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Clinical Evaluation of Moxalactam

W. K. LIVINGSTON, A. M. ELLIOTT, W. E. DISMUKES, C. K. AVENT, AND C. G. COBBS*

Department of Medicine, University of Alabama School of Medicine, Birmingham, Alabama 35294

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We investigated the clinical efficacy of moxalactam for treatment of a variety of infectious disorders in 50 patients (38 males and 12 females). Patient ages ranged from 8 days to 98 years, with a median of 66 years. Infectious disorders were confirmed by isolation of etiological bacteria in all patients. Thirty-eight patients had gram-negative bacillary disease, nine had pneumococcal infection, and three had disorders caused by staphylococci or streptococci. Twenty-three patients had pneumonia, 17 had bacteremic diseases other than pneumonia, and 10 had miscellaneous infectious diseases. The overall efficacy of moxalactam was excellent. Forty-eight patients were cured by clinical criteria, and 45 were cured by bacteriological criteria. A total of 19 adverse reactions were associated with the use of moxalactam in 18 patients, but none were severe and only one necessitated discontinuation of treatment. Moxalactam promises to be an important addition to our therapeutic armamentarium, especially for therapy of gram-negative bacillary infections.

Moxalactam disodium (LY127935) is a new semisynthetic beta-lactam antimicrobial agent. It is a 1-oxa-beta-lactam antibiotic; an oxygen molecule has been substituted for sulfur in the cephem nucleus. A previous communication from this laboratory reported the results of in vitro susceptibility testing with this agent against a large number of clinical isolates of gram-negative bacilli (6). During the last 2 years, a trial of the efficacy of moxalactam has been carried out in patients at this institution; the results are described here.

MATERIALS AND METHODS

Patients who were hospitalized at The University Hospital of the University of Alabama Medical Center and at the Birmingham Veteran's Administration Medical Center, Birmingham, Ala., were available for study (one patient was treated at an outside hospital). In most instances, medical house staff serving at these institutions identified patients suspected of fulfilling criteria for entry into the study. The patients were then interviewed by one of us (W.K.L.); if criteria were met, informed consent was solicited and obtained. This was not a controlled study; patients were selected and treated consecutively, and no other antimicrobial regimen was used. Underlying diseases were determined by examination of the patients and their medical records.

All of the following criteria were necessary for enrollment in the study: (i) suspected bacterial infection and anticipated isolation of the etiological microorganism(s) from either blood, spinal fluid, or other normally sterile fluid or from inflammatory exudate; (ii) no prior antimicrobial agent(s) effective against the etiological bacteria; (iii) no history of allergy to cephalosporin-type agents and no history of an immediate hypersensitivity reaction to penicillins; (iv) nonpregnant female; (v) no identifiable risk of life-threatening pseudomonas disease (for example, patients with acute leukemia and granulocytopenia); (vi) no evidence of prosthetic valve endocarditis; and (vii) no evidence of central nervous system infectious disease (patient 49 represents an exception; see below). For retention in the study, the etiological bacteria had to be isolated, identified, and susceptible to moxalactam by disk diffusion testing. Initially, bacteria exhibiting zone sizes of 18 mm or greater were considered susceptible. Later, during the course of the study, criteria were changed by the manufacturer; therefore, a zone size of ≥23 mm was used to define susceptible organisms, and a zone of 15 to 22 mm was used to identify intermediate ones. Thirteen strains considered susceptible were then switched to the intermediate category. Two patients with polymicrobial infectious disorders were treated with moxalactam, even though one of the bacteria was resistant to it. Patient 16, who had osteomyelitis, was infected by two bacteria, a *Pseudomonas aeruginosa* resistant to moxalactam and a *Serratia marcescens* susceptible to moxalactam. Patient 22, with gram-negative bacillary pneumonia, had *Haemophilus influenzae* and *Acinetobacter calcoaceticus* isolated from sputum. The *H. influenzae* isolate was intermediate in susceptibility to moxalactam, and the *A. calcoaceticus* isolate was resistant.

Moxalactam (supplied by Lilly Research Laboratories, Indianapolis, Ind.) was usually administered parenterally via scalp vein infusion except in two patients (42 and 44) who were discharged and treated at home with intramuscular drug. The dosage ranged from 10 to 146 mg/kg per day (mean dose, 50 mg/kg per day). The drug was generally given three times daily and infused over 20 to 40 min diluted in approximately 50 ml of either normal saline or 5% dextrose in

water. Dosage adjustment in patients with renal insufficiency was patterned after guidelines formulated for cefamandole (14). Serum drug levels were not obtained. Toxicity was monitored by daily examination of patients and by determination of laboratory tests before initiation of therapy and at intervals during and after completion of therapy. Any abnormality detected was followed up if possible with additional tests in an attempt to determine the etiology and subsequent trend of the abnormality. No antimicrobial therapy was administered after discontinuation of moxalactam.

