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Moxalactam Pharmacokinetics During Hemodialysis

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To establish dosage recommendations, moxalactam elimination kinetics were studied in six anephric patients during hemodialysis and in four anephric patients during the interdialytic period. After a single 1-g intravenous bolus injection, moxalactam elimination half-life was 18.0 ± 0.6 h with a volume of distribution of 20.2 ± 3.6 liters and a plasma clearance of 12.8 ± 2.0 ml/min in four nondialyzed patients. Moxalactam elimination half-life was decreased to 2.7 ± 0.2 h during hemodialysis in six patients. After 4 h, 48.5% of the dose was recovered in the dialysate. The maintenance dose of moxalactam should be decreased to 15% of a normal dose in patients with creatinine clearances less than 10 ml/min, and 50% of a loading dose should be given after hemodialysis.

Moxalactam is a new semisynthetic beta-lactam antibiotic which is active in vitro against clinically important gram-negative, gram-positive, and anaerobic bacteria. Specifically, it is known to inhibit the growth of most strains of *Enterobacteriaceae*, *Bacteroides*, *Clostridium*, and *Peptococcaceae* (1,5). Moxalactam's wide antimicrobial spectrum makes it a potentially useful agent in patients with renal failure. This study was performed to establish moxalactam pharmacokinetics in patients with renal failure and to determine the effect of hemodialysis on the elimination kinetics of the drug.

MATERIALS AND METHODS

Subjects. Ten adult anephric subjects were studied. Six subjects were studied during hemodialysis, and four subjects were studied during a 48-h interdialytic period. Demographic data are shown in Table 1. Subjects were excluded if they had a history of penicillin allergy, concomitant antimicrobial therapy, or major disorders of the hepatic, cardiovascular, or hematopoetic systems.

Drug. Moxalactam, 1 g, was diluted in 20 ml of 5% dextrose in water and injected into a forearm vein over 2 to 4 min.

Dialysis procedure. Hemodialysis was performed on six chronic, stable hemodialysis patients with a single-pass system (Centry 2, Cobe Laboratories, Inc.) using a 1.3-m^2 Cuprophan membrane capillary flow dialyzer (CF-1200, Travenol Laboratories, Inc.). Blood flow measured by bubble transit time was 300 ml/min, and the dialysate flow rate was 600 ml/min. The entire volume of dialysate was collected and assayed for moxalactam activity.

Samples and assay. Venous blood samples were obtained at 0.08, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36.0, and 48.0 h after moxalactam injection from four anephric patients during a 48-h interdialytic period. Thirty minutes after the initiation of dialysis, moxalactam was given to six stable chronic hemodialysis patients. Arterial blood samples entering the dialyzer were obtained at 0.08, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0 and 4.0 h after drug injection.

Plasma was separated from blood cells by refrigerated centrifugation within 1 h of collection. Plasma and dialysate were assayed immediately for moxalactam activity microbiologically by a modification of an agar well diffusion method with *Escherichia coli* ATCC 4157 as the reference organism (2). A moxalactam standard solution was prepared by diluting moxalactam of certified potency in antibiotic-free pooled human plasma for plasma samples or pH 7 phosphate buffer for dialysate samples to final concentrations of 20, 10, 5, 2.5, 1.25 and 0.625 mg/liter. Plasma samples to be analyzed were diluted with pooled human plasma until concentrations were within the standard curve. Dialysate samples did not require dilution. The standard curve was determined by a curve-fitting program on a Hewlett-Packard 97 calculator by the method of least-squares minimization. A standard curve was prepared each time samples were assayed, and all assays were performed in triplicate. The coefficient of variation for the assay was 6%.

Kinetic analysis. Data were examined by model independent methods. Plasma clearance (Cl_P) was determined from the following relationship: Cl_P = dose/AUC_0^∞ where AUC_0^∞ is the area under the semilogarithmic plasma concentration-time curve determined by the trapezoidal rule with a tail correction (8).

Dialyzer clearance (Cl_D) was determined from the following relationship: Cl_D = amount recovered/AUC_0^T where AUC_0^T is the area under the semilogarithmic plasma concentration-time curve during hemodialysis (3,6).

The volume of distribution [$Vd_{(area)}$] was calculated from the equation: $Vd_{(area)}$ = dose/$\beta(AUC_0^\infty)$, where β is the slope of the terminal elimination phase of the plasma concentration-time curve determined by a least-squares linear regression of the last five points of the curve (4). Terminal elimination half-life, $t_{1/2}$, is given by the following expression: $t_{1/2\beta} = 0.692/\beta$.

RESULTS

Mean plasma concentrations for four patients studied during the interdialytic period are shown in Fig. 1, and those for six patients studied during hemodialysis are shown in Fig. 2. Relevant kinetic data are shown in Tables 2 and 3.

Moxalactam elimination half-life was decreased from 18.0 ± 0.6 h in the four patients studied during their interdialytic period to 2.7 ± 0.2 h in six patients studied during hemodialysis. Dialyzer clearance was 43.6 ± 4.2 ml/min, and 48.5% of the administered dose was recovered in the dialysate after 4 h of hemodialysis.

