Moxalactam (LY127935) in Treatment of Meningitis Due to Gram-Negative Bacilli

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Moxalactam (LY127935; 6059S), a new broad-spectrum \(\beta\)-lactam antibiotic, was used successfully with an aminoglycoside in a patient with Serratia marcescens meningitis complicating a neurosurgical procedure. With a bioassay method, peak and trough serum and cerebrospinal fluid concentrations of moxalactam were determined during therapy. Mean peak and trough serum levels were 100.6 and 35.5 \(\mu\)g/ml, respectively. Corresponding mean peak and trough cerebrospinal fluid levels were 12.4 and 10.38 \(\mu\)g/ml. Cerebrospinal fluid levels of moxalactam exceeded the minimal bactericidal concentration for the infecting organism by more than 30-fold throughout therapy. No untoward effects of moxalactam were observed. Moxalactam may be a useful agent in the treatment of meningitis due to susceptible gram-negative bacilli.

Moxalactam (LY127935; 6059S), a new broad-spectrum \(\beta\)-lactam antibiotic, is active in vitro against a variety of gram-positive and gram-negative bacteria, including streptococci, staphylococci, Enterobacteriaceae, and Pseudomonas, as well as several species of anaerobic bacteria (1, 4, 5, 13). This agent is under current investigation in human subjects in the United States. A patient with a nosocomially acquired, gram-negative bacillary meningitis caused by Serratia marcescens resistant to multiple antibiotics afforded an opportunity for studying penetration of moxalactam into the cerebrospinal fluid (CSF).

CASE REPORT

A 53-year-old white woman, who underwent laminectomy of the fourth and fifth lumbar vertebrae (L4-5) at 15 years of age to drain an epidural abscess, noted the abrupt onset of severe low back pain after minimal spinal torsion. Pain persisted, and she was hospitalized. Radiographs and a bone scan were unrevealing. Headache and fever developed. The CSF disclosed an elevated protein level, hypoglycorrhachia, and neutrophilic pleocytosis. A Gram stain was negative, and a course of penicillin G was begun. One of three blood cultures yielded a penicillin-susceptible Staphylococcus aureus; CSF cultures were negative. Oxacillin and chloramphenicol were added. The patient failed to improve and was referred to the Medical College of Georgia Hospital for further evaluation. Upon admission, she complained of severe headache, low back pain, and right lower abdominal discomfort. She was febrile, confused, and tremulous, and she resisted anterior neck flexion. Brudzinski's and Kernig's signs were present, but no papilledema was observed. The abdomen was tense, with tenderness in the right lower quadrant. Bowel sounds were hypoactive. Rectal and pelvic examinations were unremarkable.

Oxacillin and chloramphenicol were continued in maximal doses, and isoniazid and rifampin were added. Laparoscopic examination to determine the cause of the abdominal pain was unrevealing. There was progressive improvement of all clinical findings. Chloramphenicol was discontinued after 14 days. Oxacillin was continued pending confirmation of susceptibility to penicillin G because of concern about a possible occult parameningeal staphylococcal focus of infection. Meningeal signs and confusion returned 48 h later. A repeat of the CSF examination disclosed chemical and cellular abnormalities similar to the initial findings, and chloramphenicol was reinstituted. A myelogram showed a block at L4. An emergency exploratory laminectomy disclosed only a thickened dura, a translucent arachnoid membrane, and evidence of local inflammation. The surgical wound was left open. Intraoperative cultures of paraspinal tissue yielded S. aureus with a minimal bactericidal concentration (MBC) of penicillin and oxacillin of \(\geq 0.05\) \(\mu\)g/ml. An additional 2 weeks of chloramphenicol and oxacillin resulted in marked improvement; the patient was discharged on phenoxymethyl penicillin (2 g per day) after a 3-day observation period.