Cultural techniques. Blood cultures were obtained before initiation of antimicrobial agents in all patients admitted to the study. With sterile technique, 10 ml of blood was obtained by venipuncture; 5 ml was inoculated into each of two Bactec bottles containing 30 ml of aerobic and anaerobic blood culture medium, respectively. Two separate venipunctures to inoculate a total of four bottles were performed on each patient. In addition, in all patients with lower respiratory tract infection, expectorated sputum or tracheal aspirate for Gram-stained smears and cultures was obtained. In patients with urinary tract infection, urine was examined microscopically and cultured quantitatively. In patients with cellulitis, material from sites of local inflammation was obtained for Gram stains and cultures; in instances where there was no apparent focus of inflammation, sterile saline was injected beneath the skin and aspirated, and this material cultured. One patient with liver abscess had pus aspirated at the time of surgery. In all patients, we attempted to obtain cultures of the original site after completion of treatment. If such materials were unobtainable, blood cultures were drawn.

Susceptibility testing. Moxalactam susceptibility of all bacterial pathogens was determined by disk diffusion technique. To define the minimal inhibitory concentration (MIC) and minimal bactericidal concentration, a microtiter technique was used (2). In some instances, the antimicrobial activity of serum (1) was assayed against the infectious bacteria while the patient was receiving moxalactam.

Efficacy of therapy. The efficacy of therapy was evaluated by clinical and bacteriological outcome. Patients were followed by one of us (W.K.L.) on a regular basis during and after completion of therapy. The following criteria were used as indications for bacteriological cure: for patients with pneumonia, eradication of the etiological bacteria from sputum, if available; for patients with bacteremia, a sterile blood culture; for patients with urinary tract infection, a sterile urine culture; for patients with osteomyelitis, absence of the etiological bacteria from bone aspirates; for soft tissue infection, absence of the etiological bacteria from pus if present or, if the wound had healed, sterile blood cultures; for patients with meningitis, sterile cerebrospinal fluid cultures.

Criteria for clinical cure were as follows: for patients with pneumonia, defervescence and resolution of symptoms and signs of lower respiratory tract infection together with roentgenographic improvement or resolution; for patients with bacteremia, improvement or resolution of symptoms and signs of sepsis. Clinical cure was documented in patients with osteomyelitis when signs of local inflammation disappeared, sinus tract drainage resolved, and evidence of healing was present roentgenographically. Patients with urinary tract infection were considered cured clinically when symptoms of flank pain, fever, toxicity, dysuria, frequency, and urgency had resolved.

RESULTS

Fifty patients were treated between April 1978 and December 1980. There were 38 males and 12 females; ages ranged from 8 days to 98 years, with a median of 66 years. The duration of therapy ranged from 4 to 98 days, with a median of 12 days. Dosage varied from 10 to 146 mg/kg per day.

Bacterial isolates were obtained in all patients. Twenty-three patients had pneumonia, 17 had bacteremic disease other than pneumonia, 2 had urinary tract infection, 4 had soft tissue infection, and 4 had other infectious disorders. No patient with an infectious disorder caused by anaerobic bacteria alone or in combination with aerobic species was treated. Table 1 describes clinical and bacteriological outcomes for all patients.

Table 2 summarizes the outcome of 23 patients with pneumonia. All patients were cured clinically. Two of the patients (4 and 37) had bacteremic disease, whereas the remainder were diagnosed by sputum culture. Transtracheal aspirations were not performed. The etiological microorganisms of nonpneumococcal pneumonias were determined by blood culture in one patient, by pure culture from sputum in five patients, by abundant growth from one sputum culture in four patients, and by abundant growth from more than one sputum culture in four patients. Follow-up sputum cultures were obtained in 21 patients, and in 19 the suspected etiological microorganisms were eliminated. Two patients were considered bacteriological failures. Despite clinical and radiological improvement in patient 4, bronchial washings and sputum continued to grow *Streptococcus pneumoniae* susceptible to moxalactam. The blood cultures which were initially positive for that microorganism were subsequently sterile. Patient 47, who developed gram-negative pneumonia after admission for respiratory failure, improved clinically and radiologically during treatment but continued to produce small amounts of sputum from which *Proteus mirabilis* was recovered after discontinuation of moxalactam.

Seventeen patients with bacteremic disorders other than pneumonia were treated with moxalactam, and 16 were considered clinical cures

TABLE 1. *Outcome of bacterial infections in 50 patients treated with moxalactam*

Diagnosis	No. of patients	Bacteriological results			Clinical results		
		Cure	Failure	Unevaluable	Cure	Failure	Unevaluable
Pneumonia	23	19	2	2	23		
Other infectious disorders with bacteremia	17	17			16	1	
Other infectious disorders without bacteremia	10	9		1[a]	9		1[a]
Total	50	45	2	3	48	1	1

[a] Drug discontinued because of hypersensitivity reaction.

