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Peritoneal Absorption of Moxalactam

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We evaluated the rate and extent of the systemic absorption of moxalactam given intraperitoneally to patients with peritonitis and end-stage renal disease who were being maintained on continuous ambulatory peritoneal dialysis. Moxalactam was administered at a concentration of 200 mg per 2-liter dialysate for the first dose, followed by 60 mg per 2-liter exchange for 23 1-h exchanges. Moxalactam concentrations in serum (mean ± standard deviation) were 2.5 ± 0.9 mg/liter after the first hourly dialysis, increasing to 10.3 ± 4.8 mg/liter after 24 h of drug administration. Moxalactam levels in serum at 1 h were above the minimal inhibitory concentrations for most gram-negative organisms except *Pseudomonas aeruginosa*. No adverse effects of the drug were observed.

The purpose of this study was to evaluate the rate and extent of accumulation of moxalactam into blood after intraperitoneal administration to patients with suspected bacterial peritonitis. Because of its broad spectrum and low incidence of adverse effects, moxalactam has the potential to replace aminoglycosides in the treatment of gram-negative peritonitis, except in cases due to *Pseudomonas aeruginosa*.

MATERIALS AND METHODS

The study population consisted of five adult males, ages 26 to 48 years, with end-stage renal disease who were receiving continuous ambulatory peritoneal dialysis (4). Patients were studied during seven episodes of suspected bacterial peritonitis. Two of the five subjects were studied during two separate episodes of peritonitis which were at least 3.5 months apart. Clinical diagnoses of peritonitis were established by the admitting physician of each patient. All patients had cloudly dialysate effluent and two or more of the following symptoms of peritoneal infection: abdominal pain, fever, nausea and vomiting, and diarrhea. All subjects had functional Tenckhoff peritoneal catheters in place. Informed consent was obtained from each subject, and those with a history of β-lactam allergy were excluded.

Patients were treated for suspected peritoneal infection with hourly dialysate exchanges of 2 liters of peritoneal dialysis solution (1.5% Dianeal; Travenol Laboratories, Inc.) to which heparin (500 U/liter) and potassium chloride (5 meq/liter) were added. For treatment of infection, cefazolin at a concentration of 50 mg/liter was added to each exchange. In addition, subjects 1 and 6 received vancomycin (see Table 1).

For the purpose of kinetic evaluation only, moxalactam at a dose of 100 mg/liter of dialysis solution was added to the first 2-liter exchange, followed by 30 mg/liter for 23 1-h, 2-liter dialysate exchanges. The loading dose of moxalactam was chosen empirically to provide measurable drug levels in serum at 1 h. Peak moxalactam levels in serum after a 1-g intravenous bolus injection are approximately 100 mg/liter (5). We chose this concentration as an approximation of the tolerable level in body fluids. Antibiotics were added to peritoneal dialysis solutions, and the fluids were warmed to 37°C at 30 min before infusion, infused over a 15- to 20-min period, and then drained during the last 15 min of each hour, thus yielding an approximate 30-min dwell time of the total dialysate for each exchange.

Upon admission to the hospital, each subject had blood drawn for electrolyte analysis (Sequential Multiple Analyzer; Technicon Corp., Inc.) and leukocyte count with differential, and a sample of peritoneal fluid was obtained for culture and measurement of drug susceptibility of bacterial isolates, leukocyte count differential, and protein determination. Samples (3 ml) of venous blood for assay of moxalactam concentration were obtained before administration of moxalactam and at 1, 2, 4, and 24 h after beginning dialysis.

All patients were observed during the administration of moxalactam and immediately after dialysis for adverse reactions, including anaphylaxis, local intolerance, and bleeding abnormalities.

Serum samples were analyzed by high-pressure liquid chromatography; however, results by this method were uninterpretable in serum samples from these uremic patients. Although high-pressure liquid chromatography has been used successfully for determination of moxalactam in nonuremic patient samples (2), we noted the presence of interfering substances in both base-line and dialysis samples of serum which prevented accurate measurements of moxalactam concentrations. Samples were therefore analyzed by microbiological assay with *Providencia stuartii* and samples diluted at 1:10. At least 100 mg of cefazolin or 1,000 mg of vancomycin per liter had to be present to

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affect the growth of *P. stuartii* (bioassays performed by Dennis Coleman, Eli Lilly Microbiologic Assay Development Department, Eli Lilly & Co., Indianapolis, Ind.).

Stability of moxalactam in peritoneal dialysis solutions was reported by the manufacturer (C. W. McKeehan, Symposium on the New Generation of Beta-Lactam Antibiotics, London, England, 1981) and confirmed in vitro by the following methods. Each of the antibiotics and combinations of antibiotics employed in this study were tested in peritoneal dialysis solution (1.5% Dianeal). These antibiotics and their concentrations (in milligrams per liter) included moxalactam (30), cefazolin (50), vancomycin (25), moxalactam (30) plus cefazolin (50), and moxalactam (30) plus cefazolin (50) and vancomycin (25). Each antibiotic solution in peritoneal dialysate was divided into three samples. The first set of samples thus obtained was frozen immediately; the second set was heated to 37°C for 30 min and then frozen; and the third set was kept at room temperature (25°C) for 6 h, heated to 37°C for 30 min, and then frozen. Each sample was subsequently assayed for moxalactam content by high-pressure liquid chromatography (2). No interference with moxalactam peak measurements occurred in these fluids when this method was used. All samples with cefazolin or vancomycin only yielded moxalactam concentrations of 0 mg/liter. For the other samples, error was random, and less than an 8% difference in base-line control solution of moxalactam in peritoneal fluid was reported in all cases.

