Moxalactam Penetration into Cerebrospinal Fluid in Patients with Bacterial Meningitis

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Penetration of moxalactam into the cerebrospinal fluid was studied in 11 patients with bacterial meningitis undergoing treatment with other antibiotics. Moxalactam at a dose of 20 mg/kg was administered as three 30- to 45-min infusions at 8-h intervals, once between days 2 and 4 and a second time between days 11 and 20 of treatment with the other antibiotics. Serum and cerebrospinal fluid were sampled 60, 90, or 120 min after the third moxalactam dose for measurement of the concentration of this drug by high-performance liquid chromatography. The concentration of moxalactam in cerebrospinal fluid ranged from 1.5 to 11 μg/ml, depending on the sampling time and the time elapsed since the onset of the disease. These concentrations in cerebrospinal fluid were equal to or higher than the minimum inhibitor concentrations for Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae (including ampicillin-resistant strains), and most of the gram-negative bacilli except for Pseudomonas aeruginosa. These results show that moxalactam has good penetrability when the meninges are inflamed and that it might be considered in cases of bacterial meningitis when the susceptibility of the pathogen indicates its usefulness.

Moxalactam, a new β-lactam antibiotic, is active in vitro against most bacterial species that cause meningitis, including Escherichia coli, Klebsiella, and Proteus species and β-lactamase-producing strains of Haemophilus influenzae (5). Studies in animal models (1, 6) have shown that moxalactam readily diffuses into the cerebrospinal fluid (CSF). The results of these in vitro and animal studies led to the current evaluation of the penetration of moxalactam into the CSF of patients with bacterial meningitis undergoing concurrent treatment with other antibiotics.

MATERIALS AND METHODS

Patients. Eleven hospitalized patients with bacterial meningitis, one female and ten males, were included in the study. Their mean age was 46 years (range, 20 to 80 years). All had macroscopically purulent CSF with leukocyte counts ranging from 440 to 13,900 cells per mm³ and a predominance of polymorphonuclear leukocytes (55 to 100%). The concentration of protein in the CSF was elevated (100 to 700 mg/dl), and the ratio of glucose in CSF and blood was decreased in all of the patients.

Antibiotic treatment. Eight of the patients were under treatment with ampicillin in doses of 10 or 16 g daily. Two patients were receiving chloramphenicol at a daily dose of 50 mg/kg, and one patient was treated with a combination of vancomycin and amikacin at daily doses of 2 g and 15 mg/kg, respectively.

In addition to the above regimens, each patient received three 30- to 45-min infusions of 20 mg of moxalactam per kg at 8-h intervals. These doses were administered twice, once between days 2 and 4 and again between days 11 and 20 of treatment with the other antibiotics.

The nature of the study was explained to each patient, and informed consent was obtained.

Sampling and assay. The concentration of moxalactam in serum and CSF was measured in samples drawn 60, 90, or 120 min after the third moxalactam dose. In all cases lumbar puncture was performed only when clinically indicated; in no case was it done purely for the purpose of this study. All patients were monitored for possible adverse reactions.

The concentration of moxalactam in the serum and CSF was determined by high-performance liquid chromatography (4). Standard dilutions were prepared with drug-free plasma or CSF and stored at −80°C with unknown samples. No degradation of the drug was observed over a 6-month storage period. Isopropyl alcohol (2.5 ml) was added to 0.5 ml of a standard or unknown sample in a polypropylene tube, and this preparation was then mixed on a Vortex mixer and kept on a rotator mixer for 15 min. The tubes were centrifuged for 10 min at 2,000 × g and 4°C. A 2-ml volume of supernatant was extracted by 2.5 ml of a mixture of chloroform (100 ml) and isooamyl alcohol (4 ml), mixed for 15 min on a rotator mixer, and centrifuged for 10 min at 2,000 × g and 4°C. A 0.1-ml volume of supernatant was mixed with 0.1 ml of ammonium acetate (0.1 M, pH 5), and 0.1 ml of this solution was injected into the chromatograph. This last solution is stable for up to 16 h; other extraction steps are less stable (approximately 1 h).
High-performance liquid chromatography. The mobile phase of the chromatography procedure consisted of a reverse-phase system: acetonitrile-water (40:60, vol/vol) and PIC A (0.05 M tetrabutylammonium in phosphate buffer). The column was a RAD-PACK A. The flow rate was set at 2 ml/min. The detector was fitted at 280 nm on a 0.05 absorbance unit.