(Table 3). Bacteremic illnesses included pyelonephritis in eight patients and one patient each with intraabdominal abscess, mediastinitis, thermal injury, decubitus ulcer, hepatic abscess, perinephric abscess, infective endocarditis, ulcerating colonic carcinoma, and septic phlebitis. Patient 15, who was admitted with "locked-in" syndrome after cerebral infarction, developed urinary tract infection and bacteremia with *Pseudomonas aeruginosa*. Both blood and urine cultures became sterile during moxalactam therapy, but on the 11th day of treatment, while ostensibly improving, the patient died suddenly. No post-mortem examination was performed. In all other patients in this group, follow-up cultures were obtained which documented eradication of the etiological microorganism in each.

Table 4 provides information on the patients with infectious disorders without documented bacteremia. In all patients except 25 and 31, the suspected etiological microorganisms were cultured on more than one occasion, and often on several cultures during extended periods of time. Patients 28 and 31, with nonbacteremic urinary tract infection, were cured. All four patients with soft tissue infections (20, 23, 25, and 44) were cured bacteriologically and clinically. Patients 23 and 44 required surgical intervention, whereas patients 20 and 25 received skin grafts to the involved sites after eradication of their infections.

Three patients were treated with moxalactam for osteomyelitis (16, 27, and 42), and one infant (49) required the drug for treatment of gram-negative meningitis (Table 4). Patient 16 had traumatic resection of 10 cm of his right tibia as a result of a motorcycle accident with subsequent infection by *S. marcescens* and *P. aeruginosa*. The serratia was susceptible to moxalactam and resistant to aminoglycosides, and the pseudomonas was resistant to moxalactam and susceptible to amikacin. Initial treatment at another institution for 7 weeks with cefoxitin and chloramphenicol was unsuccessful. After prolonged therapy with moxalactam and amikacin, the patient underwent bone graft and recovered. Patient 27 with thalassemia and vascular insufficiency presented with osteomyelitis of her right great toe caused by *Staphylococcus aureus*. Therapy with moxalactam, which resulted in sterilization of drainage, had to be terminated prematurely because of drug fever. Patient 42 sustained severe trauma to the right tibia and required prolonged antimicrobial therapy directed against several gram-negative bacilli cultured from the wound, among which was a multiply resistant strain of *P. maltophilia* susceptible only to moxalactam. Patient 42 also required aminoglycosides for the treatment of *P. aeruginosa* resistant to moxalactam. Patient 49 developed neonatal meningitis caused by *Escherichia coli* resistant to ampicillin, chloramphenicol, carbenicillin, and tetracycline. After 3 days of therapy with gentamicin, *E. coli* could still be isolated from the cerebrospinal fluid, and the patient was unimproved clinically. Moxalactam was then added, and subsequently clinical improvement was rapid with sterilization of the cerebrospinal fluid in 2 days.

Adverse reactions to moxalactam. Eleven patients developed abnormal liver function tests during therapy with moxalactam (Table 5). In seven patients, the only abnormality was a rise in the serum glutamic oxalacetic transaminase (SGOT). None of these patients received intramuscular injections. In three patients, only the serum alkaline phosphatase concentration was increased; in one patient, both SGOT and alkaline phosphatase levels rose above normal during moxalactam therapy. No patient developed an abnormal serum bilirubin level. Five of the patients with increased SGOT and two patients with elevated alkaline phosphatase demonstrated only mildly abnormal values, i.e., less than twice the normal levels. In those patients who had repeat studies after completion of therapy, the abnormal values returned to normal. Patient 43 had transient elevation of SGOT after surgery, thought to be caused by halothane. The serum SGOT obtained 4 days after moxalactam

