Pharmacokinetics of Cefamandole in the Presence of Renal Failure and in Patients Undergoing Hemodialysis

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The pharmacology of cefamandole in seven patients with stable renal insufficiency and in eight patients undergoing hemodialysis was determined. All patients had creatinine clearances less than 5 ml/min. The half-life of cefamandole in those patients with stable chronic renal failure was 7.7 ± 2.2 h. The mean venous level 1 h after intravenous injection of a 1-g dose was 85.3 ± 32.0 μ g/ml. The mean venous half-life of cefamandole during hemodialysis was 6.1 h. The venous serum level after 5.5 h of hemodialysis was 50.4 ± 20.8 μ g/ml. The mean coefficient of extraction was 0.155, and the mean clearance was 34.7 ml/min. The time interval between doses of cefamandole administered intravenously should be lengthened to 24 h in the presence of stable renal failure. No major change in dosage schedule is necessary for patients undergoing dialysis.

Cefamandole, 7-D-mandelamido-3-[(1-methyl-1H-tetrazol-5-yl)thio]methyl-3-cephem-4-carboxylic acid, is a new semisynthetic cephalosporin antibiotic with a broad spectrum of activity against most gram-positive and gram-negative bacteria (1, 6). It has greater in vitro activity than other commercially available cephalosporins against most strains of *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Haemophilus*, *Serratia*, and *Proteus* species (6). Preliminary data suggest that cefamandole is useful in the treatment of septicemia and serious infections of the respiratory tract, urinary tract, or soft tissues due to susceptible microorganisms (8; unpublished observations). Such infections occur frequently in patients with renal insufficiency, and many of these patients are managed by extracorporeal dialysis. Therefore, we wished to establish the pharmacokinetics of cefamandole in patients with severe renal impairment and in patients undergoing hemodialysis.

MATERIALS AND METHODS

Subjects for study included eight patients with stable chronic renal failure and creatinine clearance of 5 ml/min or less. The mean age was 44 years (range, 20 to 62 years). There were four male and four female patients. None of these patients were dehydrated or receiving other antibiotics at the time of the study. Each patient received 1 g of cefamandole nafate by intravenous (i.v.) infusion over a 5-min period. Venous blood samples were obtained at 1-, 2-, 4-, 6-, and 18-h intervals in most instances. No patient underwent dialysis during the interval of plasma sampling. Seven additional patients with stable chronic renal

failure and creatinine clearance of less than 5 ml/min were studied during dialysis. The mean age was 48 years (range, 22 to 74 years). There were four male and three female patients. Each patient was maintained on thrice weekly chronic hemodialysis. Dialyses were performed using a twin-coil Travenol RSP dialyzer with an Ultra Flow II cuprophane membrane and lasted 5.5 h per session. Dialysate flow rates were constant at 600 ml/min and blood flow rates were maintained at 200 to 250 ml/min. At the beginning of dialysis each patient received 1 g of cefamandole nafate by i.v. injection over 5 min. Specimens of arterial and venous blood and dialysate were obtained at 15 min, at 1 h, 2 h, 3 h, and 4 h, and at the termination of dialysis.

Written, informed consent was obtained from all subjects prior to their participation in the study.

Blood samples were centrifuged 30 to 45 min after collection, and the serum was separated and stored at -20°C until assayed. Serum levels of cefamandole were determined using an agar well plate technique with *Bacillus subtilis* as the assay organism. Standards of cefamandole as a lithium salt were prepared with pooled human serum, and plasma samples were diluted in pooled human serum. Assays were run in quadruplicate using a Latin-square randomization technique.

Plots of the serum concentration of cefamandole versus time were constructed, and the half-life of the antibiotic was determined when the blood levels were declining exponentially during the elimination phase. The formula used for the half-life was $T_{1/2} = (\ln 2/K_e)$, where $\ln 2$ is the natural logarithm of 2 and K_e is the slope of the regression line determined by method of least squares. The coefficients of extraction for cefamandole during hemodialysis were computed according to the formula:

$$E_c = (D_i - D_o)/D_i$$

where D_i is the concentration of cefamandole in arterial serum and D_o is the concentration of cefamandole in serum leaving the coil. Clearance during dialysis was calculated according to the formula:

$$C_d = Q_b(D_i - D_o)/D_k$$

where Q_b is the blood flow rate through the dialysis coil. Coefficients of extraction and clearances were calculated for each patient sample.

