Clinical Evaluation of Moxalactam: Evidence of Decreased Efficacy in Gram-Positive Aerobic Infections

WILLIAM SALZER, P. SAMUEL PEGRAM, JR.,†* AND CHARLES E. MCCALL

Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27103

Received 23 August 1982/Accepted 10 February 1983

Moxalactam was used as initial, empirical therapy in 69 patients with a variety of serious bacterial infections, 32% of which were accompanied by bacteremia. Overall, the success rate was 83% and drug-related adverse effects were minimal. The drug was less efficacious in infections caused by aerobic gram-positive pathogens than it was in those caused by gram-negative pathogens. The following gram-positive organisms were associated with special problems during moxalactam therapy: *Streptococcus pneumoniae* (development of meningitis and a relapse of pneumonia with a more resistant strain), *Staphylococcus epidermidis* (in vivo emergence of moxalactam resistance), and the enterococci (failure of therapy and a fatal superinfection). Moxalactam performed well in infections caused by most gram-negative organisms, including aminoglycoside-resistant strains, but the previously reported emergence of gram-negative bacillary resistance to moxalactam during therapy was reconfirmed in our series with *Serratia marcescens*. The use of moxalactam in the treatment of gram-negative meningitis was further supported by a patient with meningitis-ventriculitis caused by *Bacteroides fragilis* who was cured with moxalactam after failure on chloramphenicol.

Moxalactam is a new β-lactam antibiotic with an exceptionally broad spectrum of activity which, coupled with a low reported toxicity, makes it a potential alternative to aminoglycosides (alone or in combination with other antibiotics) in the initial treatment of serious systemic infections. In comparison with most earlier β-lactams, moxalactam is generally more β-lactamase resistant and more active against multiple drug-resistant gram-negative organisms which are often associated with hospital-acquired infections (6, 21, 22). In addition, unlike first- and second-generation cephalosporins, the use of moxalactam is supported by pharmacokinetic and clinical efficacy studies in the therapy of gram-negative bacillary meningitis (3, 10, 16). To define the clinical utility and toxicity of moxalactam, we used this agent as initial therapy in a wide variety of infections caused by susceptible gram-positive and gram-negative organisms. Our results constitute the first report of in vivo development of moxalactam resistance by a gram-positive organism (*Staphylococcus epidermidis*) and the first successfully treated case of *Bacteroides fragilis* meningitis with moxalactam; in addition, the development of pneumococcal meningitis, the emergence of in vivo resistance by gram-negative pathogens, and the establishment of enterococcal superinfection during moxalactam therapy observed in our study confirm previously published reports of these potentially significant clinical phenomena.

MATERIALS AND METHODS

**Patient selection.** All patients were hospitalized at North Carolina Baptist Hospital, Winston-Salem, and had suspected or proven infections in which moxalactam would be expected to be safe and effective therapy. Patients with a prior history of allergy to cephalosporins or anaphylactic reactions to penicillin drugs were excluded. A history of rash alone after penicillin administration was not considered an exclusion. Patients who had been treated with antibiotics in the previous 72 h were excluded unless a resistant pathogen was isolated. The study, including possible adverse effects, was explained to all patients or family members, and informed consent was obtained in each case.

**Drug administration.** Moxalactam (kindly provided by Eli Lilly & Co.) was given intravenously or intramuscularly in dosages ranging from 500 mg every 8 h to 2 g every 4 h, depending on renal function and severity and site of infection. Dosage adjustment for renal failure was made according to previously described regimens for cefazolin (1).

**Drug levels.** Serum, cerebrospinal fluid (CSF), and peritoneal moxalactam levels, when obtained, were measured with a bioassay in which the microdilution technique was used with a susceptible strain of *Escherichia coli* Seattle (18).

† Address reprint requests to P. Samuel Pegram, Jr., Division of Infectious Diseases and Immunology, Bowman Gray School of Medicine, Winston-Salem, NC 27103.
Microbiological evaluation. Minimal inhibitory concentrations (MICs) of moxalactam and other antibiotics were measured by previously described broth dilution techniques for aerobes and anaerobes (14, 19).

Patient evaluation. Patients were admitted to the study if they had signs or symptoms consistent with acute bacterial infection. Patients with clinical evidence of infection without positive cultures were considered un evaluable, except for a few patients with pneumonia in whom a presumptive etiological diagnosis was made by appropriate respiratory secretion, Gram stain, and abnormal chest radiographs consistent with pneumonia. Patients were assessed clinically before, during, and after drug administration, and the study drug was discontinued if the investigators or the physicians caring for the patient determined no clinical response.

