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Clinical Pharmacology of Cefamandole as Compared with Cephalothin

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We compared the pharmacology of cefamandole and cephalothin in six healthy adult male volunteers. After a 1-g, 20-min intravenous (i.v.) infusion, the average peak blood level of cefamandole was 87.6 versus 64.1 μg/ml for cephalothin. An i.v. infusion of 500 mg/h for 2 h (after a loading dose of 750 mg) gave an average steady-state blood level of 28.5 μg/ml for cefamandole and 18.2 μg/ml for cephalothin. Mean peak serum levels after 1 g intramuscularly were similar for the two antibiotics (about 21 μg/ml), but with cefamandole they persisted longer, and the area under the blood level curve was about 25% greater. The average $t_{\frac{1}{2}}$ as determined from both i.v. studies was 34 min for cefamandole versus 30 min for cephalothin. The mean serum clearance for cephalothin, due to its partial conversion to a metabolite, was much greater than for cefamandole (425 versus 272 ml/min per 1.73 m^2), but the renal clearances were similar for the two antibiotics (268 versus 257 ml/min per 1.73 m^2). Other values for cefamandole and cephalothin were: 24-h urinary excretion, 80 and 66%; serum protein binding, 74 and 70%; and apparent volume of distribution, 12.8 and 18.5 liters/1.73 m^2, respectively. Thus, the pharmacology of the two antibiotics was similar. Blood levels were somewhat higher with cefamandole i.v., but the results suggest that dosage regimens should be the same for the two antibiotics.

Cefamandole is a new cephalosporin antibiotic available in parenteral form as cefamandole nafate. It has been shown in vitro to be active against some *Enterobacter* and indole-positive *Proteus* strains, which are not usually susceptible to other cephalosporins, and to be more active against most susceptible *Enterobacteriaceae* and *Haemophilus* species (3, 7). The purpose of this study was to define the pharmacokinetics of cefamandole in comparison with cephalothin after intravenous (i.v.) and intramuscular (i.m.) administration in healthy adult volunteers.

MATERIALS AND METHODS

Antibiotics. One-gram ampoules for injection and standard laboratory powders were supplied as cefamandole nafate and cefamandole lithium, respectively, and as sodium cephalothin by Eli Lilly and Co.

Single i.v. injections. Six healthy adult male volunteers received 20-min i.v. infusions of 1 g of cefamandole diluted in 40 ml of 5% dextrose in water with a constant-infusion pump (Multi-Speed Transmission, Harvard Apparatus Co.). This experiment was repeated in the same volunteers with cephalothin, separated by an interval of 1 week. Specimens of blood were drawn from the other arm at 20 min (as soon as the infusion was stopped), 25, 30, 35, 46, and 60 min, and then at 30-min intervals for 3 h and hourly for another 2 h. Urine was collected from 0 to 2, 2 to 4, 4 to 6, and 6 to 24 h. Appropriate informed consent was obtained from the volunteers, whose ages ranged from 21 to 33 years (average 27.7) and who weighed from 68.25 to 81 kg (average 74.13).

Single i.m. injections. One-gram doses of cefamandole and cephalothin were injected intragluteally in six volunteers. Blood samples were collected at 30, 45, 60, and 75 min to define the peak blood level and then half-hourly up to 6 h. Urine was collected at 0 to 2, 2 to 6, and 6 to 24 h. The duration and severity of pain on injection were assessed and charted by the volunteers, who did not know which antibiotic they were receiving. The categories were entirely subjective, without any attempt to define them.

Steady-state study. Four volunteers received i.v. infusions of cefamandole and cephalothin on different days, given in 50 ml of 5% dextrose in water hourly for 3 h with the constant-infusion pump. A loading dose of 750 mg was given during the 1st h, followed by 500 mg hourly for the next 2 h. Six specimens of blood were drawn between 1 and 3 h to document the steady state, then after stopping the infusion, every 15 min for 1 h, and half-hourly for 3 h. Urine was collected at 0 to 2, 2 to 3, and 6 to 24 h.

Administration, collection of specimens, and antibiotic assay. The volunteers were admitted to the University Hospital Clinical Research Center after an overnight fast and were given a clear liquid

diet during the first 4 h of the study. Pediatric scalp vein needles (Butterfly-21, Abbott Laboratories) were inserted into a forearm vein in each arm, one for the administration of antibiotic and the other for collection of blood for assay.

Once blood samples had clotted, they were centrifuged at 4,000 rpm for 20 min, and the serum was stored at −20 C. Serum standards were prepared on the same day and were assayed along with the unknown samples within a few days. Urine samples were diluted with 0.15 M phosphate buffer (pH 7.35) to an approximate concentration of 35 μg/ml and assayed in the same manner as the serum samples, using phosphate buffer solution containing known amounts of antibiotic to prepare the standard curve.

