Developmental Pharmacokinetics of Moxalactam

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Received 15 April 1983/Accepted 6 July 1983

A pharmacokinetic evaluation of moxalactam was performed with 30 infants and children with documented or suspected bacterial infections arising outside the central nervous system. Each child received 50 mg of moxalactam per kg infused intravenously over a period of 15 min every 8 h. A total of 26 children were studied after receiving the first dose; 20 of these, along with 4 additional patients, were evaluated after receiving continuous therapy for at least 3 days. After the first dose, the elimination half-life, apparent volume of distribution, and plasma clearance averaged 1.59 h, 0.331 liter/kg, and 100.9 ml/min per 1.73 m², respectively. The biodistribution of the moxalactam epimers was also evaluated, with similar overall results. No differences in pharmacokinetic parameters were observed when the first-dose values were compared with those obtained at the steady state. Age-dependent changes in moxalactam elimination were observed for children of ≤1 year of age, suggesting that a dosage reduction may be necessary for children of ≤2 months of age.

Moxalactam is a 1-oxa-β-lactam possessing a broad spectrum of antibacterial activity (2, 11, 16). Recent studies of both adult (4, 8) and pediatric (5, 6, 12, 15) patients have demonstrated the efficacy of the drug in the management of a variety of acute and chronic infections. However, despite the antimicrobial efficacy of moxalactam, rational dosing recommendations for the treatment of serious infections in infants and children are lacking.

To date, moxalactam dosing in these patients has been largely empiric. Pharmacokinetic evaluations of children have been limited and primarily involve first-dose evaluations. The purpose of the present investigation was to describe the first-dose and steady-state pharmacokinetics of moxalactam in seriously ill infants and children. Such an analysis should permit the development of rational dosing recommendations for moxalactam in this patient population.


MATERIALS AND METHODS

Subjects. Infants and children admitted to Rainbow Babies and Childrens Hospital with presumed or documented bacterial infections arising outside the central nervous system were eligible for enrollment. The study protocol and consent form were approved by the Institutional Review Board for Human Subject Investigation of the University Hospitals of Cleveland. Written informed consent was obtained from each family, patient, or both. No child received concurrent antibiotic therapy.

Drug administration and pharmacokinetic evaluation. Moxalactam (disodium salt) was obtained as a sterile crystalline powder from Eli Lilly & Co., Indianapolis, Ind. The powder was reconstituted with 5 to 10 ml of 5% dextrose in water or normal saline solution. Each child received a dose of 50 mg of moxalactam per kg dissolved in a minimum of 10 ml (usually 25 to 30 ml) of 5% dextrose in water; the dose was infused intravenously over a period of 15 min. The dose of moxalactam was repeated every 8 h for a total daily dose of 150 mg of moxalactam per kg.

Venous blood samples (minimum, 0.5 ml) for the determination of moxalactam in serum and for pharmacokinetic evaluation were obtained at 0, 0.25, 0.5, 1, 2, 3, 6, and 8 h after the beginning of the infusion. Blood was collected in sterile glass tubes, allowed to clot on ice, and immediately centrifuged. Serum was removed and stored at −70°C until analyzed.

Concentrations of moxalactam in serum were determined by high-pressure liquid chromatography after protein precipitation with methanol (9). Chromatography was performed on an MCH 10 column, using a mobile phase consisting of 5% acetonitrile–95% of 0.09 M ammonium citrate (pH 6.5) flowing at 1 ml/min. The column temperature was maintained at 30°C with a heater block, and the effluent was monitored at 270 nm. Under these conditions, the limit of moxalactam detectability was 2 µg/ml, with a linear range of up to 400 µg/ml. The between-day coefficients of variation for the sum of the epimers at 200 and 20 µg/ml were 3.1 and 10.7%, respectively.
Concentrations of moxalactam in serum (R epimer, S epimer, and R + S) were plotted against time on a semilogarithmic scale. The biodisposition of moxalactam was characterized, and the elimination rate constant (Kd), elimination half-life (t1/2), apparent volume of distribution (Vd), and plasma clearance (Cl) were calculated using a one-compartment pharmacokinetic model by the method of Sawchuck and Zaske (13) and Sawchuck et al. (14). Statistical analysis was performed using the unpaired Student t test (1).

RESULTS

Thirty patients ranging in age from 7 days to 26.3 years were studied. A total of 26 patients were evaluated after receiving the first dose, and 20 of these patients were reevaluated after receiving the drug every 8 h for at least 3 days. An additional four patients were evaluated only under steady-state conditions.

Figure 1 depicts the overall moxalactam concentration-time curve for the 26 patients evaluated after the first dose of moxalactam. These data were analyzed using a one-compartment open model (13, 14) because insufficient datum points were obtainable during the distribution phase to warrant a more rigorous analysis. Table 1 shows the t1/2, Vd, and Cl determinations (means ± standard deviations) for moxalactam and its epimers after the administration of the first dose and again during steady-state conditions. When pharmacokinetic parameters obtained during these two dosing periods were compared, no significant differences were observed. The peak and trough moxalactam concentrations averaged 162.3 ± 45.1 and 6.7 ± 6.9 μg/ml after the first dose and 170.3 ± 54.6 and 8.6 ± 11.6 μg/ml during steady-state administration. Although substantial variation was observed between peak and trough concentrations in serum, minimal drug accumulation was observed for each individual patient. This degree of variation in concentrations of moxalactam in serum has been observed by others (6).

