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In Vitro Activity, Efficacy, and Pharmacology of Moxalactam, a New β-Lactam Antibiotic

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Moxalactam, a potent new β-lactam antibiotic with a relatively wide spectrum of activity against facultative and anaerobic gram-negative bacilli, was evaluated in vitro and in 28 patients with a variety of severe infections with moxalactam-susceptible organisms (minimum inhibitory concentration ≤31 μg/ml). Although therapy was successful in most of these patients, caution is suggested because of the development of resistance on therapy in one patient, persistence of *Bacteroides fragilis* endocarditis in another, and for certain organisms, a significant inoculum effect on the minimum inhibitory concentration and minimum bactericidal concentration of moxalactam.

Moxalactam (1-oxa-β-lactam) is a new parenteral semisynthetic β-lactam antibiotic in which oxygen replaces sulfur in the six-membered cephem ring. In vitro studies have shown that moxalactam is more active than penicillins and cephalosporins against many *Enterobacteriaceae* spp., *Pseudomonas aeruginosa*, and *Bacteroides fragilis* (6, 10). Pharmacokinetic data in normal volunteers have been reported by Parsons et al. (7); however, there have been few published studies of the clinical efficacy of moxalactam (2).

This study relates in vitro susceptibility of the patient isolates, clinical pharmacology, and therapeutic efficacy of moxalactam in 28 patients with various bacterial infections.

MATERIALS AND METHODS

In vitro susceptibility testing. In vitro susceptibilities of 36 isolates from 28 adults treated with moxalactam were determined by a broth dilution technique (9). Anaerobic condition for susceptibility testing of *B. fragilis* were achieved by the GasPak system (BBL Microbiology Systems). To study the inoculum effect, minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) were determined for 20 clinical isolates each of *Staphylococcus aureus* and *Escherichia coli*, 10 isolates of *Proteus mirabilis*, and 8 isolates of *P. aeruginosa* by utilizing a broth dilution method (9) in Mueller-Hinton broth (Difco Laboratories) with an inoculum of either 10^5 or 10^7 colony-forming units per ml. MBC was defined as the minimum concentration of antibiotic which caused at least a 99.9% decrease in the bacterial population at 18 h.

Determination of antibiotic concentration in serum and urine. The concentrations of moxalactam in serum and urine were determined in patients receiving 0.5 to 1.0 g of this drug on days 2 to 27 of therapy. Serum specimens were drawn at various intervals from 0.5 to 11.5 h after the end of a 20-min intravenous (i.v.) infusion of moxalactam. Urine specimens were obtained by having the patient void before receiving a dose of moxalactam and collecting urine voided over the dosage interval. One patient with renal failure was hemodialyzed with a Travenol RSP (Travenol Laboratories, Inc.). Serum and urine were stored (usually for less than 1 week) at −20°C until the time of assay. The concentrations of moxalactam in urine and serum were determined by the agar diffusion method with paper disks (7).

The serum half-life ($t_{1/2}$) was defined as the $\log_e$ divided by the slope of the β phase of the serum decay curve beginning at 1 h after the end of the 20-min i.v. infusion. The slope of β was determined by the method of least squares (7).

Clinical studies with moxalactam. From July 1979 to July 1980, 28 patients, ages 14 to 85 years, were treated with moxalactam at The Hospital of the Medical College of Pennsylvania. A criterion for inclusion in the study was a previously untreated bacterial infection or a failure to respond clinically and bacteriologically to prior antibiotic therapy. Moxalactam was given parenterally in dosages ranging from 500 mg to 2 g every 6 to 24 h. The following determinations were performed in all patients before, during, and after therapy: urinalysis, leukocyte and differential counts, hemoglobin, hematocrit, blood urea nitrogen, serum creatinine, bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and the direct and indirect Coombs' tests. Bleeding times were determined in five patients, and prothrombin and partial thromboplastin times were determined in seven patients.

