Pharmacokinetics of Cephradine Suspension in Infants and Children

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The pharmacokinetics of cephradine suspension were studied in 16 infants and children who were 13 months to 8 years and 3 months of age (means age, 3.5 years). Mean peak concentrations of 21.3 and 9.9 μg/ml were achieved at 30 min after administration of 60-mg/kg doses to fasting and nonfasting patients. The area under the serum concentration-time curve was 26% larger in fasting than in fed subjects. The half-life of cephradine in serum was 0.8 and 1.0 h in fasting and fed groups, respectively. Antimicrobial activity was detected in 49% of all salivary samples; in 75% of specimens, the concentrations were less than the 50% minimum inhibitory concentration for most pneumococci and group A streptococci. Urinary concentrations of cephradine ranged from 28 to 8,760 μg/ml and were independent of feeding status.

Cephradine is a new semisynthetic cephalosporin that has a chemical structure and spectrum of antimicrobial activity similar to those of cephalaxin (1). The agent has minimal toxicity in humans and is not appreciably bound to plasma proteins. Studies performed in adults and in a limited number of older children indicate that cephradine is rapidly absorbed after oral administration to fasting patients, and bioavailability is not appreciably affected by the concurrent administration of food (4, 7). Serum concentrations, half-life times, and urinary levels are comparable to those of cephalaxin when both drugs are administered in equivalent dosages.

Because of the limited amount of pharmacokinetic data for cephradine in infants and young children, the following investigation was undertaken.

MATERIALS AND METHODS

The study was conducted in the Out-Patient Clinic of Children's Medical Center, Dallas, Texas. Infants and children with impetigo were eligible for study. The decision to initiate antimicrobial therapy was made independent of the investigators. Prior to enrollment in the study written parental consent was obtained for each study patient. Sixteen infants and children aged from 13 months to 8 years and 3 months (mean, 3.5 years) were studied. Nine were male and seven were female. Their weights ranged from 7.2 to 28.2 kg (mean, 15.8 kg), and their heights ranged from 62 to 124 cm (mean, 94.8 cm). The average body surface area was 0.91 m$^2$.

Cephradine was administered as an oral suspension (125 or 250 mg per 5 ml) in a daily dosage of 60 mg/kg in four divided doses. Most children were studied twice, once while fasting and once when the antibiotic was given with 4 ounces (ca. 120 ml) of milk. The order of administration of the drug was determined by a random code. There was a 5- to 7-day interval between studies in most children. All studies were initiated between 8 and 9 a.m. after a 10- to 12-h fast. None of the children was receiving any other medication prior to or at the time of the studies. A research nurse administered the drug to all study patients. Blood samples were obtained immediately before and at 0.5, 1, 2, 4, and 6 h after the dose. Saliva was collected in capillary pipettes at 2, 4, and 6 h after the dose, and a single urine sample was obtained at random times during the 6-h period.

Assay. The concentration of the antibiotic in body fluids was assayed by an agar-disk diffusion micromethod (6) using Sarcina lutea (ATCC 9341) as the test organism. Body fluid specimens and reference samples were diluted identically either in pooled serum for measurement of serum concentrations or in phosphate-buffered saline (pH 6.0) or urine and saliva levels. The accuracy of the procedure was ±10% as determined by analysis of zone diameters of the reference standards measured during the 3-month study period.

Pharmacokinetic data. The equation for the regression line of the log serum concentrations against time was calculated by the method of least mean squares. The serum half-life was determined by dividing $2 \log_{10}$ by the slope of the line. The area-under-the-serum-concentration–time curve (AUC), expressed as micrograms per milliliter per hour, was formulated by successive trapezoidal approximation (5).

Statistical analysis. Data were analyzed using the Student t test and Bartlett's test for equal variance (8). When significant differences were found, the two groups were compared using the Mann-Whitney U
test (8). Differences in values were considered significant if the P value was <0.05, and of borderline significance when the P value was between 0.06 and 0.10.

RESULTS

Thirty-one pharmacokinetic analyses were performed in 16 infants and children. Serum concentrations, half-life times, and AUC values for cephradine are shown in Table 1.

