.5	27 ± 2 (25–29)
4	93 ± 17 (68–113)	1	64 ± 6 (52–69)
8	160 ± 23 (128–189)	2	138 ± 14[c]

[a] Values were compared by the paired t test. Differences in steady-state serum concentrations between the high and low doses and between the medium and low doses were significant at $2P < 0.001$ and $2P < 0.02$, respectively. The difference between the medium- and high-dose values was not significant.

[b] Mean ± standard deviation of the mean. Numbers in parentheses are ranges.

[c] Concentration at 195 min.

TABLE 2. *Pharmacokinetic parameters, clearance values, and cumulative urinary excretion of cefotaxime*

Dose	Terminal half-life (min)	$V_{D_{ss}}$ (liters/kg of body wt)	Cl_B (ml/min per 1.73 m^2)	Cl_R (ml/min per 1.73 m^2)	$Cl_{R_{ss}}$ (ml/min per 1.73 m^2)[a]	Cl_{Cr} (ml/min per 1.73 m^2)[b]	Cl_R/Cl_{Cr}	Cumulative urinary excretion (% of administered dose)		
								0–195 min	0–360 min	0–1,440 min
Low	78 ± 8	0.23 ± 0.03	255 ± 29	166 ± 30	160 ± 42	115 ± 17	1.50 ± 0.49	48 ± 12	63 ± 13	66 ± 13
	(68–88)	(0.18–0.27)	(218–293)	(137–210)	(105–136)	(85–136)	(1.01–2.24)	(35–66)	(50–85)	(52–88)
Medium	71 ± 4	0.22 ± 0.03	223 ± 28	134 ± 12	138 ± 43	124 ± 13	1.09 ± 0.13	46 ± 7	59 ± 7	60 ± 7
	(65–76)	(0.18–0.27)	(191–272)	(118–148)	(90–207)	(107–135)	(0.89–1.29)	(39–51)	(50–65)	(52–67)
High	78 ± 6	0.23 ± 0.02	214 ± 14	134 ± 7	134 ± 15	135 ± 33	1.03 ± 0.24	44 ± 8	60 ± 6	63 ± 7
	(72–88)	(0.21–0.25)	(200–235)	(127–145)	(120–157)	(98–173)	(0.77–1.32)	(30–50)	(50–70)	(54–73)
All	75 ± 7	0.22 ± 0.03	232 ± 30	145 ± 24	145 ± 36	124 ± 22	1.22 ± 0.37	46 ± 9	60 ± 9	63 ± 9
	(68–88)	(0.18–0.27)	(191–293)	(118–210)	(90–207)	(85–173)	(0.77–2.24)	(30–66)	(50–85)	(52–88)

[a] $Cl_{R_{ss}}$, Renal clearance during steady state (120 to 195 min).
[b] Creatinine clearance.

within the normal range of 1.7 to 13.0 mU/ml. However, during the infusion of cefotaxime, AAP excretion exhibited a striking increase which did not appear to be dose related. Immediately after the end of the infusion, AAP activity in the urine levelled off to values comparable to those of control periods; 48 ± 14% of the total daily AAP output was recovered during the infusion period (Fig. 3). All differences between the study day and the following day are significant at the 5% level.

After each infusion, participants were questioned for side effects. One volunteer experienced local pain at the site of infusion with the high dose, and another volunteer had one loose stool after each study. During the administration of cefotaxime, four volunteers noticed fatigue while in a recumbent position. After the high-dose infusions, four volunteers reported nocturnal perspiration the next morning. All side effects were judged to be minor by participants. No significant changes in hematology, serum chemistry, or urinalysis were recorded.

DISCUSSION

Serum concentrations of cefotaxime which were recorded after loading infusions of 0.5, 1, and 2 g over 15 min averaged 41, 93, and 160 μg/ml, respectively. A similar concentration of 103 ± 44 μg/ml was reported by Meyers et al. after a 1-g infusion of cefamandole over 15 min (17). Fong et al. (6) administered cefamandole in a steady-state infusion (0.5 g/h) and observed a nearly identical serum concentration, namely 28.5 μg/ml (compared with 27 μg/ml for cefotaxime recorded in our study). The fact that renal cefotaxime clearance exceeded creatinine clearance provides indirect evidence for the tubular secretion of this compound, an observation which has recently been confirmed by simultaneous administration of probenecid and cefotaxime (K. Bruch, Hoechst AG, personal communication).

With increasing doses, steady-state serum concentrations rose in a nonlinear fashion due to a decrease in total body clearance. This could possibly reflect a saturation of the tubular secretion which may become operative at the higher doses administered in this study. Total daily doses of 2 to 8 g of cefotaxime are indeed within the therapeutic range but in clinical practice are never given within 3 h as a steady-state infusion. Therefore, the practical relevance of these changes remains doubtful.

A comparison of the four β-lactamase-stable cephalosporins shows distinct similarities between cefamandole and cefoxitin on one side and cefuroxime and cefotaxime on the other side.