Concentrations of antibiotics were determined by the agar well diffusion method of Bennett et al. (1), using *Bacillus subtilis* as the indicator organism. Each sample was assayed in quintuplicate. Protein binding was determined by an ultrafiltration method using 100% pooled human serum adjusted to physiological temperature and pH, with an antibiotic concentration of 25 μg/ml (2).

Pharmacokinetic calculations. Computer analysis of serum antibiotic concentration-time plots performed by the Fortran program (Datanol), which uses a modified Marquardt, Gauss-Newton, nonlinear, least-squares regression analysis (6), was found to fit a one-compartment open model better than a two-compartment open model. The serum half-life was calculated when the blood levels were declining exponentially during the elimination phase, using concentrations beginning 30 to 45 min after the 20-min infusion, 15 min after the 3-h infusion, and 1.75 h after the i.m. injections. For the half-life the formula used was $t_{\frac{1}{2}} = (\ln 2)/K_e$, where ln 2 is the natural logarithm of 2 and K_e is the slope of the regression line determined by the method of least squares (4).

Renal clearances were determined during the elimination phase after single i.m. injections and the 20-min infusion and during the 3rd h of the steady-state study, using the formula (4)

$$C_r = \frac{U \times V}{C} \times \frac{1.73}{\text{BSA}}$$

where U is the antibiotic concentration in the urine (in micrograms per milliliter), V is the timed urine volume (in milliliters per minute), C is the antibiotic concentration in the serum (in micrograms per milliliter), and BSA is the body surface area.

The serum clearance was calculated from the steady-state data with the formula (4)

$$C_s = \frac{i}{C_0} \times \frac{1.73}{\text{BSA}}$$

where i is the infusion rate (in micrograms per minute) and C_0 is the average steady-state blood level (in micrograms per milliliter). The apparent volume of distribution (AVD) was also calculated from the steady-state data, using the formula (4)

$$\text{AVD} = \frac{i}{C_0 \times K_e \times 1{,}000} \times \frac{1.73}{\text{BSA}}$$

The area under the blood level curve was calculated by computer, using the trapezoidal rule.

Toxicity studies. Blood was collected just before and 1 week after each study for urea nitrogen, serum creatinine, electrolytes, calcium, phosphorous, bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, glucose, serum proteins, hemoglobin, leukocyte count, and differential. These tests were performed by the clinical hematology and chemistry laboratories of University Hospital. No abnormal values were obtained.

RESULTS

Single i.v. and i.m. injections. Average serum concentrations of cefamandole and cephalothin after 1-g i.v. infusions over 20 min in six volunteers are shown in Fig. 1. Peak serum levels (87.6 versus 64.1 μg/ml) were greater for cefamandole, as were levels at all other time intervals. By 2.5 h cefamandole levels had fallen to 3 μg/ml and cephalothin to less than 1 μg/ml. After 1-g i.m. injections, the peak blood levels occurred at 0.5 to 1.25 h and averaged 21.3 μg/ml (range 15 to 24) for cefamandole and 21.6 μg/ml (range 14.5 to 30) for cephalothin. When the concentrations at each time interval were averaged, the peaks were very similar and occurred at 30 and 45 min for cephalothin and cefamandole, respectively (Fig. 2). Beginning at 45 min the cefamandole blood levels were consistently higher, and the area

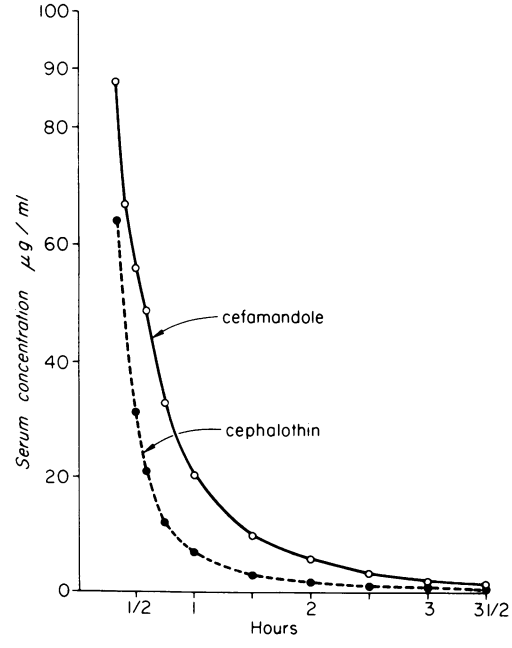

FIG. 1. *Average serum antibiotic concentrations in six volunteers beginning immediately after 1-g i.v. infusions given in 20 min.*

