Pharmacokinetics of Cefuroxime Axetil Suspension in Infants and Children

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The pharmacokinetics of cefuroxime axetil suspension in 28 infants and children, ranging in age from 3 months to 12 years (mean, 23 months), were studied. Mean maximum serum cefuroxime concentrations of 3.3, 5.1, and 7.0 μg/ml were achieved 3.6, 2.7, and 3.1 h after the administration of doses of 10, 15, and 20 mg, respectively, of cefuroxime axetil suspension per kg of body weight together with milk or milk formula. These concentrations exceeded the MICs for common respiratory tract pathogens, including β-lactamase-producing strains of Haemophilus influenzae and Moraxella (Branhamella) catarrhalis. Following a 10- or 15-mg/kg dose, serum cefuroxime concentrations are similar to those achieved in adults following the administration of a 250-mg cefuroxime axetil tablet. There were linear relationships between dose and both maximum serum cefuroxime concentration and area under the serum drug concentration-versus-time curve. The mean half-life of cefuroxime in serum was independent of dose and ranged from 1.4 to 1.9 h. No cefuroxime axetil (intact ester) was detected in the blood. The intact ester in the urine of four children was measured; however, the amount recovered represented less than 0.1% of the administered dose.

Cefuroxime axetil is the orally absorbed ester prodrug of the cephalosporin cefuroxime sodium. Since cefuroxime sodium is not absorbed orally (4), the 1-acetyloxyethyl ester was substituted for sodium on the cefuroxime molecule to increase its liposolubility and improve its gastrointestinal absorption. After oral administration, cefuroxime axetil is absorbed and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and portal blood (10) to produce concentrations of cefuroxime that exceed the MIC of common respiratory tract pathogens, including β-lactamase-positive and -negative strains (1, 11, 12, 17).

A suspension formulation of cefuroxime axetil has been developed to facilitate the administration of cefuroxime axetil to pediatric patients. In healthy adult volunteers, the suspension formulation of cefuroxime axetil is less bioavailable than the tablet formulation (8). The purpose of this study was to evaluate the pharmacokinetics of cefuroxime axetil suspension in infants and children.

MATERIALS AND METHODS

Pediatric patients, aged 3 months to 12 years, with infections which required systemic antibiotic therapy and for which cefuroxime axetil suspension was considered to be appropriate treatment were eligible for this open-label, randomized, parallel-group study. Patients receiving parenteral antibiotics for whom conversion to oral therapy was being considered were included in the study. Patients with a history of hypersensitivity reactions to beta-lactam antibiotics were excluded.

The study was conducted at the Children’s Hospital in Columbus, Ohio, and was approved by the institutional review board of the hospital. Written informed consent was obtained from the parents of all patients participating in the study. Each patient underwent a complete physical examination and routine clinical laboratory testing before study participation.

Each patient was randomly assigned to receive a single oral dose of 10, 15, or 20 mg of cefuroxime axetil suspension per kg of body weight. The medication was administered with 120 ml of milk or milk formula.

Sampling. Blood samples for serum cefuroxime concentration determination were obtained via heparin lock or direct finger stick before dosing (time zero) and 1, 2, 3, 4, 5, 6, and 8 h after the first dose of cefuroxime axetil suspension was administered. The blood was allowed to clot at room temperature for 30 min before centrifugation. The serum was separated and frozen at −70°C until analysis. Serum samples were assayed periodically throughout the course of the study. Assays were performed on average within 5 months of sample collection.

The maximum serum cefuroxime concentration occurs approximately 3 h after administration of cefuroxime axetil tablets (3). Therefore, the 3-h blood sample was also used to determine whether cefuroxime axetil (intact ester) was present in whole blood. Immediately after collection of the 3-h blood sample, 1 ml of blood was transferred to a polyethylene tube, and 2 ml of acetonitrile-ethanol (95:5, vol/vol) was added within 20 s to inactivate blood esterases. The tube was vortexed for approximately 20 s and centrifuged (IEC Centra-4B; International Equipment Co., Needham Heights, Mass.) at 2,000 rpm for 5 min. The clear supernatant was frozen at −70°C until analysis. Urine was collected from time zero to 4 h for determination of cefuroxime axetil (intact ester) concentration. Urine and whole blood samples were assayed within 36 h of sample collection.