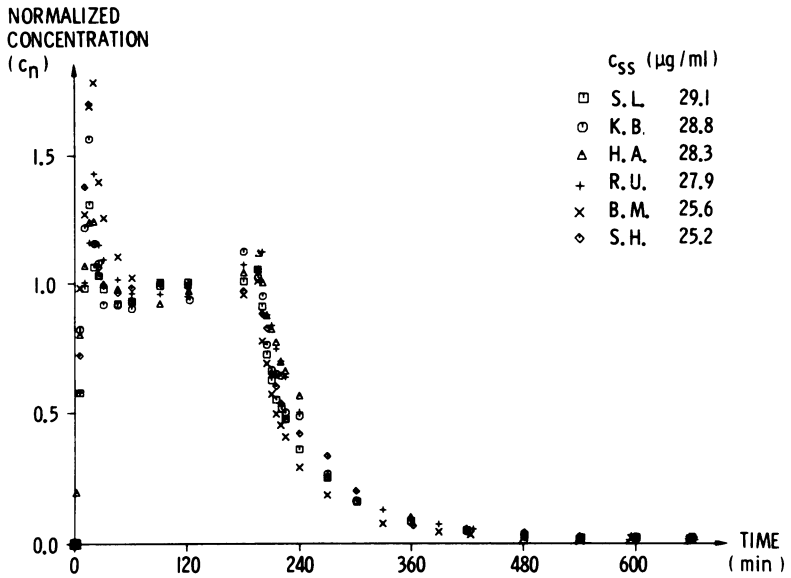

FIG. 2. *Normalized serum concentration time curves of six volunteers during and after the administration of cefotaxime (0.5-g loading dose, 0.5-g/h sustaining infusion). Normalized concentration* $c_n(t) = c(t)/c_{ss}$.

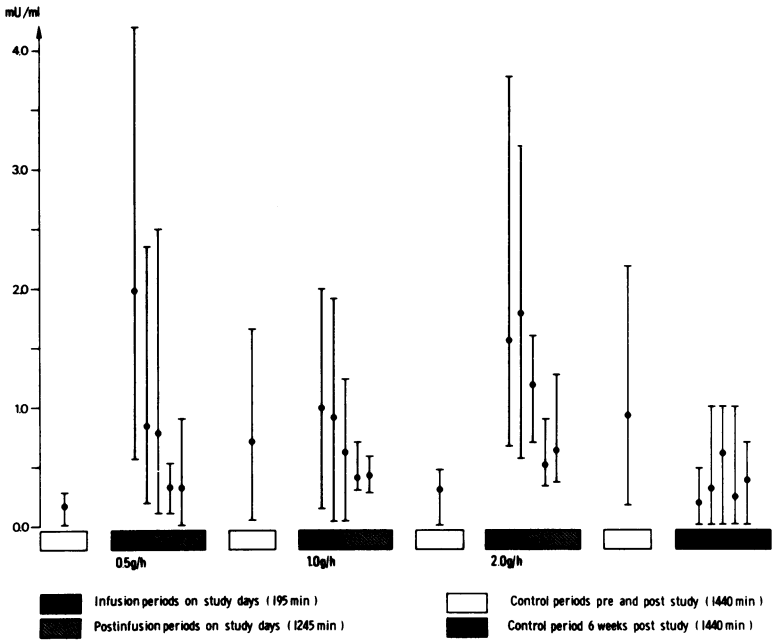

FIG. 3. *Urinary AAP excretion of six volunteers before, during, and after the administration of three different doses of cefotaxime. Mean values and range of AAP activity per milliliter of urine.*

Because of a higher tubular secretion, the renal clearance of cefamandole and cefoxitin exceeds the values reported for cefuroxime and cefotaxime, which are only slightly higher than creatinine clearance (Table 3). Nevertheless, approximately 40% of cefuroxime is eliminated by tubular secretion (7) (cefotaxime quantitative data are not yet available).

TABLE 3. *Synopsis of pharmacokinetic parameters of cefamandole, cefoxitin, cefuroxime, and cefotaxime*

Compound	Terminal half-life (min)	Urinary fraction excreted (% of administered dose)	Cl_R (ml/min per 1.73 m^2)	Total vol of distribution (liters/1.73 m^2)	Protein binding (%)	References
Cefamandole	34–54	80–100	257–264	13–19	67–74	1, 2, 6, 17, 23
Cefoxitin	42–52	90–99	280–300	14–19	25–75	1, 14, 15, 27
Cefuroxime	64–70	89–103	139–148	12–13	20–33	7,10, 22, 26
Cefotaxime	71–78	60–66	134–166	13–17	~40[a]	

[a] Personal communication from K. Bruch, Hoechst AG.

In contrast to cefamandole, cefoxitin, and cefuroxime, cefotaxime undergoes a deacetylation in vivo similar to that of cephalothin (13), which accounts for the major differences in the excreted urinary fraction of cefotaxime (Table 3). In addition to the different degree of protein binding, this metabolism could also explain why identical doses of cefamandole and cefotaxime produce very similar serum concentrations, despite the fact that renal clearance of cefamandole is approximately 1.8 times higher.

Mondorf et al. have recently shown that the administration of various aminoglycosides and cephalosporins to human volunteers and patients is reproducibly associated with an increased urinary AAP output (19, 21). This is apparently due to increased shedding of the brush border membranes of the proximal tubules of the kidney.

Our observations of a significant increase in AAP excretion during the administration of cefotaxime may indicate transient tubular damage (Fig. 3). Its clinical significance cannot be assessed by our single-dose studies. In an animal study, Sack et al. compared the tubulotoxic effects of cefotaxime and cefoxitin by means of cellular excretion, urinary enzymes, and histopathology. They concluded that the former was even better tolerated than the latter (24).

Systemic side effects of cefotaxime were dose related. Considering the fact that 2 to 8 g (equivalent to the total daily doses recommended for clinical use) were administered over a short period of time, the observed side effects may be viewed as minor and, with the possible exception of nocturnal perspiration (after high doses), considered to be nonspecific.

We draw the following practical conclusion from our study. Bolus infusions of 1 or 2 g of cefotaxime over 15 min, which are well tolerated, produce therapeutically useful serum concentrations over a time period of 4 to 6 h. Because of the short half-life of 75 min, the dosage interval should probably not exceed 6 h until more experience is accumulated from the ongoing clinical efficacy trials.

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