The retention time of moxalactam was 4.5 min in this system. The peak height representing the sum of the enantiomers of moxalactam was used for quantification. The limit of sensitivity was evaluated to be 0.5 μg/ml on a strip chart recorder. The reproducibility and recovery error of the procedure were less than 10% under these conditions.

RESULTS

The concentration of moxalactam in the serum and CSF is shown in Table 1. The concentration of moxalactam in both CSF and serum at each of the sampling periods varied from patient to patient. The mean concentrations of this drug found in the CSF between days 2 and 4, when the meninges were the most inflamed were somewhat larger than the mean concentrations found between days 11 and 20, when the meninges were supposedly healed. By the Student t test for paired differences, the difference was not significant at any sampling time.

Although all of the patients were followed for adverse reactions to moxalactam, none was noted. Because moxalactam was administered only intermittently, no attempt was made to evaluate its contribution to control of the disease.

DISCUSSION

The concentration of moxalactam in the CSF of all of the patients in this study was equal to or higher than the reported minimum inhibitory concentration of this drug for meningococci, pneumococci, and H. influenzae type b (5). Potentially, therefore, moxalactam might replace ampicillin or penicillin in the treatment of infections with these organisms. The concentration of moxalactam in the CSF of most of the patients in this study was also within the therapeutic range against the gram-negative bacilli responsible for meningitis, specifically E. coli, Klebsiella, and Proteus species. These concentrations were achieved with low dosages (60 mg of moxalactam per kg daily); with the larger dosages (up to 300 mg/kg per day) delivered to pediatric patients, a greater concentration of moxalactam in the CSF could be expected.

Cordera and Pekarek (1) found that moxalactam penetrated the CSF of both normal infant rats and those with experimentally induced H. influenzae type b meningitis. The concentration in the CSF was approximately 10% of that in the blood of the same animal. Schaad et al. (6) found that moxalactam readily penetrated the CSF of rabbits with experimentally induced E. coli meningitis, but penetrated the CSF of normal rabbits to a lesser degree. Thus, the concentration of moxalactam in the CSF was 23% of that in the serum in rabbits with meningitis, compared with 1.4% in uninfected healthy rabbits.
Landesman et al. (3) observed that CSF trough levels in patients with bacterial meningitis who received 2 g of moxalactam intravenously every 8 h were 6 μg/ml or greater; CSF levels at approximately 2.5 h after administration of the drug ranged from 25 to 39 μg/ml.

In a study by Kaplan et al. (2), the mean concentration of moxalactam in the CSF of children with bacterial meningitis was 5.7 μg/ml (range, 8.0 to 17.3 μg/ml) after three 50-mg/kg doses at 8-h intervals; the mean CSF-to-serum concentration percentage was 18.5% (range, 2.0 to 61%) for all of the children on any day of therapy or at any hour after administration of the last dose.

Schaad et al. (7) found that the concentration of moxalactam in the CSF of infants with bacterial meningitis or neonatal sepsis ranged from 2.3 to 33.7 μg/ml (mean, 14.3 μg/ml) after repeated doses (50 mg/kg every 12 h) at 1 to 2 h after the dose. The CSF-to-serum concentration percentages ranged from 11 to 50% (mean, 30%).

Our results on the penetration of moxalactam into the CSF correlated well with the results obtained in both animals and humans with bacterial meningitis. They indicate that moxalactam penetrates well into the CSF of patients with bacterial meningitis.

LITERATURE CITED