In patients with urinary tract infections, cultures were taken within 24 h before therapy, after 3 or 4 days, and 5 to 14 days after the discontinuation of therapy. The criterion for urinary tract infection was

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$\geq 10^5$ organisms per ml of urine obtained in a clean-voided, midstream manner or by urethral catheterization. These patients were further classified as asymptomatic or symptomatic based on the presence or absence of urinary frequency, dysuria, or urgency. Upper urinary tract infection was diagnosed if, in addition, fever (>101°F [33.3°C] rectally) and flank pain occurred with or without bacteremia. The absence of significant bacteriuria with the original pathogen on therapy and on follow-up was the criterion for cure. Recurrent infection with the same organism after initial sterilization of the urine was the criterion for relapse. Recurrent infection with a different organism was indicative of reinfection. Persistence was defined as the inability to sterilize the cultures after 3 to 4 days of therapy.

RESULTS

At 10^5 colony-forming units per ml, the MBC of moxalactam was the same as or up to fourfold higher than the MIC for 7 of 10 strains of *P. mirabilis*, all 20 strains of *E. coli*, 7 of 8 strains of *P. aeruginosa*, and 17 of 20 strains of *S. aureus*.

When inocula of 10^5 versus 10^7 colony-forming units per ml were compared, a sixfold or greater increase in MIC was seen in all 10 strains of *P. mirabilis* (to an MIC of >50 μg/ml), 17 of 20 strains of *E. coli* (to an MIC of ≤6.3 μg/ml), 1 of 20 strains of *S. aureus*, and 0 of the 8 strains of *P. aeruginosa*. When determinations were compared by using inocula of 10^5 versus 10^7 colony-forming units per ml, only 1 of 10 strains of *E. coli* had a sixfold or greater increase in MBC, whereas 6 of 8 strains of *P. aeruginosa* had a sixfold or greater increase in MBC.

Moxalactam concentrations in serum and urine. In five patients with creatinine clearances of ≥58 ml/min per 70 kg receiving 1.0 g of moxalactam i.v. every 6 to 8 h, serum levels 30 min after the end of a 20-min i.v. infusion ranged from 63.5 to 87.5 μg/ml, with a mean ± standard deviation of 78.1 ± 8.8 μg/ml on days 2 to 9 of therapy (Table 1). In these patients, the mean serum $t_{1/2}$ ± standard deviation was 2.2 ± 0.9 h, and 65 to 115% of the drug was excreted in the urine in 6 to 8 h. In three patients with severe renal failure receiving 0.5 to 1 g every 12 h, serum levels 30 min after the end of infusion ranged from 64.5 to 193.6 μg/ml, and the serum $t_{1/2}$ ranged from 9.9 to 13.9 h. The serum $t_{1/2}$ in one patient fell from an average of 11.8 h to an average of 5.8 h on hemodialysis. Urine concentrations ranged from 317 to 2,661 μg/ml in patients with normal renal function and 41 to 74 μg/ml in one patient with severe renal failure during 6 to 8 h after dosing.

Clinical studies with moxalactam. The data on the outcome of 28 patients treated with moxalactam show that 22 had urinary tract infections and 6 had miscellaneous infections (Table 2). Of the 22 patients with urinary tract infections, 3 had asymptomatic bacteriuria. Of the 19 patients with symptomatic infections, all had evidence of upper tract infection, and 6 had bacteremia. Of 22 patients, 17 had prompt clinical and bacteriological responses and were cured. Two patients had persistent bacteriuria. In one (patient 9), the urinary pathogen remained susceptible to moxalactam (*P. aeruginosa*, MIC, 31.3 μg/ml); in the other (patient 20), the MIC of the pathogen (*Serratia* sp.) increased from 25 to >50 μg/ml, and this patient