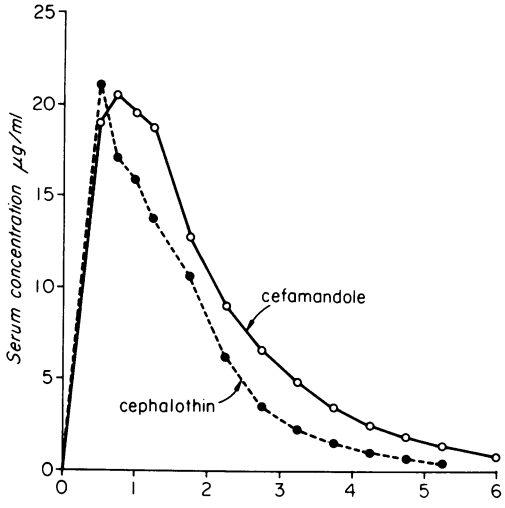

FIG. 2. *Average blood levels for six volunteers after 1-g i.m. injections showing consistently higher levels for cefamandole beginning at 45 min, and an area under the curve about 25% greater than for cephalothin.*

under the blood level curves was significantly greater (about 25%) for cefamandole than for cephalothin (41.1 and 29.1 μg·h/ml.) The comparative severity and duration of pain with i.m. injections as recorded by the volunteers appeared to be about the same for the two antibiotics (Table 1).

Steady-state study. With a continuous i.v. infusion of 750 mg, average serum concentrations of 35.2 μg/ml for cefamandole and 28.3 μ/ml for cephalothin were present at the end of 1 h (Fig. 3). Steady-state blood levels of 28.5 and 18.2 μg/ml for cefamandole and cephalothin were then attained with a sustaining dose of 500 mg/h for the next 2 h.

Serum half-life. The half-life of cefamandole calculated from the i.v. studies (Table 2) was very similar to that of cephalothin (34 ± 2 versus 30 ± 3 min). There was a significant increase in half-life of both drugs after i.m. injections, to 59 ± 6 and 42 ± 5 min for cefamandole and cephalothin, respectively, and this occurred whether the half-life was calculated from blood levels starting at 1.75 h or 2.5 h after i.m. injections. The coefficients of correlation of the regression lines, plotted on a semilogarithmic scale, with a straight line were ≥ 0.98.

Serum and renal clearance and urinary excretion. The renal clearances for the two antibiotics were very similar, but the serum clearance of cephalothin was more than 1.5 times greater than for cefamandole (425 versus 272 ml/min per 1.73 m²) (Table 2). Rapid urinary excretion of cefamandole occurred after the i.v. injection of 1 g over 20 min, 66% being recovered in 2 h and 75% by 6 h, as compared with 68% for cephalothin (Fig. 4). After i.m. injections, only 45% was recovered in the 2-h urine sample due to the depot effect, but by 6 h 70% of the dose was excreted, as compared with 55% for cephalothin. The average excretion in 24 h for all the studies is given in Table 2. The apparent volume of distribution was appreciably smaller for cefamandole than for cephalothin (18.5 versus 12.8 liters).

Protein binding. The protein binding of the two antibiotics measured in 100% serum under simulated physiological conditions was very similar, 74% for cefamandole and 70% for cephalothin.

DISCUSSION

These results suggest that the pharmacological characteristics of cefamandole are similar to those that might be observed with cephalothin if it was not partially converted to a less active metabolic breakdown product, desacetylcephalothin. Since the serum protein binding and renal clearance are similar for the two antibiotics, the lower blood levels, smaller area under the blood level curve, greater serum clearance, slightly shorter serum half-life, and lower percentage recovered in the urine for cephalothin (see Table 2) could all be accounted for on this basis. The larger apparent volume of distribution of cephalothin may be an artifect due to the same phenomenon; its calculation is dependent on the serum concentration, which is appreciably lower for cephalothin as measured by bioassay since it consists in part of the less active metabolite. We have not performed chromatographic studies to measure the total amounts of cephalothin plus the metabolite to determine whether the actual volume of distri-

TABLE 1. *Pain on intramuscular injection of cefamandole and cephalothin*

Volunteers	Cefamandole		Cephalothin	
	Severity of pain	Duration (min)	Severity of pain	Duration (min)
1	Moderate	50	Mild	30
2	Moderate	5	Moderate	10
3	Mild	15	Moderate	5
4	Severe	40	Moderate	10
5	Moderate-Severe	20	Mild-Moderate	15
6	Mild	30	Moderate	40