Clinical signs and symptoms of meningitis returned 12 h after discharge, and the patient was readmitted. The CSF was cloudy. Gram-positive cocci were seen in stained smears. A CSF leak was suspected, and intravenous nafcillin, penicillin G, and chloramphenicol were begun. After transient improvement, the patient developed a generalized seizure, increasing headache, confusion, and nuchal rigidity. S. marcescens resistant to gentamicin (minimal inhibitory concentration [MIC], 50 \(\mu\)g/ml), amikacin (MIC, 12 \(\mu\)g/ml), carbencillin, chloramphenicol, and ceftoxitin, but susceptible to tobramycin (MIC, 1.2 \(\mu\)g/ml) and moxalactam (MIC and MBC, \(\geq 0.2\) \(\mu\)g/ml), was isolated from the CSF. No gram-positive organisms were recovered. Tobramycin (80 mg every 8 h) and moxalactam (2 g every 4 h) were given intravenously. A plastic cannula was inserted into the subarachnoid space at L1 and
connected to a closed sterile drainage system to decrease CSF leakage into the operative wound. Additional tobramycin (5 mg per day) was given intrathecally through this cannula. The patient showed dramatic clinical improvement by 48 h, with diminishing meningeal signs and complete mental clearing. The CSF cell count diminished rapidly, and cultures became sterile. CSF leakage continued throughout the 14-day therapy. Near the completion of therapy, another neutrophilic CSF pleocytosis was noted. Cultures yielded *Candida albicans*. The patient responded to 6 weeks of amphotericin B and flucytosine. The CSF leakage stopped, and the patient remains well after 8 months.

MATERIALS AND METHODS

Blood and CSF samples were obtained just before a moxalactam dose and 1 h afterward. According to the manufacturer, peak serum concentrations are to be expected 20 min after an intravenous infusion. Data concerning peak CSF concentrations are not available. The 1-h serum and CSF concentrations are referred to as the peak concentrations to allow for the CSF equilibration of moxalactam. CSF samples were obtained through the plastic cannula. All samples were placed immediately into an ice bath, processed, and stored at −60°C for batch testing. The effect of such storage on antibiotic concentrations in serum or CSF was not determined.

Serum and CSF moxalactam concentrations were bioassayed as suggested by the manufacturer, using *Escherichia coli* ATCC 10536. The assays were run in quadruplicate. Standards were prepared in normal human serum or 0.1 M potassium phosphate buffer (pH 6.0) for spinal fluid determinations. Potassium phosphate buffer was chosen as the diluent for the construction of the standard curves of CSF concentrations principally because of the instability of moxalactam. The large amount of human CSF needed for the daily preparation of standards was unavailable. Filter paper disks 0.25 in. (ca. 0.63 cm) in diameter were saturated with 20 μl of moxalactam at concentrations of 1.0, 2.5, 5.0, and 10.0 μg/ml. Blank filter paper disks were then saturated with 20 μl of test serum or CSF. Disks were placed on 20 ml of seeded agar in petri dishes (150 mm by 15 mm) and incubated at 30°C overnight; zone diameters were then measured, and a standard curve was constructed. Zone diameters for standards and test sera or CSF did not vary significantly among the four determinations. All test samples were treated with cellulose phosphate powder to remove aminoglycosides before testing (12). To ensure the reliability of this method, serum and phosphate buffer containing 24 μg of tobramycin per ml were tested before and after treatment with cellulose phosphate powder. The treated tobramycin standards showed no zones of inhibition against the test organism.

RESULTS

The mean peak serum moxalactam level after a 2-g intravenous dose was 100.6 μg/ml (range, 89 to 150 μg/ml) (Table 1). The explanation for the isolated peak level of 150 μg/ml, a value greater than the mean of the other available peak serum levels (90.8 μg/ml) by a factor of 1.65, is not clear. Possibilities include serum collection before equilibration in the circulation, inadvertent excessive dosing, alteration in renal clearance of the drug, or laboratory error. There was no other evidence that the drug accumulated during therapy. This dosage produced a mean peak CSF moxalactam level of 12.4 μg/ml (range, 10.1 to 14.5 μg/ml). This mean level is 62-fold higher than the MBC for the strain of *S. marcescens* causing the meningitis. Moreover, trough moxalactam levels in CSF before dosing ranged from 6.7 to 14.5 μg/ml (mean 10.38 μg/ml). Corresponding trough serum levels ranged from 32 to 51 μg/ml (mean 35.5 μg/ml). In this patient, CSF levels of moxalactam exceeded the MBC for the infecting organism by a factor of at least 33.5 in all samples obtained during treatment.