DISCUSSION

Moxalactam elimination is prolonged in patients with renal failure. A serum elimination half-life of 2.3 h with serum and renal clearances of 85.4 and 54.5 ml/min, respectively, have been reported in four men with normal renal function (7). Elimination half-life in four anephric patients in the present study was increased to 18 h. Plasma clearance was decreased to 12.8 ± 2 ml/min. From the relationship $D_{(anephric)} = [Cl_{P(anephric)}/Cl_{P(normal)}] \times D_{(normal)}$, where D is the dose, the maintenance dose of moxalactam appropriate for patients with creatinine clearances less than 10 ml/min should be approximately 15% of the normal dose. Because about half of the moxalactam in the body is removed during a 4 h hemodialysis, 50% of a loading dose should be given after each dialysis.

TABLE 1. *Demographic data*

Subject	Age (yr)	Wt (kg)
1	61	60.5
2	58	95.0
3	57	81.8
4	63	65.0
5	57	65.0
6	46	64.5
7	58	95.0
8	53	77.5
9	65	61.3
10	53	79.1
Mean ± SEM[a]	57 ± 2	74.5 ± 4.2

[a] SEM, Standard error of the mean.

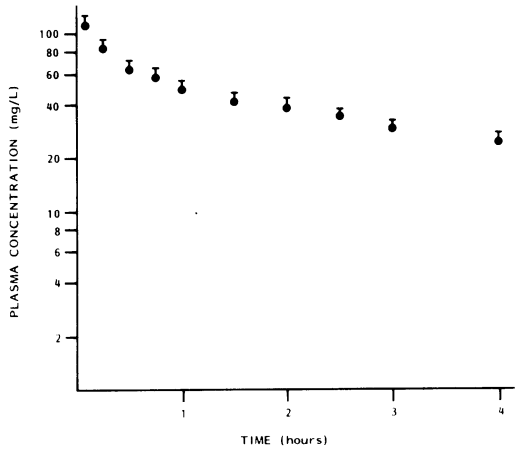

FIG. 2. *Mean plasma moxalactam concentrations (± standard error of the mean) after a single 1-g intravenous dose in six anephric patients during hemodialysis.*

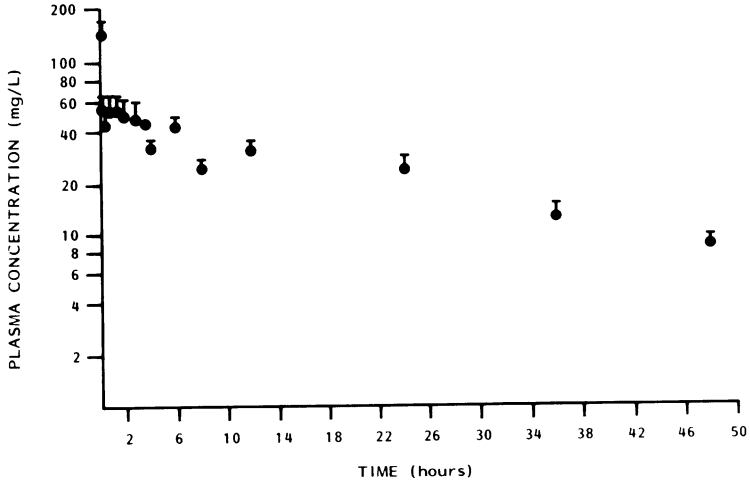

FIG. 1. *Mean plasma moxalactam concentrations (± standard error of the mean) after a single 1-g intravenous dose in four anephric patients during the interdialytic period.*

TABLE 2. *Pharmacokinetic parameters in four anephric patients after a single 1-g intravenous dose of moxalactam during the interdialytic period*

Subject	β (h^{-1})	$t_{1/2\beta}$ (h)	AUC_0^∞ (mg-h/liter)	$Vd_{(area)}$ (liters)	Cl_P (ml/min)
1	0.037	18.7	1,600	16.9	10.4
2	0.036	19.3	894	31.1	18.6
3	0.040	17.3	1,433	17.4	11.6
4	0.042	16.5	1,565	15.2	10.6
Mean ± SEM[a]	0.039 ± 0.001	18.0 ± 0.6	1,373 ± 164	20.2 ± 3.6	12.8 ± 2.0

[a] SEM, Standard error of the mean.

TABLE 3. *Pharmacokinetic parameters in six anephric patients after a single 1-g intravenous dose of moxalactam during hemodialysis*

Subject	β (h^{-1})	$t_{1/2\beta}$ (h)	Moxalactam recovered (mg)	AUC_0^∞ (mg-h/liter)	Cl_D (ml/min)
5	0.277	2.5	476	222	35.7
6	0.239	2.9	467	210	37.1
7	0.248	2.8	418	145	48.0
8	0.248	2.8	652	205	53.0
9	0.330	2.1	359	190	31.5
10	0.210	3.3	536	158	56.5
Mean ± SEM[a]	0.259 ± .017	2.7 ± 0.2	485 ± 41	188 ± 12	43.6 ± 4.2

[a] SEM, Standard error of the mean.

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