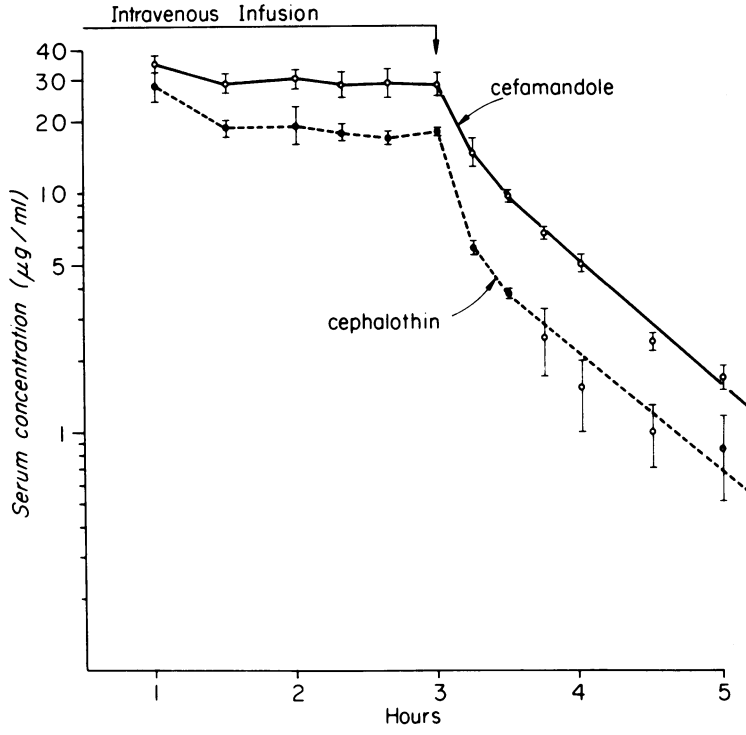

FIG. 3. *Three-hour constant i.v. infusion giving average blood levels about a third higher for cefamandole at the steady state (28.5 versus 18.2 μg/ml) and similar regression lines during the elimination phase.*

TABLE 2. *Pharmacokinetic data for cefamandole and cephalothin*

Determination	Cefamandole	Cephalothin
Serum half-life (min)		
After i.v. infusions	34 ± 2[a]	30 ± 3
After i.m. injections	59 ± 6	42 ± 5
Serum clearance (ml/min per 1.73 m²)	272 ± 17	425 ± 44
Renal clearance (ml/min per 1.73 m²)	257 ± 27	268 ± 65
Creatinine clearance (ml/min per 1.73 m²)	121 ± 14	118 ± 8
Renal excretion (% of dose in 24 h; avg of all studies)	80 ± 8	66 ± 9
Protein binding (%)	74	70
Apparent volume of distribution (liters/1.73 m²)	12.8 ± 1.2	18.5 ± 0.8
Area under the serum level curve (μg·h/ml)		
After i.v. infusion	45.8 ± 4.7	19.6 ± 4
After i.m. injection	41.1 ± 2.8	29.1 ± 4

[a] Standard deviation.

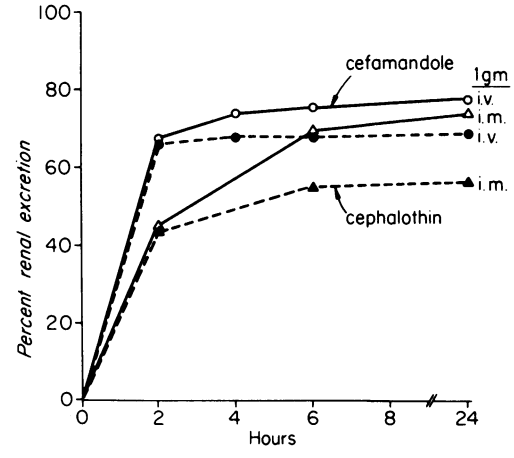

FIG. 4. *Average urinary excretion (cumulative percentage of dose administered) showing the delayed excretion with the i.m. route and the lower recovery of cephalothin, which is partially converted to a less active metabolite.*

bution is different for cephalothin than cefamandole.

The considerably longer serum half-life after i.m. than after i.v. injection despite straight regression lines, especially with cefamandole (Table 1), almost surely represents steady, prolonged absorption from muscle tissues. This depot effect has been observed by others. Kunin and Atuk (5) obtained a serum half-life of 51

min with cephalothin i.m., and Regamey et al. (8) observed a prolonged half-life for cephalexin with i.m. as compared with i.v. administration. Interestingly, the two antibiotics seemed to cause an equal amount of discomfort when the six volunteers recorded their impressions after each i.m. injection without knowing in which order the drugs were given (Table 1).

Thus, cefamandole has basically the same clinical pharmacology as cephalothin, but with higher blood and urine concentrations and a larger area under the blood level curve. Whether these differences will be translated into demonstrably greater therapeutic efficacy can be determined only by clinical trials, but these characteristics, together with the enhanced and broadened activity against certain gram-negative pathogens, suggest that cefamandole may be a superior cephalosporin.

ACKNOWLEDGMENT

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