TABLE 2. *Patients with pneumonia*

Patient no.	Age (yr)	Underlying disease[a]	Organism isolated[b]	Days of treatment	Result	
					Bacteriological	Clinical
4	54	COPD, alcoholism, smoking	*Streptococcus pneumoniae* (S, B)	10	Failure	Cure
5	66	Anemia, chronic renal failure, CHF, diabetes mellitus	*S. pneumoniae* (S)	7	Cure	Cure
9	69	Pneumoconiosis	*S. pneumoniae* (S)	10	Cure	Cure
12	36		*S. pneumoniae* (S)	5	Cure	Cure
13	37	Smoking	*S. pneumoniae* (S)	4	Cure	Cure
17	88	COPD, hypertension	*Haemophilus influenzae* (S)	8	Cure	Cure
18	53	COPD	*Serratia marcescens* (S)	12	Cure	Cure
22	60	COPD, GI bleeding	*Acinetobacter calcoaceticus* (S) *H. influenzae* (S)	10	Cure	Cure
24	71	COPD, CHF, prostatic nodule	*Streptococcus pneumoniae* (S)	8	Cure	Cure
26	60	Fractured rib	*Staphylococcus aureus* (S)	7	Cure	Cure
29	82	COPD, anemia, prostatic hypertrophy	*Pseudomonas fluorescens* (S)	10	Cure	Cure
32	45	Astrocytoma (chronic), CHF, diabetes mellitus	*P. aeruginosa* (S)	10	Cure	Cure
34	54	CHF, mild renal insufficiency, obesity	*Proteus mirabilis* (S) *Enterobacter aerogenes* (S)	14	Cure	Cure
35	73	Cerebral infarction, old myocardial infarction	*Streptococcus pneumoniae* (S)	7	Cure	Cure
37	68	CVA, chromophobe adenoma	*Serratia marcescens* (S, B, U)	13	Cure	Cure
38	91	COPD	*Streptococcus pneumoniae* (S)	10	Cure	Cure
39	88	COPD, hypertension	*H. influenzae* (S)	8	Cure	Cure
40	50	Diabetes mellitus	*Proteus mirabilis* (S) *Citrobacter diversus* (S)	11	Cure	Cure
45	66	Malnutrition, metastatic squamous cell carcinoma (lung), tuberculosis, alcoholism	*Streptococcus pneumoniae* (S)	10	Follow-up culture not obtained	Cure
46	64	GI bleeding, secondary uremia, seizure disorder, acute renal failure	*Pseudomonas aeruginosa* (S)	7	Follow-up culture not obtained	Cure
47	64	CHF, peptic ulcer disease, interstitial lung disease	*Proteus mirabilis* (S) *Klebsiella pneumoniae* (S)	14	Failure	Cure
48	98	CHF, COPD, prostate nodule	*Serratia marcescens* (S)	11	Cure	Cure
50	67	Diabetes mellitus	*Streptococcus*, group B (S)	9	Cure	Cure

[a] COPD, Chronic obstructive pulmonary disease; CHF, congestive heart failure; GI, gastrointestinal; CVA, cerebrovascular accident.

[b] S, Sputum; B, blood; U, urine.

therapy ended was normal. Patient 40, who had pneumonia, demonstrated an increase in SGOT from 18 to 177 IU/liter and a rise in alkaline phosphatase from 202 to 920 IU/liter during 11 days of moxalactam therapy. The patient was asymptomatic at the completion of antibiotic therapy and was lost to follow-up. Patient 12, with nonbacteremic pneumococcal pneumonia, had a normal serum SGOT before therapy; on the day therapy was discontinued, the value

TABLE 3. *Other infectious disorders with bacteremia*

Patient no.	Age (yr)	Underlying disease	Type or site of infection	Organism isolated	Days of treatment	Result	
						Bacteriological	Clinical
1	31	Gunshot wound, renal failure	Abdominal abscess	*Serratia marcescens* (B, W)	14	Cure	Cure
2	25	Mediastinitis	Operative wound	*S. marcescens* (B)	13	Cure	Cure
3	25	Burn, 55% body surface area	Burns	*S. marcescens* (B)	14	Cure	Cure
6	71	COPD, carcinoma of prostate and lungs, diabetes mellitus	Pyelonephritis	*Klebsiella pneumoniae* (B, U, W)	14	Cure	Cure
7	76	Organic brain syndrome, atrial fibrillation	Decubitus ulcers	*Proteus mirabilis* (B, W)	20	Cure	Cure
8	55	Multiple myeloma	Pyelonephritis	*S. marcescens* (B, U)	31	Cure	Cure
10	80	Polyclonal gammopathy	Pyelonephritis	*Escherichia coli* (B, U)	14	Cure	Cure
11	47	Diabetes mellitus, chronic renal insufficiency	Pyelonephritis	*E. coli* (B, U)	15	Cure	Cure
14	79		Pyelonephritis	*Enterobacter aerogenes* (B, U)	15	Cure	Cure
15	59	Cerebral infarction, GI bleeding	Pyelonephritis	*Pseudomonas aeruginosa* (B, U)	11	Cure	Death
19	36	GI bleeding, chronic pancreatitis, diabetes mellitus	Hepatic abscess	*Klebsiella pneumoniae* (B, W) Viridans *Streptococcus* (B) *Enterobacter cloacae* (W) *Lactobacillus* sp. (B) Diphtheroids (W)	29	Cure	Cure
21	47	Renal insufficiency, carcinoma of cervix	Perinephric abscess	*S. marcescens* (B, W)	21	Cure	Cure
30	58	Rheumatoid arthritis	Pyelonephritis	*Escherichia coli* (U) *Pseudomonas fluorescens* (B) *Streptococcus pneumoniae* (B)	13	Cure	Cure
33	84	Chronic mild renal insufficiency, calcific aortic stenosis with CHF, history of GI bleeding	Pyelonephritis Endocarditis	*Proteus mirabilis* (U) *E. coli* (U) *K. pneumoniae* (U) *Staphylococcus aureus* (B)	28	Cure	Cure
36	73		Pyelonephritis	*E. coli* (B, U)	8	Cure	Cure
41	80	CHF, hypertension, carcinoma of colon, aortic stenosis, anemia	GI tract	*E. coli* (B) *K. pneumoniae* (B)	17	Cure	Cure
43	43	Epidural tumor	Septic phlebitis	*Serratia marcescens* (B, W)	14	Cure	Cure

[a] See Table 2.
[b] B, Blood; W, wound; U, urine.

