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Clinical Pharmacology of Cefadroxil in Infants and Children

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The pharmacokinetics of cefadroxil suspension were studied in 30 children, 13 months to 12 years of age (mean age, 5.7 years). Average peak concentrations in serum of 11 to 14 μg/ml and of 7 to 10 μg/ml after 15- and 10-mg/kg doses, respectively, were not substantially affected by the feeding status. The serum half-life values were 1.3 to 1.5 h. Cefadroxil was detected in saliva of all children 2 h after 15-mg/kg doses: the levels ranged from 0.17 to 2.6 μg/ml (mean, 0.46 μg/ml). The average concentrations in urine were 1,700 and 2,620 μg/ml at 0 to 2 and 2 to 4 h, respectively, after 15-mg/kg doses. In a randomized controlled study of 50 children with impetigo, cefadroxil was as effective as penicillin G in curing existing lesions and in preventing development of new lesions. Cefadroxil may be useful for therapy of mucocutaneous and urinary tract infections in infants and children.

Cefadroxil is a new semisynthetic oral cephalosporin antibiotic which is similar to cephalexin in structure and in spectrum of antibacterial activity (1). Pharmacological studies in adults have demonstrated that cefadroxil is more slowly absorbed and has lower peak serum concentrations, longer serum half-life values, and slower urinary excretion than cephalexin when given in equivalent doses (2, 3). Substantial concentrations of cefadroxil are present in urine for at least 12 h after administration of a 500-mg dose.

The present study was undertaken to determine the pharmacokinetic properties of cefadroxil suspension in pediatric patients and to assess the effect of fasting and concomitant food ingestion on its bioavailability.

MATERIALS AND METHODS

Study patients. Pharmacological investigations were conducted in the outpatient clinic of Children's Medical Center, Dallas, Tex. Infants and children with impetigo and pharyngitis were eligible for study. The decision to initiate antimicrobial therapy was made independent of the investigators. The parents of each patient were informed of the nature of the study and the possible benefits and liabilities of receiving cefadroxil. Informed, written consent was obtained prior to enrollment in the study.

Cefadroxil monohydrate was administered as an oral suspension (125 or 250 mg per 5 ml) in a dosage of 40 to 60 mg/kg per day in four divided doses. Most children were studied twice, once while fasting and once when antibiotic was given with 4 ounces (ca. 120 ml) of milk. A research nurse administered the drug to all study patients. Blood samples were obtained through a heparin-lock and wing-tip needle inserted in a peripheral vein 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 during the 6-h study period.

A complete blood count, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, creatinine, bilirubin, and complete urinalysis were obtained at initiation and completion of therapy.

Assay. The concentrations of cefadroxil in serum and other body fluids were assayed by a modification of the micromethod of Simon and Yin (5) using *Sarcina lutea* (ATCC 9341) as the test organism. Assay standards were prepared in an identical fashion to the test samples.

Pharmacokinetic analysis. The equation for the regression line of the log serum concentrations of cefadroxil against time was calculated by the method of least mean squares. The serum half-life was determined by dividing $\log_{10}2$ by the slope of the line. The area under the serum concentration time curve (expressed as micrograms per milliliter × hours) was formulated by successive trapezoidal approximation (4).

Efficacy trial. Infants and children with impetigo were assigned treatment randomly with potassium penicillin G (30 mg/kg per day in four doses) or cefadroxil (45 mg/kg per day in three doses) in suspension or capsular form, depending on age. The parents were instructed to clip the fingernails and to bathe the child daily with a mild soap. Topical medications were not used. Informed, written parental consent was obtained prior to enrollment in the study. The extent and location of all active lesions were recorded on a body map before therapy. A characteristic impetiginous lesion was photographed, and a swab culture was taken of the throat and of a freshly uncovered lesion. Swabs were inoculated onto 5%

sheep blood agar plates, and bacterial growth was identified by standard methods after overnight incubation at 36°C. Beta-hemolytic streptococci were classified as group A if they were inhibited by bacitracin disks.

Follow-up examinations were performed on days 3 and 8 of antibiotic therapy. The number and extent of healed and new lesions were recorded on the body map, and representative lesions were photographed. A routine urinalysis for presence of erythrocytes and erythrocyte casts was obtained on day 8. A patient was considered cured if there was no evidence of inflammation, and complete epithelialization of the lesions had occurred. Resolving lesions were those showing no inflammation and incomplete epithelialization.