RESULTS

The peak serum levels and $T_{1/2}$ in the seven patients with chronic renal failure are given in Table 1. Venous serum levels at 1 h ranged from 45 to 150 $\mu\text{g/ml}$, with a mean of $85.3 \pm 32 \mu\text{g/ml}$. The correlation of the height of serum level with mean body surface area was fair for most patients.

The mean concentrations of cefamandole in arterial serum, venous serum, and dialysate for the eight hemodialyzed patients are listed in Table 2. Serum arterial and venous levels when plotted versus time on dialysis describe similar

curves (Fig. 1). The mean half-life for arterial plasma was 5.9 h and for venous plasma 6.1 h. Mean arterial and venous serum levels at 1 h were 108.3 ± 32.0 and $94.4 \pm 31.9 \mu\text{g/ml}$, respectively. At termination of dialysis mean arterial and venous levels were 61.4 ± 23.3 and $50.4 \pm 120.8 \mu\text{g/ml}$, respectively. The mean coefficients of extraction and the mean clearance of cefamandole at 1, 2, 3, and 4 h are listed in Table 2. Based on the dialysate levels, there was $143.3 \pm 58.9 \text{ mg}$ of cefamandole recovered during the 5.5-h hemodialysis periods.

DISCUSSION

The pharmacokinetics of cefamandole in individuals with normal renal function are similar to those of cephalothin in normal individuals (5). The $T_{1/2}$ of cefamandole is 27 to 34 min, whereas the $T_{1/2}$'s for the other cephalosporins are: cephalothin, 30 to 50 min; cephaloridine, 66 to 90 min; cefazolin, 96 to 120 min; and cephalexin, 36 to 54 min (2, 4). Cefamandole is predominantly excreted by renal mechanisms. The

TABLE 1. Data from dialysis and uremic studies

Study	Patient	Age (yr)	Sex	Wt (kg)	Ht (cm)	Surface area (m^2)	Diagnosis*	Peak serum level ($\mu\text{g/ml}$)	$T_{1/2}$ (h)
Dialysis	R.G.	48	F	43.8	165	1.42	Sarcoid-CRF	243	8.6
	M.S.	56	F	62.3	175	1.76	DM	105	4.7
	E.G.	74	M	62.8	168	1.73	CGN	270	5.2
	A.V.	46	M	66.0	188	1.89	CPN	103	9.0
	E.B.	64	F	72.8	160	1.77	DM	79	3.9
	O.E.	44	M	62.0	165	1.70	CGN	145	4.6
	J.P.	32	M	70.6	163	1.78	CGN	150	5.2
	J.C.	22	F	52.9	163	1.56	DM	124	3.7
Uremic	J.P.	32	M	60	163	1.66	CGN	120	5.5
	B.Mc	29	M	61	175	1.74	HRD	63	9.7
	M.D.	56	F	38.6	152	1.37	HRD	117	8.5
	B.R.	61	F	73.8	165	1.80	DM	70	5.0
	F.S.	46	M	89.0	180	2.10	DM	47	11.0
	M.C.	62	F	39.0	152	1.32	CPN	175	9.0
	M.W.	20	F	55.0	160	1.55	HRD	95	5.5

* Abbreviations: CRF, Chronic renal failure; DM, diabetes mellitus; CGN, chronic glomerulonephritis; CPN, chronic pyelonephritis; HRN, hypertensive renal disease.