TABLE 1. *Pharmacokinetic data on moxalactam in eight patients*

Patient	Serum creatinine (mg/dl)	Creatinine clearance (ml/min per 70 kg)	i.v. dose (g)	Frequency of administration (h)	Serum concn (μg/ml)		$t_{1/2}$ Serum (h)	Urinary excretion (% dose)
					Peak[a]	Trough		
1	1.2	145	1 (14)[b]	6	73.9	24.0	3.9	115
2	0.6	128	1 (17)	8	63.5	2.1	1.4	65
3	0.8	127	1 (20)	6	86.0	6.5	1.5	74
4	0.8	122	1 (20)	8	79.7	3.7	1.7	107
5	1.3	58	1 (11)	6	87.5	20.5	2.4	93
6	5.8		1 (12)	12	64.5		13.9	
7	9.7	<5	0.5 (7)	12	78.6	22.9	11.6	
8	14	<5	1 (16)	12	76.0[c]	34.7[c]	9.9[d]	
			1 (16)	12	193.6		13.9[d]	
			0.75 (12)	12	102.1	42.4	11.6[d]	
							5.0, 6.9, 5.4[e]	

[a] 30 min after the end of a 20-min i.v. infusion.
[b] Mg/kg of body weight.
[c] First dose.
[d] Off hemodialysis.
[e] On hemodialysis.

TABLE 2. *Clinical data*[a]

Patient	Age (yr)	Sex	Diagnosis	Pathogen	MIC (μg/ml)	Dosage/ interval	Day of therapy	Outcome	Comments
1	68	M	UTI/upper, bacteremia	*P. aeruginosa* *P. aeruginosa*	6.3 (U) 25 (B)	1 g/6–8 h	13	Relapse	Indwelling cystotomy catheter
2	21	F	UTI/upper, bacteremia	*E. coli* *E. coli*	0.195 (U) 3.1 (B)	1 g/8 h	10	Cure	
3	70	F	UTI/upper, bacteremia	*E. coli* *E. coli*	(U) 0.39 (B)	1 g/6 h	14	Cure	Diabetes mellitus
4	36	F	UTI/upper	*E. coli*	0.098 (U)	1 g/6 h	10	Cure	Addison's disease
5	23	F	UTI/upper	*E. coli*	0.098 (U)	1 g/8 h	10	Cure	
6	63	M	UTI/upper, bacteremia	*E. coli* *E. coli*	0.195 (U) 0.195 (B)	1 g/8 h	14	Cure	
7	28	F	UTI/upper	*E. coli*	0.049 (U)	1 g/8 h 500 mg/8 h	1 4	Cure	
8	30	F	UTI/upper	*E. coli*	0.098 (U)	1 g/8 h 500 mg/8 h	6 5	Relapse	
9	29	M	UTI/upper	*P. aeruginosa*	31.3 (U)	1 g/8 h	4	Persistence	Indwelling bladder catheter
10	19	F	UTI/upper	*E. coli*	0.098 (U)	1 g/8 h	10	Cure	
11	62	M	UTI/upper	*Enterobacter cloacae*	25 (U)	1 g/8 h	10	Reinfection	Indwelling bladder catheter
12	76	M	UTI/asymptomatic	*Serratia* sp. *P. aeruginosa*	0.39 (U) 12.5 (U)	500 mg/8 h	14	Cure	
13	50	M	UTI/asymptomatic	*Serratia* sp.	1.56 (U)	500 mg/8 h	10	Cure	
14	32	F	UTI/upper	*E. coli*	0.39 (U)	500 mg/8 h	10	Relapse	
15	69	F	UTI/upper, bacteremia	*E. coli* *E. coli*	0.098 (U) (B)	1 g/8 h	10	Cure	
16	24	F	UTI/upper	*E. coli*	0.098 (U)	500 mg/12 h	7	Cure	