TABLE 4. *Other infectious disorders without bacteremia*

Patient no.	Age (yr)	Underlying disease	Type or site of infection	Organism isolated[a]	Surgery	Days of treatment	Result	
							Bacteriological	Clinical
16	15	Trauma	Osteomyelitis tibia and fibula	*Serratia marcescens* (W) *Pseudomonas aeruginosa* (W)	Debridement	98	Cure	Cure
20	56	Alcoholism, schizophrenia	Soft tissue, left hip	*S. marcescens* (W)	None	47	Cure	Cure
23	60	Peripheral neuropathy	Soft tissue, left foot	*Escherichia coli* (W) *Streptococcus* group B (W)	Debridement	9	Cure	Cure
25	72	Peripheral vascular disease	Soft tissue, right ankle	*Citrobacter diversus* (W) *Streptococcus pyogenes* (W)	None	12	Cure	Cure
27	25	Thalassemia minor, sclerodactyly with Reynaud's, rheumatic valvular disease	Osteomyelitis, right foot	*Staphylococcus aureus* (W)	Debridement	14	Unevaluable	Drug reaction
28	64	Indwelling urinary catheter, Huntington's chorea, glaucoma	Urinary tract	*E. coli* (U)	None	10	Cure	Cure
31	42	Uterine carcinoma	Urinary tract	*E. coli* (U)	None	9	Cure	Cure
42	22		Osteomyelitis tibia	*Pseudomonas maltophilia* (W) *P. aeruginosa* (W) *Acinetobacter calcoaceticus* (W) *Aeromonas hydrophilia* (W)	Debridement	107	Cure	Cure
44	22		Soft tissue, left forearm	*Enterobacter cloacae* (W)	Removal of infected plate, left radius	53	Cure	Cure
49	8 days		Meningitis	*E. coli* (CSF)	None	22	Cure	Cure

[a] W, Wound; U, urine; CSF, cerebral spinal fluid.

TABLE 5. *Adverse reactions to moxalactam*

Disorder	Patient no.	Total
Hypersensitivity		
Eosinophilia	23, 41[a]	2
Pruritus	31	1
Fever	27	1
Hepatotoxicity	4, 6, 9, 12, 13, 17, 19, 37, 39, 40, 43	11
Anemia	5	1
Anorexia	42	1
Oral candidiasis	47	1
Confusion	21, 41[a]	2
Total		19[a]

[a] Patient 41 is listed in two categories.

was three times normal. The patient was discharged, and a follow-up determination was not obtained. Patient 21 developed perinephric abscess and renal insufficiency after surgery for carcinoma of the cervix. During moxalactam therapy renal insufficiency improved, but serum alkaline phosphatase increased from a pretreatment value of 156 IU/liter (1.5 times normal) to 413 IU/liter. One month after discontinuation of moxalactam, the alkaline phosphatase had increased to 808 IU/liter; by 3 months, the level had fallen to 261 IU/liter. Shortly afterwards, the patient died of underlying disease.

Eosinophilia of 8 and 11%, respectively, was noted in two patients. Patient 27 developed drug fever on the 11th day of therapy, and fever resolved after discontinuation of drug 3 days later. Patient 31 developed pruritus, without eosinophilia or rash, which responded partially to an oral antihistamine. However, the pruritus did not fully resolve until 1 month after completion of antibiotic therapy.

Patient 42 experienced mild anorexia, which improved rapidly after moxalactam was stopped. One patient with mild chronic renal insufficiency experienced a decrease in hemoglobin, from 10.4 to 8.6 g/100 ml, during 9 days of treatment without evidence of hemolysis or a bleeding source. Patient 47 developed oral candidiasis.

Two patients developed mental confusion during treatment with moxalactam. Patient 41, an 80-year-old woman with serious underlying disease, became disoriented while receiving 91 mg/kg per day, almost twice the average dose used in the study. Patient 21, a 47-year-old woman with cervical carcinoma, became confused while receiving 50 mg/kg per day. Both patients continued to be confused for at least 1 month after moxalactam was discontinued. In addition, both continued to receive other drugs, though not in doses ordinarily considered excessive.