Serum concentrations. After ingestion of 15-mg/kg doses of cephradine, mean peak serum concentrations of 21.3 and 9.9 μg/ml were attained at 0.5 h in fasting and nonfasting children, respectively. The difference between these values is statistically significant. There were no significant differences in serum concentrations at 1 and 2 h after the dose for fasting and fed patients. However, the levels were significantly larger at 4 and 6 h in children who received drug and milk concomitantly. At 6 h after the dose, 64% of fasting and 87% of nonfasting patients had measurable antimicrobial activity in serum. There was no correlation between the age of the patients and the concentrations of the drug in the serum and saliva. Serum half-life values were similar in the two study groups. The mean AUC value was 26% greater (29 μg/ml·h) in fasting individuals.

Concentration in saliva. Cephradine was detectable in saliva of 67% of subjects at 2 h (mean, 0.44 μg/ml; range, 0 to 0.9 μg/ml), of 46% at 4 h (mean, 0.31 μg/ml; range, 0 to 0.6 μg/ml), and of 44% at 6 h (mean, 0.25 μg/ml; range, 0 to 0.4 μg/ml). The salivary concentrations were independent of the feeding status.

Urinary concentrations. A single urine specimen was obtained randomly during the 6-h study period. Urinary concentrations of cephradine ranged from 28 to 8,760 μg/ml and were independent of feeding status. The average concentration in urine obtained from 0 to 2 h after the dose was 2,420 μg/ml (range, 1,000 to 4,810); from 2 to 4 h it was 3,933 μg/ml (range, 460 to 8,760); and from 4 to 6 h the mean value was 3,177 μg/ml (range, 28 to 6,720 μg/ml).

DISCUSSION

The pharmacokinetics of cephradine are similar to those of cephalixin after oral administra-

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Status</th>
<th>Conc in serum (μg/ml)* at time (h) after dose:</th>
<th>AUC (μg/ml·h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>15 Fasting</td>
<td></td>
<td>21.3 ± 2.1</td>
<td>12.6 ± 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10.0-32.4)</td>
<td>(6.4-27)</td>
</tr>
<tr>
<td>16 Fed</td>
<td></td>
<td>9.9 ± 1.2</td>
<td>9.4 ± 0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.4-16.4)</td>
<td>(2.4-16.4)</td>
</tr>
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* Average ± 1 standard error of the mean (range of values).

tion to infants and children. The bioavailability of both cephalosporins is substantially affected by concomitant ingestion of drug and milk. Data for cephalixin in comparably aged pediatric patients were published previously from this Center (3). The peak concentration of cephalixin in serum (23.4 μg/ml) was lowered by 62%, whereas that for cephradine (21.3 μg/ml) was lowered by 54%, by coadministration of antibiotic and milk (Fig. 1). The AUC values for cephalixin and cephradine were 40 and 21% reduced, respectively, in the nonfasting children. Serum half-life times were unaffected by the feeding status. These findings are different from those of Harvengt and co-workers (2), who found comparable peak serum levels and AUC values in fasting and fed adult volunteers who received 500-mg doses of cephalixin suspension. By contrast, Mischler and associates (4) reported lower peak serum concentrations in adults given cephalixin with food, but the AUC values were comparable to these observed in fasting individuals.

Concentrations of cephradine in saliva were independent of feeding status and inversely related to time after administration. Fifty-one percent of all specimens had no measurable antimicrobial activity. At 2 h after the dose only 25% of salivary samples had cephradine levels of 0.5 μg/ml or greater, a concentration that would inhibit 50% of group A streptococci and pneumococci. There was not sufficient activity in saliva to inhibit Haemophilus influenzae strains. Previously we reported that 50% of salivary specimens obtained from comparably aged children given 15-mg/kg doses of cephalixin had measurable antimicrobial activity and that one-third of samples collected at 2 h were inhibitory for 50% of group A streptococci (3). The clinical significance of these in vitro findings is unknown.

Because the antimicrobial activity and pharmacokinetics of cephalixin and cephradine are nearly identical and because differences in clinical efficacy and safety of these two agents have not been demonstrated, selection of one drug over the other must be based on personal experience and on cost to the patient. In the present study 24% of infants and children had no detectable antibiotic activity in serum at 6 h after a 15-mg/kg cephradine dose. Thus, the recom-
mendment in the package insert that cephradine be administered every 12 h for children greater than 9 months of age may be incorrect from a pharmacological standpoint. We recommend a dosage of 60 mg/kg per day in four divided doses given approximately every 6 h.

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LITERATURE CITED