Cerebrospinal Fluid Penetration of Moxalactam in Ventriculostomy Patients

RICHARD J. CREGER,1,2* RONALD I. COWAN,1,2 HOWARD S. NEARMAN,3,4 JEFFREY L. BLUMER,5 WARREN R. SELMAN,6 AND LARRY H. DANZIGER1,4

Departments of Pharmacy Services,1 Anesthesiology,3 Medicine,2 Pediatrics,5 Surgery,4 and Neurosurgery,6 University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio 44106

Received 3 June 1985/Accepted 26 September 1985

The cerebrospinal fluid penetration of moxalactam was simultaneously investigated in three patients with presumed bacterial meningitis. When ratios of simultaneously drawn ventriculostomy to serum moxalactam levels of 1, 2, 3, and 4 h were examined, the penetration ratios were 7.8 ± 2.4, 11.2 ± 1.3, 14.2 ± 2.5, and 15.0 ± 4.9%, respectively. These ratios were not statistically different from the penetration of moxalactam calculated by the area under the concentration-time curve technique (8.97 ± 1.89%).

Enteric gram-negative bacillary meningitis is a serious infection that often complicates neurosurgical procedures as well as head trauma (11). The mortality rate in adults approaches 50% and has failed to decrease since the advent of antibiotics (4). The disappointing results are, in part, due to the lack of adequate antibiotic penetration into the cerebrospinal fluid (CSF).

The introduction of broad-spectrum cephalosporins has renewed hope for the successful treatment of gram-negative meningitis. Positive results have been reported with moxalactam, cefotaxime, and ceftriaxone (3, 9). Moxalactam is a beta-lactam antibiotic active against most bacterial species causing gram-negative meningitis, including Escherichia coli, Klebsiella species, and beta-lactamase-producing strains of Hemophilus influenza. Although moxalactam has been shown to achieve adequate levels in CSF, there are data that tend to demonstrate a wide variability in its penetration (19, 20). Because of this controversy, we evaluated the degree of moxalactam CSF penetration (MP) in three acutely ill neurosurgical patients.

Three patients admitted to the Neurosurgery Service, University Hospitals of Cleveland, were referred for evaluation of MP. All patients had normal renal function and were being treated with moxalactam doses of 2 g every 4 h for presumed or culture-positive meningitis. All patients, because of their clinical conditions, had functional ventricular catheters from which ventricular fluid (VF) samples were obtained. To ensure that VF samples were from the ventricular system and not from the extraventricular drainage catheter, 1.5 ml of fluid was aspirated and discarded; 0.5 ml was then obtained for antibiotic concentration determination. Blood samples were simultaneously drawn from an arterial pressure catheter; 5 ml was aspirated and discarded, and 2 ml was then withdrawn for antibiotic concentration determination. VF and blood samples were obtained at eight time periods over the dosing interval, i.e., at time zero, the end of the infusion, and approximately 40 min, 60 min, 90 min, 2.5 h, 3 h, and 4 h after the drug infusion. All patients had been receiving moxalactam for at least 2 days before being studied and were assumed to be dosed to steady state. The blood and VF samples, once collected, were immediately centrifuged and decanted; the supernatant, either serum or VF, was stored at −70°C until assayed. Moxalactam quantification, both R and S epimers, was performed by using a high-pressure liquid chromatographic procedure (12).

Serum and VF concentration-time data were used to derive the noncompartmental pharmacokinetic parameters of total body clearance (CL) and volume of distribution at steady-state (Vss) (6). These parameters were calculated to account for steady-state conditions and infusion times (2, 17). The area under the concentration-time curve (AUCss) and under the first moment of the concentration-time curve (AUMCss) were evaluated over the dosing interval (τ) by using the trapezoidal rule (6). The following equations were utilized to calculate CL and Vss (2, 17).

\[
CL = \frac{\text{Dose}_{iv}}{\text{AUC}_{ss}}
\]

\[
V_{ss} = CL \cdot \left( \frac{\text{AUMC}_{ss} - T/2 + T \times C(\text{min})_{ss}}{\beta \times \text{AUC}_{ss}} \right) (2)
\]

where \( T \) is the time of intravenous infusion, \( \text{Dose}_{iv} \) is the intravenous dosage of moxalactam, \( C(\text{min})_{ss} \) is the minimum serum concentration at steady-state conditions, and \( \beta \) is the terminal-phase disposition rate constant, calculated from 0.693/\( \tau_{1/2,\beta} \).