Overall, 19 patients developed some adverse reaction while receiving moxalactam. In only one instance, however, did the reaction necessitate discontinuation of the drug (patient 27). Most of the side effects were mild and resolved after completion of therapy. As noted, the majority of the patients were older, were seriously ill before initiation of therapy, and had one or more underlying diseases; most were also receiving additional medications.

Tolerance to parenteral administration. Patients who received intravenous moxalactam experienced no phlebitis and reported no pain during infusion. This is in agreement with an earlier published clinical study of moxalactam therapy (9). Patients 42 and 44 received deep intramuscular moxalactam for 3 and 6 weeks, respectively. No undue local reactions were experienced. Patient 42 noted mild dysesthesia on her right thigh where injections had been given repeatedly. The dysesthesia improved gradually when the injection sites were changed.

Bacterial susceptibility. Table 6 lists the 71 bacterial isolates obtained from the 50 patients in this study. A previous study (3) indicated bacterial strains inhibited by 8 μg or less of moxalactam per ml may be considered susceptible, those with MICs of 16 to 32 μg/ml are intermediate, and those with MICs greater than or equal to 64 μg/ml are resistant. These MIC values correspond to Kirby-Bauer disk zone sizes of ≥23 mm (susceptible), 15 to 22 mm (intermediate), and ≤14 mm (resistant). By these criteria 54 of the 71 strains were susceptible, 15 were intermediate, and 2 were resistant. Three patients (15, 32, and 46) with *P. aeruginosa* infection caused by strains of intermediate susceptibility were treated with moxalactam alone. Two improved, and one patient (46) died suddenly while improving clinically. Patient 16 had disease caused by *P. aeruginosa* which became more resistant during therapy (MIC of 12.5 μg/ml initially and 250 μg/ml after treatment) and *Serratia marcescens*. Moxlactam was combined with an aminoglycoside to which the *P. aeruginosa* isolate was susceptible but to which the serratia was not. Patient 30 had polymicrobial bacteremia caused by *Streptococcus pneumoniae* and *P. fluorescens*. The latter was of intermediate susceptibility to moxalactam.

Two patients, in addition to patient 16, demonstrated emergence of resistant *P. aeruginosa* during therapy with moxalactam. Patient 8, who had an indwelling Foley catheter and received

TABLE 6. *Susceptibilities of isolates to moxalactam*

Organism	No. of isolates	MIC (μg/ml)	
		Median	Range
Gram-positive cocci			
Staphylococcus aureus	3	6.25 (all)	
Streptococcus pneumoniae	11	0.39	0.10–0.39
Streptococcus pyogenes	1	0.39	
Group B *Streptococcus*	2	6.25	
Viridans *Streptococcus*	1	1.56	
Gram-positive bacilli			
Diphtheroids	1	0.78	
Lactobacillus	1	12.5	
Gram-negative bacilli			
Escherichia coli	10	0.20	0.10–6.25
Klebsiella pneumoniae	5	0.39	0.39–0.78
Enterobacter sp.	4	0.78	0.10–6.25
Serratia marcescens	11	1.56	0.20–6.25
Proteus mirabilis	5	1.56	0.39–6.25
Pseudomonas aeruginosa	5	250	12.5–1,000
P. maltophilia	1	1.56	
P. fluorescens	2	1.56	12.5–25
Aeromonas hydrophilia	1	250	
Acinetobacter calcoaceticus	2		25–50
Haemophilus influenzae	3	0.39	0.05–0.78
Citrobacter diversus	2		0.78, 6.25
Total	71		

moxalactam for serratia bacteremia, developed a subsequent urinary tract infection with *P. aeruginosa* resistant to moxalactam; it responded subsequently to tobramycin. Patient 34 presented with a pneumonia caused by *Proteus mirabilis* and *Enterobacter aerogenes*. After 10 days of treatment with moxalactam, the patient had clinically and radiologically improved, but *P. aeruginosa* resistant to moxalactam was cultured from sputum. No additional antibiotics were added, and the pneumonia resolved.

We treated nine patients with infectious disorders caused by multiresistant gram-negative bacilli. Patients 1, 2, 3, 8, 16, 20, and 21 developed infection with a strain of *Serratia marcescens* resistant to amikacin, gentamicin, tobramycin, carbenicillin, and cefoxitin. It is probable some of these cases represent a nosocomial outbreak caused by the same strain of serratia. Patient 42 had osteomyelitis, and one of the etiological bacteria, a strain of *Pseudomonas maltophilia*, was resistant to amikacin, gentamicin, tobramycin, cefoxitin, and carbenicillin and susceptible only to moxalactam. Patient 47 had pneumonia, and on multiple occasions *Proteus mirabilis* and *Klebsiella pneumoniae* were cultured from sputum. The klebsiella was resistant to gentamicin, tobramycin, cefoxitin, cefamandole, and carbenicillin and susceptible only to amikacin and moxalactam.