To assess developmental aspects of the biodisposition of moxalactam, patient pharmacokinetic data were further analyzed by dividing patients by age into three groups: (i) children of ≤1 year, (ii) children of >1 and <10 years, and (iii) children of >10 years (Table 2). The elimination t1/2 of moxalactam correlated inversely with age in all four groups but was only statistically significant for children of <1 year of age (P < 0.05). A similar, but positive, correlation was observed between the Cl of moxalactam and age. In children of <1 year of age, the Cl of moxalactam correlated directly (r = 0.883; P < 0.01) with age (Fig. 2). Figure 2C depicts the logarithmic increase observed in the Cl of moxalactam as a function of increasing age. The change in moxalactam Cl was not related to alterations in the Vd (Fig. 2B) but was a result of the age-related increase in the elimination of moxalactam (Fig. 2A). Interestingly, a negative correlation (r = −0.372; P < 0.05) was observed between the Vd and age for the entire group of patients.

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<th>Moiety</th>
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<td></td>
<td>t1/2 (h)</td>
<td>Vd (liter/kg)</td>
<td>Cl (ml/min per 1.73 m²)</td>
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<tr>
<td>Moxalactam</td>
<td>1.6 ± 0.6</td>
<td>1.7 ± 0.9</td>
<td>0.33 ± 0.11</td>
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<tr>
<td>R epimer</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.8</td>
<td>0.38 ± 0.14</td>
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<tr>
<td>S epimer</td>
<td>1.7 ± 0.6</td>
<td>1.8 ± 1.0</td>
<td>0.29 ± 0.1</td>
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DISCUSSION

The results of the present investigation revealed only minimal differences between the first-dose and the steady-state pharmacokinetics of moxalactam and its epimers in infants and children (Table 1). When moxalactam biodisposition in children of ≤1 year of age was compared with that observed in children of >1 year of age, the serum t1/2 was found to be significantly prolonged (P < 0.05), and the Cl was significantly reduced (P < 0.05).

The relationship of t1/2, Cl, and Vd in children of ≤1 year is shown in Fig. 2. The immaturity and variation in renal excretory development (7) are reflected by the reduced Cl and prolonged t1/2 during the first 2 months of life. After 2 months of age and as renal function matures, Cl increases and t1/2 decreases logarithmically to values observed with older infants and children. This significant inverse relationship between t1/2 and age (P < 0.05) for these infants is in agreement with the data of Schaad et al. (15) and is further supported by the positive relationship of Cl or Kd and age (P < 0.05; Table 2).

In children of ≤1 year of age, the Vd of moxalactam was larger than that observed in older children (Table 2). This reduction in the Vd of moxalactam in children of ≤1 year of age was most likely a result of the developmental changes observed with age in total body water content of neonates and infants (3). The variation observed in the Vd of moxalactam may also have been a result of the effects of the underlying disease state which has been reported with other drugs in adults but which has not been adequately evaluated in children (18).

Moxalactam is a mixture of R and S epimers: 52.6% R and 47.4% S. The pharmacokinetic evaluation of the R and S epimers is shown in Table 1. The t1/2 was slightly longer and the Vd and Cl were reduced for the S epimer as compared with the R epimer. Nahata et al. reported similar differences between the R and S epimers after a single dose of moxalactam in 12 infants and children ranging in age from 10 months to 3.8 years (10). However, their reported t1/2 is longer and their Cl is reduced for both the R and S epimers as compared with the values obtained for our patients. This difference is most likely the result of the age difference of the two study populations. The exact clinical significance of the individual epimer pharmacokinetics is unknown. The R epimer appears to be twice as active microbiologically in vitro as the S epimer (17). This difference, combined with the possible tissue diffusion differences between the epimers, needs to be evaluated.

The results of the present investigation suggest that in children of >1 year of age a dose of 50 mg of moxalactam per kg administered every 8 h will result in drug concentrations in serum which exceed the minimal inhibitory concentration for most susceptible pathogens throughout the entire dosing interval (data not shown). The only exceptions to this are some of the susceptible strains of Staphylococcus aureus (minimal inhibitory concentration, ≥4 μg/ml) and Pseudomonas aeruginosa (minimal inhibitory concentration, ≥16 μg/ml). For children between 2 and

FIG. 2. Ontogeny of moxalactam elimination. The developmental changes in moxalactam elimination kinetics were evaluated in infants during year 1 of life. Curves were fit to the datum points by computer. The relationship of both t1/2 and Cl to postnatal age was best described by a logarithmic relationship. Vd was relatively constant during year 1 of life.
12 months of age, a similar dosing regimen may be employed. Some drug accumulation may occur in these patients depending upon the degree of renal functional maturation present. In infants of ≤2 months of age, a 12-h dosing interval may be required to prevent excessive moxalactam accumulation.

ACKNOWLEDGMENTS

This work was supported in part by a grant from Eli Lilly & Co. and by a Pharmacology/Toxicology Center grant from the Rainbow Babies and Childrens Hospital Board of Trustees.

LITERATURE CITED


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<td>Cpmax</td>
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a Cpmax, Peak moxalactam concentration; Cl, clearance; V1, volume of distribution; V2, volume of distribution; Cl, clearance; Cpmax, peak moxalactam concentration.

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