DISCUSSION

Meningitis due to gram-negative bacilli is being reported with increasing frequency (2). This infection is generally nosocomially acquired in all but neonates and accounts for less than 5% of bacterial meningitis (8). Commonly used antimicrobial agents have included chloramphenicol, carbenicillin, and aminoglycosides, alone or in combination. The concentrations of chloramphenicol achievable in CSF are independent of the presence of inflammation but are only one-half to one-third those of corresponding serum levels (9). Kirby-Bauer determinations of susceptibility to chloramphenicol are based upon achievable serum levels and may be misleading when applied to a gram-negative bacillus causing meningitis. Higher and potentially more toxic doses of this agent may be required for effective treatment (6). These considerations coupled with the bacteriostatic nature of the compound make chloramphenicol less than ideal for the therapy of meningitis due to gram-negative bacilli. The penetration of first-generation cephalosporins into CSF is unpredictable, and use of these agents has been generally discouraged. Although studies documenting therapeutic concentrations of cefamandole in CSF generated initial enthusiasm for this compound (10), failures in the treatment of *Haemophilus influenzae* meningitis (11) suggest caution in its use in meningitis due to gram-negative bacilli. The CSF penetration of the cephamycin compound cefoxitin has been studied recently (3). The authors concluded that, in a dosage of 12 g daily with probenecid, therapeutic concentrations against *E. coli*, *Klebsiella*, and *Proteus* could be...
regularly achieved. The poor penetration of aminoglycosides into CSF and the lack of therapeutically achievable concentrations of these agents in ventricular fluid after intralumbar administration are well known (6). Since ventriculitis is common in meningitis due to gram-negative bacilli, strong consideration must be given to potentially dangerous neurosurgical procedures to provide ventricular access for the delivery of an aminoglycoside (6). For these reasons, an antimicrobial agent which can be given safely and which penetrates into CSF in bactericidal concentrations is desirable.

In light of the negative cultures of CSF, the etiology of the patient’s original episode of meningitis remains speculative. The isolation of a penicillin-susceptible *S. aureus* from a blood culture and subsequently from paraspinous tissue at surgery suggests a parameningeal source of infection dormant for 38 years. The cause of the spinal fluid block was likely to have been related to the previous surgery. The development of a CSF leak at the operative site very likely resulted in at least two episodes of nosocomial meningitis.

The response of this patient to a parenteral and intralumbar aminoglycoside in combination with moxalactam was dramatic. Moribund at the outset of therapy, the patient was alert and conversant within 48 h. Therapeutic concentrations of tobramycin in CSF (mean peak, 69.25 µg/ml; mean trough, 5.57 µg/ml) were also documented throughout therapy. Thus, it is impossible to determine the contribution of either agent to the rapid clinical response. Nevertheless, a 2-g intravenous dose of moxalactam given every 4 h resulted in CSF levels which exceeded the MBC for the infecting strain of *S. marcescens* by 30- to 60-fold. The possibility that the presence of an indwelling cannula favorably affected the levels of moxalactam achievable in CSF must be acknowledged, although recent data (7) support the contention that therapeutic concentrations of moxalactam are attainable in the absence of such devices. No untoward effects of the compound on hematopoietic, eighth cranial nerve, or renal function were observed during treatment in this individual.

- The occurrence of candidal meningitis in this patient toward the end of moxalactam and tobramycin therapy was disturbing. This complication was not surprising in light of the broad antibacterial spectrum of the combination, the persistent CSF leak into an open surgical wound, and the indwelling cannula in the subarachnoid space. Such an occurrence would be anticipated with other broad-spectrum antibiotics as well. It is of interest that the highest CSF peak and trough concentrations of moxalactam were observed after the development of candidal meningitis and evidence of increasing CSF neutrophil pleocytosis (Table 1). A trend is apparent, but the suggestion of inflammation-dependent penetration of moxalactam into CSF remains purely speculative.

- These data indicate that the agent could have been safely administered alone for this infection. In vitro data (1, 4, 5, 13) and similarly impressive responses of other types of infections due to gram-negative bacilli (unpublished data) suggest that controlled clinical trials be undertaken comparing the combination of an aminoglycoside and moxalactam with moxalactam alone in the treatment of meningitis due to susceptible gram-negative bacilli.

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**LITERATURE CITED**


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