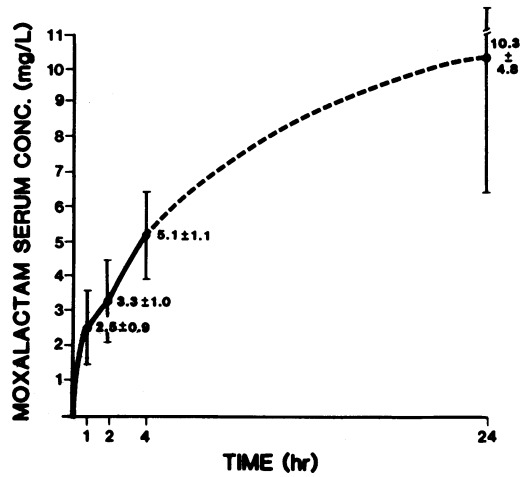

FIG. 1. Moxalactam concentrations in serum achieved after intraperitoneal administration. A dotted line is drawn between the drug level in serum at 4 h and that at 24 h, since levels were not measured between these times. The 1-h sample of patient 4 is missing because of inadequate volume. Only four sample measurements were done on patient 7 because treatment was curtailed at 8 h. Numbers represent means ± standard deviation.

RESULTS

Mean moxalactam concentrations in serum after intraperitoneal administration are shown in Fig. 1. Concentrations (mean ± standard deviation) were 2.5 ± 0.9 mg/liter at 1 h and 10.3 ± 4.8 mg/liter after 24 h of drug administration.

Four of the subjects were anuric during episodes of suspected peritonitis. The remaining three had urine outputs of 300 to 500 ml (Table 1) during the 24-h study period. Moxalactam levels in urine were not measured. Serum creatinine measurements of >10 mg/dl were obtained in five patients.

Peripheral leukocyte counts and differentials were within normal limits for all patients, except patient 3, in whom a shift to the left was documented with 28% bands.

Cultures of peritoneal fluid yielded *Staphylococcus epidermidis* in two subjects and a *Staphylococcus aureus* infection surrounding the Tenckhoff catheter in another patient. Tests to determine the susceptibilities of these organisms to moxalactam were not performed. The leukocyte counts of peritoneal fluid were above 250/mm^3 in all patients; protein concentrations were elevated in four. Moxalactam was well tolerated by all patients.

DISCUSSION

Moxalactam concentrations in serum attained by delivery of 100 mg/liter of dialysate, followed by 30 mg/liter for 23 1-h dialyses, in patients with clinical peritonitis were comparable to the cephalothin and cefazolin concentrations attained when constant doses of these agents were administered intraperitoneally to patients without peritoneal infection (1, 3). Moxalactam concentrations in serum ranged from 1.4 to 3.6 mg/liter within 1 h of intraperitoneal administration. These levels are above the minimal inhibitory concentrations of moxalactam for most gram-negative aerobes except *P. aeruginosa*. There

TABLE 1. Patient data

Patient no.[a]	Wt (kg)	$Serum_{Cr}$ (mg/dl)[b]	Urine output (ml/24 h)	Other antibiotics given[c]
1	57	24.3	0	Cefazolin (i.p.) + vancomycin (1 g i.v.)
2	99	12.5	300	Cefazolin (i.p.)
3	70	13.6	400	Cefazolin (i.p.)
4	55	ND[d]	0	Cefazolin (i.p.)
5	68	13.2	500	Cefazolin (i.p.)
6	58	15.1	0	Cefazolin (i.p.) + vancomycin (1 g i.v. and 25 mg/liter i.p.)
7	95	ND	0	Cefazolin (i.p.)

[a] Patients 1 and 4 are the same patient; patients 2 and 7 are the same patient.
[b] $Serum_{Cr}$, Serum creatinine.
[c] i.p., Intraperitoneally; i.v., intravenously.
[d] ND, Not done.

were subject-to-subject variations in moxalactam concentrations at each time of sampling in all patients; however, there was an increase in moxalactam levels over the 24-h period of dialysis. The ratio of the mean drug concentration in serum to that in dialysate at 24 h was 0.34.

The extent of peritoneal inflammation and its contribution to drug transfer in these patients cannot be estimated. Although all patients had a clinical diagnosis of peritonitis, subsequent laboratory data did not provide support for this diagnosis in all patients.

Moxalactam was instilled hourly, in keeping with standing hospital orders established for similar patients for hourly peritoneal dialysate lavage with cefazolin. Whether moxalactam could be administered less frequently is not known.

Firm recommendations regarding the need for concomitant intravenous moxalactam administration in cases of suspected coexisting systemic infection cannot be made on the basis of the observations reported here. Serum concentrations above the minimal inhibitory concentrations for most gram-negative aerobes except *P. aeruginosa* were attained after the first dose administered, and perhaps higher loading and maintenance doses would achieve higher drug levels in serum for treatment of systemic infection without intravenous doses. Treatment of peritonitis must be accompanied by continuous clinical monitoring of patient response; we do not recommend that administration of moxalactam intraperitoneally be limited to institutions in which moxalactam concentrations in serum can be measured concomitantly.

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