RESULTS

Pharmacokinetics in serum. Thirty children, 13 months to 12 years of age (mean age, 5.7 years), were studied. The pharmacokinetics of cefadroxil in these patients are shown in Table 1. Average peak serum concentrations of 13.7 and 11.0 μg/ml were attained at 1 h after 15-mg/kg doses in fasting and nonfasting children, respectively. The serum levels at 2, 4, and 6 h were not substantially affected by co-administration with milk. Drug was present in serum of all patients at 6 h; the concentrations ranged from 0.28 to 2.6 μg/ml. Serum half-life times (1.3 and 1.5 h) and area-under-the-curve values (41 and 39 μg/ml × h) were similar for the fasting and fed patients, respectively.

After ingestion of 10-mg/kg doses, mean peak serum levels of 10.1 μg/ml in fasting and 7.4 μg/ml in nonfasting children were noted at 1 h. Serum concentrations of cefadroxil detected at 4 and 6 h were similar to those observed in patients treated with 15-mg/kg doses. All children had measurable activity at 6 h after the dose. Serum half-life values were almost identical to those seen in patients receiving the larger dosage. The average area-under-the-curve value was approximately 20% greater in fasting (34 μg/ml × h) than in nonfasting (28 μg/ml × h) individuals.

Salivary concentrations. Cefadroxil was detected in saliva of all children at 2 h, 74% of the children at 4 h, and 46% of the children at 6 h after 15-mg/kg doses (Fig. 1). The average salivary concentrations at each time interval were independent of feeding status. The salivary levels of cefadroxil 2 h after 10-mg/kg doses were approximately half those observed following 15-mg/kg doses (average concentrations, 0.26 versus 0.46 μg/ml, respectively). The mean values at 4 and 6 h were similar for both dosage groups.

Urinary levels. Urine was obtained randomly during the 6-h study period. Urinary concentrations of 765 to 2,225 μg/ml (average, 1,700 μg/ml) at 0 to 2 h, of 424 to 8,000 μg/ml (average, 2,620 μg/ml) at 2 to 4 h, and of 750 and 930 μg/ml (two values) at 4 to 6 h were observed after 15-mg/kg doses. Mean urinary values of 2,980 and 995 μg/ml were noted at 0 to 3 and 3 to 6 h, respectively, after 10-mg/kg doses of cefadroxil.

Efficacy. Seventy-one children, 8 months to 8 years of age (average age, 3.1 years) received either cefadroxil or penicillin G for therapy of impetigo. Twenty-one patients were excluded from analysis because of failure to return for both followup examinations. Of the remaining 50 children, 26 were treated with penicillin G, and 24 received cefadroxil suspension or capsules. The groups were comparable with regard to age, sex, race, and extent of skin lesion.

Group A beta-hemolytic streptococci and coagulase-positive staphylococci were recovered from 64 and 78% of lesion cultures, respectively. Fifty percent of lesions contained both organisms. Patients with pure streptococcal impetigo and those with mixed cultures were divided equally between the two treatment groups. On day 8 of therapy, impetiginous lesions from 21

TABLE 1. *Pharmacokinetic properties of cefadroxil in infants and children*

Dosage (mg/kg)	No. of patients	Status	Mean concn[a] in serum (μg/ml) at: 0.5 h	1 h	2 h	4 h	6 h	Serum half-life (h)	Area under curve (μg/ml × h)
10	10	Fasting	6.9 ± 1.4 (0.46–12.4)	10.1 ± 0.88 (5.7–13.7)	9.2 ± 0.66 (4.4–11.7)	2.7 ± 0.30 (1.1–4.2)	1.2 ± 0.18 (0.56–2.5)	1.4	34
10	11	Fed	4.3 ± 0.91 (0.75–9.2)	7.4 ± 1.3 (1.9–14.7)	7.4 ± 0.81 (2.9–13.9)	3.0 ± 0.38 (1.2–5.1)	1.1 ± 0.11 (0.35–1.8)	1.5	28
15	16	Fasting	11.0 ± 1.33 (6.9–2.50)	13.7 ± 0.97 (6.2–20.5)	10.5 ± 0.84 (4.6–18.4)	3.0 ± 0.34 (0.90–6.4)	1.1 ± 0.10 (0.56–1.8)	1.3	41
15	17	Fed	7.4 ± 1.38 (0.29–16.5)	11.0 ± 1.1 (1.8–18.1)	10.7 ± 1.2 (3.9–19.5)	3.4 ± 0.36 (1.0–5.4)	1.2 ± 0.16 (0.28–2.6)	1.5	39

[a] Mean ± 1 standard error of mean. Range of values is in parentheses.