Quantitation of cefuroxime in serum. Serum samples were deproteinized with a 5% perchloric acid solution. After thorough mixing and centrifugation, the supernatant, which contained cephaloridine as an internal standard, was analyzed by a high-performance liquid chromatography (HPLC) procedure. The effluent was monitored for UV A273. The standard curve was linear over the concentration range of 0.05 (lower limit of quantitation) to 20 μg/ml. The intraday coefficients of variation were 12.9, 3.2, and 2.4% for cefu-
oxime concentrations of 0.15, 1.5, and 15 µg/ml, respectively. The interday coefficients of variation were 10.9, 3.8, and 6.3% for cefuroxime concentrations of 0.15, 1.5, and 15 µg/ml, respectively.

Quantitation of cefuroxime axetil in blood and urine. Acetonitrile-ethanol extracts of the 3-h blood samples were assayed as previously described (10) for cefuroxime axetil by an HPLC procedure. The limit of quantitation was 0.25 µg/ml. Urine obtained from patients was directly assayed for cefuroxime axetil by a similar method. The limit of quantitation was 0.125 µg/ml.

Pharmacokinetic calculations. Pharmacokinetic parameters evaluated included maximum observed serum cefuroxime concentration (C_{max}), time to maximum serum cefuroxime concentration (T_{max}), area under the serum drug concentration-versus-time curve to the last time point (AUC_{0-\infty}), area under the serum drug concentration-versus-time curve from time zero to infinity (AUC_{0-\infty}), and elimination half-life (t_{1/2}).

Since some patients received a parenteral dose of cefuroxime sodium before study enrollment, concentrations (C) measured after the first dose of cefuroxime axetil suspension were adjusted by the principle of superposition (5). C (adjusted) = C (measured) − [C (baseline) × e^{(-k_{el}t)}], where t represents the time elapsed from the collection of the baseline sample and k_{el} is the elimination rate constant. Adjusted concentration data were used for all pharmacokinetic calculations.

C_{max} and T_{max} were obtained directly from individual concentration time curves (5). The AUC_{0-\infty} was calculated by linear trapezoidal integration (5). The AUC_{0-\infty} was calculated by the formula AUC_{0-\infty} = AUC_{0-\infty} + [(last measured concentration)/k_{el}]. k_{el} was calculated by using weighted nonlinear least-squares regression of the concentration-time curve. The t_{1/2} was calculated as 0.693/k_{el}.

Statistical analysis. Multiple regression was used to determine the effects of age, weight, and dose on the pharmacokinetic parameters. Linear regression was used to evaluate the relationship of dose to C_{max}, T_{max}, AUC, t_{1/2}, and the length of time during which the serum cefuroxime concentration exceeded 1 µg/ml. C_{max} and AUC were normalized for dose by dividing the value of each parameter by the administered dose. The slope for the line for each dose-normalized parameter versus dose was compared with 0 to test for dose proportionality.

RESULTS

Thirty-six infants and children with a mean age of 23 months (range, 3 months to 12 years) were enrolled in this study. Eight patients were excluded from all pharmacokinetic analyses because of blood sample collection difficulties. The demographic characteristics of the 28 evaluable patients are listed in Table 1. Ten patients had quantifiable serum cefuroxime concentrations at baseline because they had received either an intramuscular or an intravenous dose of cefuroxime sodium prior to study enrollment. In these cases, the concentrations were adjusted for the previous dose of cefuroxime as described in Materials and Methods.