TABLE 2. Mean concentrations of cefamandole in arterial serum, venous serum, and dialysate, mean coefficients of extraction, and mean clearance after i.v. injection of 1.0 g

Min after $\bar{p}$ injection	Arterial plasma ($\mu\text{g/ml}$)	Venous plasma ($\mu\text{g/ml}$)	Dialysate ($\mu\text{g/ml}$)	Coefficients of extraction	Clearance
60	108.3 ± 32.0	94.4 ± 31.9	1.99 ± 1.40	$0.140 \pm .089$	31.4 ± 20.0
120	95.9 ± 24.7	79.6 ± 28.8	1.11 ± 0.92	$0.187 \pm .109$	42.0 ± 24.5
180	82.5 ± 28.7	70.4 ± 20.8	1.47 ± 0.92	$0.127 \pm .103$	28.6 ± 22.9
240	75.4 ± 24.4	62.7 ± 26.3	0.70 ± 0.14	$0.165 \pm .172$	37.0 ± 38.8
330	61.4 ± 23.3	50.4 ± 20.8	0.70 ± 0.40

FIG. 1. Mean arterial plasma levels of cefamandole in the seven patients during dialysis.

half-life of cefamandole is prolonged to 7.7 ± 2.2 h in patients with severe stable chronic renal failure. The $T_{1/2}$'s of the other cephalosporins in uremia are: cephalothin, 12 to 18 h; cephaloridine, 20 to 25 h; cefazolin, 35 to 56 h; and cephalexin, 14 to 20 h (5, 7). Hemodialysis with a Travenol RSP machine and a UF II coil reduces the half-life of cefamandole to approximately 6.0 h. Although the half-life is only moderately decreased, the antibiotic is removed, as demonstrated by the clearances (range, 28.6 to 42 ml/min) and by the amount of drug removed, based on dialysate levels (143.3 ± 58.9 mg, 14.3%). Nevertheless, serum levels at the end of 5.5 h of hemodialysis are still sufficiently high (mean venous serum level, 50.4 ± 20.8 µg/ml) to inhibit most strains of susceptible microorganisms if the cefamandole has been given by i.v. injection.

The serum levels after i.v. administration in the patients with $C_{cr} < 5$ ml/min are comparable to those achieved in normal volunteers (3). There appears to be a fair correlation of the

height of the serum level with body surface area.

From these data, certain recommendations regarding the dosage of cefamandole in patients with renal dysfunction may be made. If a 1-g dose is given i.v. to a patient with normal renal function (every 4 h), this time interval should be extended in the face of severe renal failure. If a standard dose were given every three half-lives, the drug would be administered at 1 g every 23 h. For convenience of administration, this dose could be given every 24 h. If the patient is undergoing extracorporeal dialysis, a similar schedule is reasonable. An additional dose of cefamandole is not needed after hemodialysis if the patient has received a dose of the drug just prior to the institution of dialysis. These recommendations apply only to an i.v. administered drug, since the blood levels after intramuscular administration are considerably lower.

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LITERATURE CITED

1. Eykyn, S., C. Jenkins, A. King, and I. Phillips. 1973. Antibacterial activity of cefamandole, a new cephalosporin antibiotic, compared with that of cephaloridine, cephalothin, and cephalexin. *Antimicrob. Agents Chemother.* 3:657-661.
2. Fong, I. W., E. D. Ralph, E. R. Engelking, and W. M. Kirby. 1976. Clinical pharmacology of cefamandole as compared with cephalothin. *Antimicrob. Agents Chemother.* 9:65-69.
3. Meyers, B. R., R. Ribner, S. Yancovitz, and S. Z. Hirschman. 1976. Pharmacological studies with cefamandole in human volunteers. *Antimicrob. Agents Chemother.* 9:140-144.
4. Moellering, R. C., and M. N. Swartz. 1976. The newer cephalosporins. *N. Engl. J. Med.* 294:24-28.
5. Neu, H. C. 1973. Guidelines to antibiotic therapy in renal failure. *Med. Times* 11:47-53.
6. Neu, H. C. 1974. Cefamandole, a cephalosporin antibiotic with an unusually wide spectrum of activity. *Antimicrob. Agents Chemother.* 6:177-182.
7. Nightingale, C. H., D. S. Greene, and R. Quintiliani. 1975. Pharmacokinetics and clinical use of cephalosporin antibiotics. *J. Pharm. Sci.* 64:1899-1927.
8. Shemonsky, N. K., J. Carrizosa, and M. E. Levison. 1975. In vitro activity and pharmacokinetics in patients of cefamandole, a new cephalosporin antibiotic. *Antimicrob. Agents Chemother.* 8:679-693.