DISCUSSION

Moxalactam is one of a number of so-called third-generation cephalosporin antimicrobial agents which have recently become available for clinical trials. These compounds, which include cefoperazone, ceforanide, cefotaxime, ceftizoxime, and cefsulodin, exhibit a significantly increased spectrum of activity against many gram-negative bacilli, particularly *Enterobacteriaceae* (10, 12, 19). In addition, they broaden the spectrum of cephalosporins to include *P. aeruginosa*, serratia, and some acinetobacter strains. These third-generation cephalosporins are, in general, less active than penicillin G and semisynthetic penicillins against gram-positive microorganisms such as staphylococci and streptococci (18, 19). However, disease caused by these latter microorganisms has been sucessfully treated with moxalactam. Moxalactam has been shown to be effective in vitro against multiply resistant gram-negative bacilli (10) and against anaerobic microorganisms such as *Bacteroides fragilis* and *Clostridium perfringens* (4, 8, 12). It is also active against strains of *Legionella* (7). Moxalactam is not active against enterococci (11). A previous report from this laboratory (6) confirmed the effectiveness of moxalactam in vitro against gram-negative isolates from this institution and encouraged us to use the agent in a clinical trial.

For the most part, the microorganisms isolated from the patients included in this study were highly susceptible to moxalactam. By the current criteria for susceptibility, 54 of 72 strains were susceptible, 15 were intermediate, and only 2 were resistant. Moxalactam was especially useful in the management of disease caused by a multiresistant strain of *Serratia marcescens*.

The patients treated in this study are representative of the complex clinical problems encountered in a tertiary care institution. Many suffered serious underlying disorders, including 7 which could be classified as ultimately fatal and 43 as nonfatal. No patients with rapidly fatal underlying disease were treated with moxalactam. The infectious disorders included pneumonia, infective endocarditis, urinary tract infection with and without bacteremia, intraabdominal infection, soft tissue infection, meningitis, and osteomyelitis. Moxalactam should not be used for therapy of any bacterial infectious disorder when a safer, narrower-spectrum, less expensive agent is available. For example, in patients with presumed pneumococcal pneumonia, penicillin remains the agent of choice. Patients with pneumococcal disease who were begun on moxalactam when the precise etiology was unclear were continued on this agent to determine efficacy and toxicity. In practice, if a broad-spectrum agent is initially chosen for therapy and pneumococcus is found to be the etiological agent, one should change to standard therapy.

Results of studies of moxalactam therapy at 12 different medical centers in almost 440 patients were recently presented (D. Bauman, B. Holmes, B. Pollack, R. Beville, and W. J. Mogabgab, Program Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 370, 1980; S. A. Gall, W. A. Addison, and G. B. Hill, 20th ICAAC, abstr. no. 373; H. Giamarellou, J. Tsagarakis, and G. K. Daikos, 20th ICAAC, abstr. no. 364; M. Kramer, W. El-Sadr, P. Tee, A. Pollock, M. S. Simberkoff, and J. J. Rahal, Jr., 20th ICAAC, abstr. no. 374; A. Lentnek, L. Kidd, and R. Ryan, 20th ICAAC, abstr. no. 369; R. V. McCloskey and R. Goren, 20th ICAAC, abstr. no. 366; R. G. Penn, L. C. Preheim, C. C. Sanders, and W. E. Sanders, Jr., 20th ICAAC, abstr. no. 375; C. Perlino, D. Jones, and S. McGlohn, 20th ICAAC, abstr. no. 372; R. Platt, S. L. Ehrlich, J. E. Pennington, and E. H. Kass, 20th ICAAC, abstr. no. 371; C. B. Savitch, R. Lowe, R. Jacobs, J. E. Conte, Jr., S. Barriere,

and J. Mills, 20th ICAAC, abstr. no. 367; S. Srinivasan, E. L. Francke, and H. C. Neu, 20th ICAAC, abstr. no. 365; L. S. Young, T. O. Kurtz, D. Winston, and R. W. Busuttil, 20th ICAAC, abstr. no. 368). The infectious disorders included lower respiratory infection in 175 patients, urinary tract infection in 102, and bacteremia in approximately 50. In general, the outcome of moxalactam therapy in these preliminary reports was good, with an 85% overall cure rate. Side effects reported included eosinophilia, mild abnormalities of liver function, and mild intolerance to parenteral therapy. An important problem described in some of the reports was the emergence during therapy of resistant bacteria, particularly strains of *P. aeruginosa*. Only one patient in our study, patient 16, demonstrated a change in the susceptibility of an infecting bacterial species repeatedly isolated from bone during a treatment course of 3 months. Superinfection occurred in one other case (42), a patient who also received a prolonged course of therapy.