Pharmacokinetic parameters of cefuroxime in serum. The mean pharmacokinetic parameters are summarized in Table 2, and the mean cefuroxime serum concentrations at each sampling time for the three doses studied are shown in Fig. 1. Multiple regression analysis showed that age and weight did not significantly affect the pharmacokinetic parameters. Regression analysis revealed linear relationships between dose and C_{max} and between dose and AUC, as evidenced by intercepts of the regression lines that were not statistically different from zero and slopes of the regression lines that were statistically different from zero (P < 0.001). Regression analysis of dose-normalized C_{max} and dose-normalized AUC versus dose revealed slopes that were not significantly different from zero, indicating proportionality between dose and C_{max} and between dose and AUC. T_{max} and t_{1/2} were independent of dose. These findings are consistent with a linear pharmacokinetic profile: C_{max} and AUC increased proportionately with increasing doses of cefuroxime axetil.

Cefuroxime axetil concentrations in blood. Blood samples were obtained from 14 patients for determination of cefuroxime axetil (intact ester) concentration. Cefuroxime axetil was not detected in any of the blood samples.

Cefuroxime axetil concentrations in urine. Urine samples were obtained from 11 patients for determination of cefuroxime axetil concentration. Four patients had quantifiable amounts of intact ester in the urine sample collected from 0 to 4 h following drug administration. The amount of cefuroxime axetil (µg/ml) was not significantly different from zero.

<table>
<thead>
<tr>
<th>Cefuroxime axetil suspension dose (mg/kg)</th>
<th>C_{max} (µg/ml)</th>
<th>T_{max} (h)</th>
<th>AUC_{0-\infty} (µg/ml h)</th>
<th>t_{1/2} (h)</th>
<th>Time during which concn in serum &gt; 1 µg/ml (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (n = 8)</td>
<td>3.3 (0.8)</td>
<td>3.6 (1.4)</td>
<td>12.4 (2.5)</td>
<td>1.9 (0.7)</td>
<td>4.2 (0.6)</td>
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<tr>
<td>15 (n = 12)</td>
<td>5.1 (1.4)</td>
<td>2.7 (1.1)</td>
<td>22.5 (9.3)</td>
<td>1.4 (0.7)</td>
<td>5.9 (1.3)</td>
</tr>
<tr>
<td>20 (n = 8)</td>
<td>7.0 (2.0)</td>
<td>3.1 (1.6)</td>
<td>32.8 (10.2)</td>
<td>1.9 (1.6)</td>
<td>6.6 (1.0)</td>
</tr>
</tbody>
</table>

* Values shown are means, with standard deviations in parentheses.

Table 1. Patient demographic characteristics

<table>
<thead>
<tr>
<th>Cefuroxime axetil suspension dose (mg/kg)</th>
<th>Age of patients (mo)</th>
<th>Wt of patients (kg)</th>
<th>No. of patients</th>
<th>No. diagnosed with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>10 (n = 8)</td>
<td>18.1</td>
<td>3-60</td>
<td>9.8</td>
<td>5-17</td>
</tr>
<tr>
<td>15 (n = 12)</td>
<td>21.0</td>
<td>5-72</td>
<td>10.1</td>
<td>6-18</td>
</tr>
<tr>
<td>20 (n = 8)</td>
<td>29.6</td>
<td>4-144</td>
<td>13.9</td>
<td>7-47</td>
</tr>
</tbody>
</table>
TABLE 1. Mean serum cefuroxime concentration-versus-time profiles for infants and children receiving a 10-, 15-, or 20-mg/kg dose of cefuroxime axetil suspension. Vertical bars indicate standard error.

氧化物在尿液中的检测范围从21.7到240.8 μg，低于正常值的1%。

DISCUSSION

The pharmacokinetics of cefuroxime axetil suspension in infants and children are similar to the pharmacokinetics of cefuroxime axetil tablets in adults. Although the suspension formulation of cefuroxime axetil is less bioavailable than the tablet formulation, the Cmax achieved in pediatric patients receiving a 10- or 15-mg/kg dose of cefuroxime axetil suspension is similar to the Cmax reported for adults receiving a single 250-mg cefuroxime axetil tablet (3). Following the administration of a 20-mg/kg dose of cefuroxime axetil suspension to pediatric patients, the Cmax was similar to the Cmax observed in adults receiving a single 500-mg cefuroxime axetil tablet (3, 19). The Cmax observed in our patients receiving 15- or 20-mg/kg doses of cefuroxime axetil suspension was nearly identical to concentrations observed in children receiving crushed cefuroxime axetil tablets suspended in 85% sucrose at identical doses (7).