Laboratory studies. The following studies were performed before, after, and periodically during drug administration: complete blood count with differential, platelet estimation, blood urea nitrogen, serum creatinine, serum glutamic oxalacetic transaminase, serum bilirubin, alkaline phosphatase, and urinalysis. Appropriate roentgenograms were obtained when clinically indicated. Cultures of blood and apparent infection sites were obtained within 24 h before the onset of therapy in all patients. Positive culture sites were recultured 3 to 4 days after therapy was started and within 48 h of discontinuation of the study drug.

RESULTS

Of 87 patients who received moxalactam, 69 (79%) were considered evaluable. Of the 18 patients considered un evaluable, 5 had therapy for less than 48 h, 9 had negative cultures, and 4 had other antibiotics added to their regimen before moxalactam efficacy could be determined. Of the 69 evaluable patients, 36 were male and 33 were female. Their ages ranged from 3 months to 84 years, with a mean age of 52 years and a median age of 56 years. Duration of treatment ranged from 1 to 32 days. The majority of patients had one or more underlying conditions, including chronic renal failure (27%), history of corticosteroid or other immunosuppressive therapy (29%), diabetes mellitus (16%), chronic obstructive lung disease (16%), alcoholism (12%), congestive heart failure (12%), paraplegia (10%), malignancy (9%), and renal transplantation (4%).

Clinical response. Overall, 83% of the evaluable infections were cured, 13% were treatment failures, and 4% initially responded but subsequently relapsed (Table 1). Table 2 shows response rates according to infection site and bacterial organism isolated. The response rate ranged from 75% for peritonitis to 100% for abscess, joint, and soft tissue infections.

Bacteremias. There were 22 episodes of bacteremia, with 20 cures (91%). The sites of origin were abdomen (six), urinary tract (five), lung (four), skin (two), self-induced (two) (in the same patient 5 months apart), hemodialysis graft (one), and unknown (two). There were two episodes of polymicrobial bacteremia. The most common isolates were E. coli (eight cases) and staphylococcal species (six cases). Of the two failures, one was a 48-year-old male with chronic renal failure, diabetes mellitus, and osteomyelitis of the foot whose pretherapy blood cultures grew Staphylococcus aureus with a moxalactam MIC of 64 µg/ml; he did not respond clinically to moxalactam, was switched to nafcillin and tobramycin, and did well. The second failure was a 38-year-old alcoholic male with bacteremic pneumococcal pneumonia. CSF obtained on day 2 of therapy contained 24 leukocytes (62% polymorphonuclear) and normal glucose levels; culture and Gram stain were negative. On day 4 of therapy, a lumbar puncture was repeated because of continued fever and deteriorating mental status. Gram-positive cocci consistent with pneumococci were seen on Gram stain of the CSF, which had a glucose level of 0 mg/dl. Counterimmunoelectrophoresis performed on CSF was positive when pneumococcal organisms were used, but pneumococci were not cultured. Moxalactam levels in CSF from the second tap were >32 but <64 µg/ml. The moxalactam MIC for a Streptococcus pneumoniae blood isolate from this patient was 0.25 µg/ml. The patient was switched to intravenous penicillin G and recovered without neurologic sequelae.

Pulmonary infections. The 26 pulmonary infections included 25 cases of pneumonias and 1 case of empyema. Four of these infections occurred in patients who had bacteremia. Twenty-one patients (81%) were cured, four (15%) failed, and one had a relapse. One pneumococcal failure was described above. Another failure was a 54-year-old male with carcinoma of the lung with extensive metastases and pneumonia whose sputum cultures grew S. aureus (moxalactam MIC, 8 µg/ml). Despite a high dose of moxalactam (12 g/day) and supportive measures, the patient experienced a rapid downhill
course and expired after 3 days of therapy. The third failure was an 84-year-old female with acute renal failure, left lower lobe pneumonia, and empyema. Cultures of empyema fluid grew *E. coli* and *Staphylococcus epidermidis* with moxalactam MICs of 0.5 and 8 μg/ml, respectively. Repeat thoracentesis after 8 days of moxalactam therapy grew only *Staphylococcus epidermidis* with a moxalactam MIC of 64 μg/ml. Two weeks later, infectious pericarditis developed with impending tamponade. At thoracotomy, the empyema was no longer evident. Cultures of the pericardial fluid grew *Staphylococcus epidermidis* with a moxalactam MIC of 64 μg/ml. Moxalactam was discontinued at this point.