17	20	F	UTT/upper	*E. coli*	1.56 (U)	500 mg/8 h	10	Cure	
18	81	M	UTI/upper, bacteremia	*E. coli* *E. coli*	0.098 (U) 0.048 (B)	1 g/8 h 500 mg/8 h	10 10	Cure	Obstructive uropathy
19	21	F	UTI/upper	*E. coli*	0.048 (U)	500 mg/8 h	7	Cure	
20	85	M	UTI/asymptomatic	*Serratia* sp.	25.0 (U)	500 mg/24 h 1 g/12 h	5 12	Persistence	Chronic renal failure Obstructive uropathy, indwelling bladder catheter
21	44	M	UTI/upper	*P. aeruginosa*	12.5 (U)	500 mg/8 h	7	Reinfection	Multiple sclerosis
22	36	F	UTI/upper	*E. coli*	0.098 (U)	500 mg/8 h	9	Cure	
23	58	M	Subdiaphragmatic abscess	*E. coli* *P. aeruginosa* *B. thetaiotaomicron*	0.098 25.0 1.56	1 g/6 h	21	Cure	
24	34	F	Cellulitis	*S. aureus*	6.25	1 g/8 h	8	Improved	Diabetes mellitus
25	28	M	Endocarditis	*B. fragilis* *H. parainfluenzae* Viridans streptococcus	3.13 1.56 25.0	2 g/8 h	8	Persistence of *B. fragilis*	Received ampicillin and gentamicin. Addict. *B. fragilis* resistant to ampicilin
26	70	M	Mycotic aneurysm Vertebral osteomyelitis	*E. coli*	0.195 (B)	1 g/12 h 750 mg/12 h 1 g/12 h	10 25 8	Cure	Renal failure
27	14	M	Osteomyelitis Compound fracture	*Citrobacter freundii* *E. cloacae* *Clostridium bifermentens* *Clostridium* sp. *Bacteroides oralis*	0.049 0.098	600 mg/8 h 1 g/8 h	6 37	Failure	Relapse organism (C. freundii) susceptible to moxalactam (MIC, 0.098 μg/ml)
28	78	M	Bacteremia	*E. coli*	0.195	500 mg/8 h	12	Cure	

[a] Abbreviations: M, male; F, female; UTI, urinary tract infection; U, urine isolate; B, blood isolate.

developed bacteremia due to this organism after prostatic manipulation. The infection in three patients relapsed (patients 1, 8, and 14). Two patients became reinfected with a new urinary pathogen within 2 weeks after discontinuation of moxalactam.

One patient had a subdiaphragmatic abscess due to *E. coli*, *P. aeruginosa*, and *Bacteroides thetaiotaomicron* and was cured with drainage and moxalactam therapy. One patient had a lower extremity cellulitis due to *S. aureus* that improved clinically with moxalactam, but because of residual fluctuance, heat and erythema on day 8, and the development of an upper gastrointestinal hemorrhage without change in bleeding time, platelets, prothrombin time, or partial thromboplastin time, moxalactam treatment was discontinued and the area was surgically drained. A culture of the drainage was sterile. One patient with an *E. coli* mycotic aortic aneurysm and osteomyelitis of an adjacent lumbar vertebral body was cured. One patient with tricuspid endocarditis due to ampicillin-resistant *B. fragilis* (moxalactam MBC, 6.3 μg/ml), a viridans *Streptococcus*, and *Hemophilus parainfluenzae* had persistent fever and *B. fragilis* bacteremia after 1 week of moxalactam, ampicillin, and gentamicin therapy, but ultimately responded to metronidazole therapy. One patient with osteomyelitis of the ulna secondary to a compound fracture failed to respond to moxalactam, but later was cured after debridement of foreign bodies. One patient had *E. coli* bacteremia from an unknown source and was cured.

Side effects of therapy. The side effects of moxalactam were minimal. One patient developed a generalized maculopapular rash that regressed after discontinuation of moxalactam, and one patient had mild phlebitis. After 7 days of moxalactam therapy, one patient with uremia developed prolonged prothrombin and partial thromboplastin times which were, responsive to vitamin K, and a prolonged bleeding time which eventually returned to normal as the renal function improved, despite continuance of moxalactam therapy. Four patients receiving intramuscular moxalactam did not complain of excessive pain at the injection site.