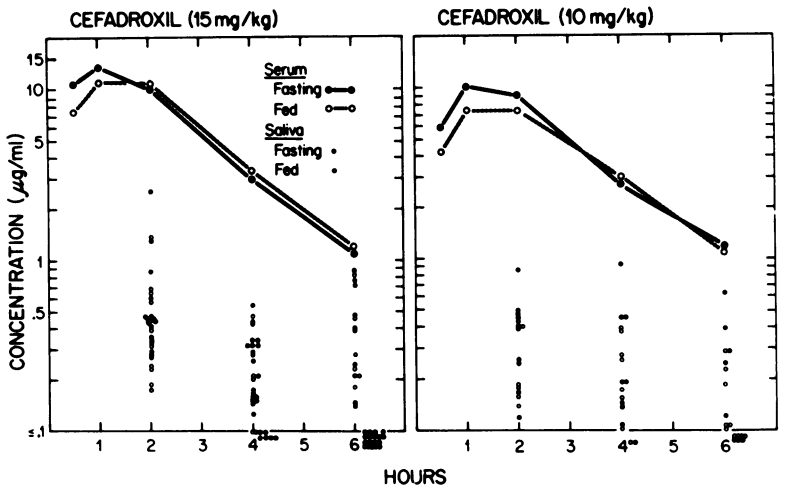

FIG. 1. *Serum concentration time curves for cefadroxil after 10- and 15-mg/kg doses to infants and children. Concentrations of cefadroxil in saliva are shown at 2, 4, and 6 h after oral administration.*

of 24 (87.5%) cefadroxil-treated patients and from 23 of 26 (88.5%) penicillin-treated patients were considered resolving or cured. Two children in each group developed new lesions while on therapy. One patient was removed from the study because of vomiting that was temporally associated with cefadroxil administration.

Safety. With the exception of the one child in the efficacy trial, cefadroxil was well tolerated by all study patients. There was no clinical or laboratory evidence of hematological, renal, or hepatic toxicity after 5 to 10 days of therapy.

DISCUSSION

Similar to the results of studies in adults (2, 3), the pharmacokinetics of cefadroxil suspension in children differed from those of cephalexin suspension in comparably aged patients (C. M. Ginsburg and G. H. McCracken, Pediatrics, in press). A mean peak serum concentration of 23 μg of cephalexin per ml was observed at 30 min compared with 14 μg of cefadroxil per ml at 60 min after 15-mg/kg doses to fasting patients. The half-life values of cefadroxil were approximately 50% greater than those of cephalexin. Whereas the bioavailability of cefadroxil was not substantially affected by co-administration with food, peak concentrations of cephalexin in serum of fed children were 60% lower than the levels in fasting patients. The area-under-the-curve values for cefadroxil were unaffected by the feeding status, whereas those for cephalexin were 43% lower in fed than in fasting children (Ginsburg and McCracken, in press).

The concentrations of cefadroxil in saliva were lower than the median minimal inhibitory concentrations for *Streptococcus pneumoniae* and *Staphylococcus aureus* (1). By contrast, the salivary levels at 2 and 4 h after 15-mg/kg doses were usually two- to fourfold greater than the minimal inhibitory concentration for *Streptococcus pyogenes*. These salivary concentrations were comparable to those observed in children receiving an equivalent dosage of cephalexin (Ginsburg and McCracken, in press.) The clinical implications of these data are unknown.

The minimal inhibitory and bactericidal concentrations of cefadroxil for *Enterobacteriaceae* causing pediatric urinary tract infections are similar to those for cephalexin (G. H. McCracken, unpublished data). The urinary concentrations of cefadroxil for 6 h after 15-mg/kg doses exceeded by at least 100-fold the mean minimal inhibitory concentration (7 μg/ml) and minimal bactericidal concentration (8 μg/ml) values for 27 *Escherichia coli* strains isolated from children with urinary tract infections (McCracken, unpublished data). We are presently assessing the efficacy of cefadroxil for therapy of urinary tract disease in infants and children.

These pharmacokinetic data and the results of the limited comparative efficacy study of impetigo suggest that cefadroxil may be useful for treatment of mucocutaneous and urinary tract infections in infants and children. A dosage of 15 mg of cefadroxil per kg given three or four times daily should provide adequate and safe therapy for these conditions.

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