A 61-year-old female with morbid obesity and breast carcinoma became colonized with enterococci during moxalactam treatment of *Haemophilus influenzae* pneumonia. Five days after moxalactam therapy, she became febrile, and blood cultures yielded enterococci (moxalactam MIC, >64 μg/ml). She experienced a rapid downhill course and expired 48 h later.

The patient who apparently relapsed was a 68-year-old male with severe chronic obstructive pulmonary disease complicated by right middle lobe pneumonia due to *Streptococcus pneumoniae* (moxalactam MIC, 0.12 μg/ml). Moxalactam (3 g/day) was given for 9 days with clinical and radiological improvement. Two days after discontinuing moxalactam, the patient became febrile and hypotensive and was placed on tobramycin and ticarcillin. He died 4 days later, and at autopsy there was bilateral pneumonitis. Postmortem lung cultures grew *Streptococcus pneumoniae* with a moxalactam MIC of 2 μg/ml.

**Urinary tract infections.** There were 16 urinary tract infections. Five of these patients were bacteremic, and 11 had pyelonephritis based on the presence of bacteremia, urinary lactate dehydrogenase isoenzyme fractionation, or bladder washout (Fairley technique). One of the two relapses had acute myelocytic leukemia and a multiple drug-resistant *Serratia marcescens* urinary tract infection (moxalactam MIC, 16 μg/ml); after 14 days of moxalactam treatment, urine cultures became sterile. Seven days later, urine and blood cultures yielded *Serratia marcescens* with a moxalactam MIC of 64 μg/ml. This patient was successfully treated with amikacin. Moxalactam was successful in the treatment of seven patients with aminoglycoside-resistant organisms, including five different *Pseudomonas aeruginosa* isolates.

**Peritonitis.** Six of eight patients with peritonitis were treated successfully with moxalactam intravenously, and three were bacteremic. Peritonitis was related to indwelling peritoneal catheters for chronic dialysis in seven patients. The eighth patient was an alcoholic with spontaneous peritonitis due to *E. coli*. One failure involved a resistant enterococcus and the other a multiple drug-resistant diphtheroid.

**Meningitis.** One case of menigitis and ventriculitis due to *B. fragilis* occurring in a 3-month-old female with congenital hydrocephalus and associated with a ventriculo-peritoneal shunt

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**TABLE 2. Etiological organisms, site of infection, and response to moxalactam**

| Organism                              | Lung | Blood | CSF | Abscess-joint-skin | Peritoneum | Urine |
|---------------------------------------|------|-------|-----|-------------------|------------|------|
| *Haemophilus influenzae*               | 10/10| 1/1   |     | 3/3               | 1/1        | 5/5  |
| *Escherichia coli*                    | 2/2  | 8/8   |     |                   | 2/2        |      |
| *Staphylococcus epidermidis*          | 0/1  | 3/3   |     |                   | 1/1        | 2/2  |
| *Proteus morganii*                    | 1/1  |       |     |                   | 1/1        | 2/2  |
| *Peptococcus sp.*                     | 1/1  |       |     |                   | 1/1        | 2/2  |
| *Pseudomonas aeruginosa*              | 1/1  |       |     | 1/1               | 1/1        | 5/6  |
| *Serratia marcescens*                 | 9/11 | 1/2   |     | 3/3               | 1/1        | 1/2  |
| *Proteus mirabilis*                   | 4/5  | 2/3   |     | 2/2               | 1/1        | 2/2  |
| *Streptococcus pneumoniae*            |      |       |     |                   |            | 0/1  |
| *Neisseria gonorrhoeae*               |      |       |     |                   |            | 0/1  |
| *Staphylococcus aureus*               | 1/1  | 1/1   |     | 2/2               | 2/2        |      |
| Group D *streptococcus*               |      |       |     |                   | 1/1        | 1/1  |
| *Bacteroides fragilis*                | 2/2  | 1/1   |     | 2/2               | 1/1        | 1/1  |
| *Proteus rettgeri*                    | 1/1  |       |     | 2/2               | 1/1        | 1/1  |
| *Klebsiella pneumoniae*               | 1/1  |       |     | 1/1               | 1/1        | 1/1  |
| *Enterobacter cloacae*                |      |       |     |                   | 1/1        | 1/1  |