DISCUSSION

Moxalactam has been reported to have exceptional activity against many *Enterobacteriaceae* spp. compared with other β-lactam antibiotics and also has good activity compared with cefoxitin against *B. fragilis* and carbenicillin against *P. aeruginosa*. In the present study, at an inoculum of 10^5 colony-forming units per ml, there was little difference between the MICs and MBCs of moxalactam for *P. mirabilis*, *E. coli*, *P. aeruginosa*, and *S. aureus*. At higher inocula, which correspond more closely to bacterial populations in infected tissues, sixfold or greater increases in MIC were seen with *E. coli* and *P. mirabilis*. With *E. coli*, the MIC at the higher inoculum was ≤6.3 μg/ml, a concentration well below achievable blood levels, whereas with all *P. mirabilis* strains, the MIC at the higher inoculum was >t50 μg/ml. Although the MBC remained the same for most *E. coli* strains tested, six of eight strains of *P. aeruginosa* tested had a sixfold or greater increase in MBC with the higher inoculum, suggesting that infections in the compromised host or endocarditis due to *P. aeruginosa*, which may require bactericidal activity, are not optimally treated with moxalactam alone.

An inoculum effect in vitro may suggest an emergence of resistance on therapy in vivo. Indeed, urinary tract infection persisted in two patients, one of whom, while on moxalactam therapy, was associated with the development of a resistant *Serratia* sp. isolated from blood. The development of resistance, usually involving *P. aeruginosa*, has also been noted in preliminary reports of moxalactam therapy (L. S. Young, T. O. Kurtz, D. Winston, and R. W. Busuttil, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 368, 1980; R. Platt, S. L. Ehrlich, J. E. Pennington, and E. H. Kass, 20th ICAAC, abstr. no. 371; C. Perlino, D. Jones, and S. McGlohn, 20th ICAAC, abstr. no. 372).

In general, moxalactam was clinically efficacious and well tolerated. The doses used achieved levels in the blood and urine in excess of the MICs of susceptible pathogens. Peak serum levels after injecting 1 g i.v. were similar to those reported in normal volunteers (7) and are comparable to those of cefamandole and cephalothin. The serum $t_{1/2}$ of moxalactam in patients with normal renal function was similar to that reported in normal volunteers (7). In patients with severe renal failure, the serum $t_{1/2}$ was approximately 12 h, and serum levels could be maintained between about 20 and 100 μg/ml with dosing of 0.5 to 0.75 g every 12 h. Supplemental dosing would be required after each hemodialysis (1).

Caution should be employed in the use of moxalactam in gram-positive infections in which the MIC for the organism may be relatively high. One patient with an uncomplicated *S. aureus* cellulitis had persistence of clinical signs on moxalactam therapy. Similarly, the development of probable pneumococcal meningitis on therapy and recurrent pneumococcal pneumonia 3 days after moxalactam therapy had been stopped have recently been reported (Perlino et

al., 20th ICAAC, abstr. no. 372). The emergence of enterococcal superinfection and colonization has also been reported recently (11).

Side effects of therapy with moxalactam were minimal. One uremic patient developed elevations of prothrombin and partial thromboplastin times which reverted to normal with vitamin K while on moxalactam therapy. An elevation of prothrombin time with bleeding has been reported by others. (S. Srinivasan, E. L. Francke, and H. C. Neu. 20th ICAAC, abstr. no. 365; A. Lentnek, L. Kidd, and R. Ryan. 20th ICAAC, abstr. no. 369) in patients given moxalactam and has also been reported in patients treated with cephalothin, cefazolin, and cefamandole (3–5, 8).

Moxalactam is active against many *Enterobacteriaceae* spp. in very low concentrations and has a spectrum of activity encompassing that of the aminoglycosides, but unlike the aminoglycosides, also has good activity against *B. fragilis* and streptococci. Because of these attributes, it would be anticipated that moxalactam could be used in relatively low doses and could replace the nephrotoxic aminoglycosides in many infections. However, the inoculum effect in vitro and the emergence of resistance, especially among *P. aeruginosa* strains in vivo, suggest caution with the use of this antibiotic, especially in patients with compromised host defense mechanisms.

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