MP is defined as follows:

\[
\text{MP} \% = \left( \frac{\text{AUC(VF)}_{ss}}{\text{AUC(serum)}_{ss}} \right) \times 100
\]

where \( \text{AUC(VF)}_{ss} \) is the area under the VF moxalactam concentration-time curve. MP with \( \text{AUC}_{ss} \) and concentration ratios was statistically evaluated by using one-way analysis of variance with a level of significance of 0.05.

The serum and VF concentration-time curves are displayed in Fig. 1. The concentration of moxalactam in both VF and serum show interpatient variation, although all received the same moxalactam dose. Pertinent pharmacokinetic parameters from moxalactam are listed in Table 1. These data are consistent with previous literature and validate the accuracy of the AUC determination (10, 18). Lag times before increases in VF concentrations were observed in patients 1 and 2. These lag times appeared to correlate with extended infusion periods of 23 and 35 min, respectively. Patient 3, who received the drug over 10 min, exhibited no lag time. The MP based on \( \text{AUC}_{ss} \) ranged from 5.65 to 12.2%, with a mean of 8.97 ± 1.89%. Calculation of the mean MP, with the ratio of VF to serum samples obtained at 1, 2, 3, and 4 h after the start of the antibiotic infusions, yielded mean values of 7.8 ± 2.4, 11.2 ± 1.3, 14.2

* Corresponding author.


\[ \text{MP at 1, 2, 3, and 4 h were not statistically different from the MP calculated by using the AUC technique.} \]

MP after intravenous administration has been reported to range from 0 to 186\% (5, 7-9, 13, 16, 19, 20). Although the majority of literature shows MP to be high, Thirumoorthi et al. found MP to be highly variable and less reliable than others and recommended caution in its use alone in the evaluation and treatment of meningitis (19).

To date, penetration calculated during the entire dosing interval has only been evaluated in the animal model and in selected patients treated with ceftazidine (14, 15). These studies suggested that calculations based on infusion and AUC ratios are the most appropriate techniques to be used for evaluating the penetration of antibiotics.

Bergan recently suggested that the ability of an antibiotic to penetrate into a specific fluid is best evaluated by use of the ratio of the AUC for an antibiotic in the peripheral locus to the AUC for serum (1). Most published penetration data are calculated from a single CSF-to-serum concentration ratio and not from AUC ratios (7, 8, 19). The analysis of these three patients over a single dosing interval shows that moxalactam ventricular concentrations are above the usual MICs for the most common gram-negative bacilli which are seen in meningitis (20). The question of when to draw simultaneous VF and serum samples to evaluate penetration has never been determined. Our data show that when dosing moxalactam at 4-h intervals there is no difference between MP calculated from the ratio of specifically timed VF and serum levels compared with that determined with AUC data. This observation, however, may not be true for dosing intervals of 6 and 8 h.

An interesting anomaly was discovered on close evaluation of the data. Patients 1 and 2, who had infusion times of

\[ \text{TABLE 1. Moxalactam pharmacokinetic parameters and MP} \]

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Wt (kg)</th>
<th>CL (ml/min · kg)</th>
<th>Vm (liters/kg)</th>
<th>MP (%)</th>
<th>MP ratio (CFS/serum concn. [10^6]) (%) at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td>1</td>
<td>75</td>
<td>1.20</td>
<td>0.211</td>
<td>12.2</td>
<td>12.5</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>1.79</td>
<td>0.298</td>
<td>9.05</td>
<td>6.2</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>1.88</td>
<td>0.262</td>
<td>5.65</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Mean ± SEM 59 ± 8 1.62 ± 0.21 0.257 ± 0.025 8.97 ± 1.89 7.8 ± 2.4 11.2 ± 1.3 14.2 ± 2.5 15.0 ± 4.9
23 and 35 min, respectively, both exhibited a lag phase before VF concentrations began to rise. Although unsubstantiated, we feel that this lag phase may be secondary to the prolonged infusion times in these patients. It is possible that this would be seen in other patients with extended infusion times, but this has never been systematically evaluated.

Our results in evaluating the penetration of moxalactam into the VF show that adequate penetration occurs over the entire dosing interval. We feel that, because of its penetration, moxalactam is useful for patients with bacterial meningitis caused by moxalactam-sensitive organisms.

LITERATURE CITED