*a Certain patients appear in more than one category; there were 29 responses of 33 lung infections (88%), 20 of 22 blood (91%), 1 of 1 CSF (100%), 14 of 14 abcess-joint-skin (100%), 6 of 8 peritoneum (75%), and 12 of 16 urine (75%) infections.
was successfully treated with moxalactam. She was admitted with meningitis and placed empirically on intravenous nafcillin and chloramphenicol. Pretherapy CSF cultures grew *B. fragilis* with a chloramphenicol MIC of 8 μg/ml. After 6 days of therapy, CSF cultures continued to grow *B. fragilis*. The organism was susceptible to moxalactam, having an MIC of ≤1 μg/ml. The chloramphenicol and nafcillin were discontinued, and she was begun on moxalactam, 200 mg intravenously every 8 h (160 mg/kg per day). On this regimen, moxalactam levels were as follows: peak serum, 72 μg/ml; trough serum, 20 μg/ml; CSF (2 h after intravenous dose on two occasions), 7 and 20 μg/ml. The CSF of the patient was bactericidal at a 1:20 dilution against the organism. All subsequent CSF cultures were sterile. The patient was treated with moxalactam for a total of 19 days. One month after completion of therapy, her CSF remained sterile, and her ventriculo-peritoneal shunt was replaced.

**Adverse effects.** Eleven percent of the patients experienced adverse effects. An elevation of various liver function tests which was transient and unaccompanied by clinical manifestations or elevations in serum bilirubin occurred in six patients. Two patients had eosinophilia, one with a rash. Transient neutropenia occurred in an alcoholic after 8 days of moxalactam. There was one case of phlebitis related to drug administration. One case each of symptomatic candidal vaginitis and fatal enterococcal bacteremia developed in relation to moxalactam therapy and were considered superinfections. Three patients experienced bleeding episodes shortly after moxalactam therapy (two gastrointestinal and one epistaxis). Prothrombin time, partial thromboplastin time, and platelet counts were normal in all three patients, and it was presumed that these episodes were not related to moxalactam therapy. Bleeding times were not obtained.

**DISCUSSION**

Moxalactam is the first member of the 1-oxa-β-cephem class of β-lactam antibiotics. When compared with other third-generation cephalosporins, moxalactam has less gram-positive aerobic activity in vitro but is generally more active against anaerobes, including *B. fragilis* (15). In clinical studies, moxalactam has been effective as a single agent in the therapy of a wide variety of bacterial infections and has been especially successful in gram-negative bacillary meningitis (11, 15). Our study highlights certain problems which may occur with the use of moxalactam in gram-positive aerobic infections.

Gram-negative isolates from patients in this study were generally very susceptible to moxalactam. Assuming that an MIC of 32 μg/ml to be the upper limit of susceptibility, only 16% of these organisms were resistant. As has been the experience in other studies, many (40%) of our *P. aeruginosa* strains were resistant (2, 6–9, 21). *H. influenzae* and *Neisseria gonorrhoeae* isolates were uniformly susceptible to moxalactam.

Moxalactam was effective in vitro against most gram-positive organisms, except enterococci, all of which were resistant. Of 14 *Staphylococcus aureus* isolates, 12 were susceptible to 16 μg or less of moxalactam per ml; none had an MIC of less than 4 μg/ml. Against *Staphylococcus epidermidis*, moxalactam was less active, 5 of 10 isolates requiring more than 16 μg/ml for inhibition. This relative insusceptibility of *Staphylococcus epidermidis* to moxalactam has been reported previously (6). The nine *Streptococcus pneumoniae* isolates in this study were all susceptible to 4 μg or less of moxalactam per ml, but all isolates were more susceptible to penicillin G or cephalothin. Ward and Moellering examined the susceptibility of 54 pneumococcal isolates to 14 β-lactam antibiotics (20). For penicillin-susceptible strains, moxalactam and cefoxin were the least active of the drugs tested. Moxalactam was ineffectual against penicillin-resistant strains. In general, moxalactam is one of the least potent β-lactam antibiotics against gram-positive aerobic bacteria. This has been shown in in vitro comparisons with other β-lactam antibiotics against *Staphylococcus aureus* (2, 6–7, 9), *Streptococcus pyogenes* (2, 6, 7, 9, 20), and *Listeria monocytogenes* (7). The resistance of moxalactam to hydrolysis by β-lactamase elaborated by *Staphylococcus aureus* (4) and the infrequent production of this enzyme type by other gram-positive organisms argue against a β-lactamase enzymatic mechanism as an explanation of relative moxalactam insusceptibility in this population. It would seem more likely that moxalactam is less effective against gram-positive organisms because of decreased affinity for binding proteins in bacterial cell membranes, as has been shown for penicillin in penicillin-resistant pneumococci and for other β-lactam drugs in *Staphylococcus aureus* and *Streptococcus faecalis* (5).