The results in our 23 patients with pneumonia together with the 175 cases previously reported confirm the general effectiveness of moxalactam in lower respiratory tract infection. It remains unclear whether superinfection with resistant microorganisms or emergence of resistance among bacteria already present will be a serious problem during therapy with moxalactam. In our study, these complications occurred in three patients. The bacteriological and clinical outcomes of our other patients treated with moxalactam were also very good. Bacteriological cure was documented in 45 of 50 patients, and clinical cure was achieved in 48 of 50.

We were particularly gratified by the response to moxalactam therapy of patients with bacteremic illnesses including pyelonephritis, serious intraabdominal disease, burns, and infective endocarditis. Clinical cures were obtained in 16 of our 17 patients. We generally treated bacteremic patients for at least 2 weeks unless there was evidence of intravascular infection.

The effectiveness of moxalactam in our one patient with gram-negative meningitis is noteworthy. Reports of therapy of experimental meningitis in rabbits and infant rats (5, 16) and in six patients with gram-negative meningitis (13; Kramer et al., 20th ICAAC, abstr. no. 374; Srivivasan et al., 20th ICAAC, abstr. no. 365) have provided optimism among pediatricians that moxalactam will provide an effective therapy for infants with gram-negative bacterial meningitis. Cerebrospinal fluid levels of moxalactam after intravenous administration to neonates appear to provide quite adequate concentrations against most gram-negative bacilli (17). In contrast, a recent abstract describes a patient who developed pneumococcal meningitis complicating pneumococcal pneumonia while receiving moxalactam therapy (Perlino et al., 20th ICAAC, abstr. no 372). In our judgment, moxalactam should not be used alone for treatment of meningeal infection unless susceptibility of the infecting microorganism can be documented and adequate cerbrospinal fluid levels can be confirmed by laboratory testing.

The toxicity of moxalactam may be compared and contrasted with that associated with cefamandole therapy since these two antimicrobial agents are relatively similar. Previous studies with cefamandole have indicated phlebitis associated with intravenous administration in 1 to 10% of patients. Eosinophilia occurred in 15% of patients in one study (15), and abnormal liver function tests were present in 14 to 24%. In this series, moxalactam administration was associated with no instance of phlebitis, whereas eosinophila and abnormal liver function tests were found in 4 and 22% of patients, respectively. Importantly, moxalactam therapy had to be discontinued in only one patient.

The broad antibacterial spectrum of moxalactam, its relative lack of toxicity, and the encouraging results of clinical trials such as this one will probably result in widespread consideration of the agent once it is released for general use. An important clinical decision in the management of patients with suspected or proven bacterial disorders will be whether or not moxalactam alone is adequate therapy before the infecting bacteria are isolated and identified. Patients who were granulocytopenic and therefore at risk for life-threatening disease caused by *P. aeruginosa* were not recruited into this clinical trial. Thirty percent of the strains of *P. aeruginosa* from this institution have MICs of moxalactam greater than 32 μg/ml. The number of patients in this series with infections involving *P. aeruginosa* is small, and several of these required treatment with aminoglycosides due to resistance to moxalactam. As a result, we do not feel justified in using moxalactam alone in granulocytopenic patients, nor would we recommend the use of moxalactam alone for other patients likely to have pseudomonas disease. We did not investigate in vitro or in vivo synergism or antagonism between moxalactam and other antimicrobial agents, such as the aminoglycosides. Although the combination of moxalactam and an aminoglycoside may be quite active against strains of *P. aeruginosa* with MICs greater than 32 μg/ml, until in vitro and in vivo data are available, "standard" regimens against pseu-

domonas such as carbenicillin or ticarcillin combined with gentamicin or tobramycin should be used.

We also advise that moxalactam therapy not be used for patients with serious intravascular infections caused by gram-positive microorganisms. There is no good clinical evidence presently available to indicate how effective moxalactam will be in this group. Patients with prosthetic valve endocarditis caused by *Staphylococcus epidermidis* or *S. aureus* are an especially vexing problem and should not routinely be treated with moxalactam until its efficacy in these disorders has been proven.

In contrast, moxalactam may prove very useful in bacterial disorders caused by more than one species. Cellulitis and intraabdominal infections due to aerobic and anaerobic bacteria should respond well to this agent alone, eliminating the necessity for aminoglycosides to treat resistant aerobic gram-negative bacilli and clindamycin or chloramphenicol to treat *Bacteroides fragilis*.

Many of the patients described in this report had disorders caused by bacteria which are susceptible to older and clinically proven agents. Penicillin G remains the drug of choice for pneumococcal disease, and urinary tract infection caused by "susceptible" *E. coli* can be managed with ampicillin. Moxalactam will probably be most valuable if clinicians restrict its use to initial therapy of bacterial disorders due to potentially resistant microorganisms and for follow-up treatment of difficult disorders such as pneumonia, osteomyelitis, and intraabdominal disease caused by resistant or multiple bacteria.

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