Both Cmax and AUC increased proportionately with dose over the dose range of 10 to 20 mg/kg. This finding is identical to that observed with cefuroxime axetil tablets for adults. Twelve healthy adults participated in a study (3) designed to evaluate the dose proportionality of four oral doses of cefuroxime axetil (125, 250, 500, and 1,000 mg) administered after a meal. Linear relationships between the dose of cefuroxime axetil and both Cmax and AUC were demonstrated. The enhanced absorption of cefuroxime axetil in the presence of food, as observed by Finn et al. (3), is in agreement with the results of other studies (7, 10, 19). On the basis of these findings, we decided to administer cefuroxime axetil suspension with milk or milk formula in the present study.

The MIC of cefuroxime for 90% of β-lactamase-positive strains of Haemophilus influenzae and Moraxella (Brachamella) catarrhalis is 1.0 μg/ml, and the MIC of cefuroxime for 90% of tested strains of most common respiratory tract pathogens is far below this concentration (12). The amount of time during which the serum cefuroxime concentration exceeded 1 μg/ml increased with increasing doses of cefuroxime axetil suspension in infants and children. In addition, the mean t1/2 of cefuroxime was independent of dose and ranged from 1.4 to 1.9 h. This is longer than the t1/2 of cefaclor (42.5 min), cephalixin (0.98 h), and cephradine (1.0 h) in pediatric patients and slightly longer than the mean t1/2 (range, 1.1 to 1.4 h) observed for children receiving crushed cefuroxime axetil tablets (6, 7, 13, 14). Cefuroxime axetil tablets administered twice daily have proved effective in the treatment of otitis media (2, 15) and group A streptococcal pharyngitis (9, 18) in infants and children. Since 10- or 15-mg/kg doses of cefuroxime axetil suspension produce serum cefuroxime concentrations similar to those observed after administration of a 250-mg cefuroxime axetil tablet, it is likely that cefuroxime axetil suspension will be efficacious when administered twice daily. Clinical trials with cefuroxime axetil suspension have confirmed the effectiveness of these doses with twice-daily dosing in otherwise healthy patients with mild to moderate infections caused by susceptible pathogens (8).

In the present study, cefuroxime axetil (intact ester) was not detected in the systemic circulation of infants and children. This is in agreement with results obtained with healthy adults (10) and confirms that cefuroxime axetil is rapidly hydrolyzed to cefuroxime, the microbiologically active form of the drug. Cefuroxime axetil (intact ester) was detected in the urine of four children; however, the amount recovered was less than 0.1% of the administered dose. Taken together, these results indicate that in children hydrolysis of cefuroxime axetil to active drug is rapid, with little prodrug excreted unchanged. Unlike cefuroxime axetil, some antibiotic prodrugs are excreted by the kidneys before they can be hydrolyzed to the microbiologically active form. We reported earlier that the bioavailability of chloramphenicol following the administration of intravenous chloramphenicol succinate was extremely variable in infants and children (16). The urinary recovery of unchanged chloramphenicol succinate ranged from 7 to 42% of the administered dose.

We conclude that serum cefuroxime concentrations and the area under the serum cefuroxime concentration-versus-time curve increase with dose in a linear fashion and that the observed serum cefuroxime concentrations exceed the MIC for common respiratory tract pathogens, including β-lactamae-producing strains. In addition, cefuroxime axetil is rapidly hydrolyzed to its active moiety, cefuroxime, in infants and children.

ACKNOWLEDGMENTS

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REFERENCES