Moxalactam as a single agent was effective in treating bacteremia in this and other studies (12, 13, 17). Of 22 patients, 20 (91%) were cured. Most of these patients had serious underlying illnesses, and many of the gram-negative isolates were resistant to cephalothin. In our series, both patients in whom moxalactam therapy failed had infections with gram-positive organisms; one patient was infected with resistant *Staphylococcus aureus* (MIC, 64 μg/ml), whereas another with bacteremic pneumococcal pneumonia developed pneumococcal meningitis.

In the treatment of pneumonia, moxalactam was moderately successful, curing 21 of 26 pa-
patients. A disturbing finding in this group was the documentation of a rise in the moxalactam MIC for gram-positive organisms from two patients during therapy. In a patient with empyema, moxalactam eradicated an initial *E. coli* isolate, but during therapy, *Staphylococcus epidermidis* was repeatedly cultured and associated with an increasing MIC from 8 to 64 μg/ml. Eventually, purulent pericarditis due to *Staphylococcus epidermidis* developed. The emergence of moxalactam resistance during therapy has been reported for gram-negative but not for gram-positive organisms (13, 17). In addition, one of our patients who relapsed with pneumococcal pneumonia after an apparently adequate course of moxalactam therapy demonstrated an increase in moxalactam MIC for pneumococci from 0.12 μg/ml pretherapy to 2 μg/ml postmortem. Relapse of pneumococcal pneumonia after therapy with moxalactam has been reported previously (C. Perlino, D. Jones, and S. McGlohn, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 372, 1980).

Moxalactam was very effective in treating urinary tract infections other than those caused by enterococci. The majority of our patients had either pyelonephritis or infections with multiple drug-resistant, hospital-acquired, gram-negative organisms. Most of our patients with *Pseudomonas* urinary tract infections had been on aminoglycosides and had developed aminoglycoside-resistant strains which were successfully eradicated by moxalactam. One patient with aminoglycoside-resistant *Serratia marcescens* pyelonephritis developed a moxalactam-resistant strain (MIC, 64 μg/ml) while receiving moxalactam and subsequently relapsed with a bacteremic urinary tract infection.

Moxalactam was effective in treating peritonitis, most of which was related to peritoneal dialysis and caused by staphylococcal species. Failures were noted only in patients with moxalactam-resistant organisms, including the enterococcus and a multiple drug-resistant diphtheroid.

Moxalactam is considered by many to be the drug of choice in the treatment of gram-negative bacillary meningitis (11, 15). Our patient with meningitis was an infant with a ventriculo-peritoneal shunt who developed meningitis and ventriculitis secondary to *B. fragilis* and in whom chloramphenicol therapy failed after the shunt was removed but who was cured with moxalactam.

In contrast to the encouraging experience in treating gram-negative meningitis with moxalactam, one of our patients apparently developed or had progression of pneumococcal meningitis while on moxalactam therapy for bacteremic pneumococcal pneumonia. The development of pneumococcal meningitis during moxalactam therapy has been reported previously (20th ICAAC, abstr. no. 372). In our patient, the level of moxalactam in CSF exceeded the moxalactam MIC for his pneumococcal blood isolate by over 100 times.

Moxalactam appears to be relatively nontoxic, and in our series an elevation of liver function tests was the most common side effect, occurring in 7% of the patients. One patient developed fatal enterococcal bacteremia after therapy, emphasizing the importance of monitoring colonization and superinfection by resistant organisms.

In summary, although moxalactam is a generally safe and effective agent in the treatment of a wide variety of infections caused by susceptible organisms, our data suggests that it is less efficacious in infections caused by aerobic gram-positive organisms than in those caused by gram-negative organisms. Pneumococci, enterococci, and staphylococci may be associated with special problems, including therapeutic failures, superinfections, and the in vivo development of resistance.

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