

Pharmacokinetics and Bactericidal Activity of Cefuroxime Axetil

CHARLES M. GINSBURG,* GEORGE H. McCracken, JR., MARY PETRUSKA, AND KURT OLSON

Department of Pediatrics, Southwestern Medical School, Dallas, Texas 75235

Received 18 March 1985/Accepted 9 July 1985

The pharmacokinetics of cefuroxime axetil were studied in 10 adult volunteers aged 24 to 31 years (mean age, 27), 22 infants and children aged 11 to 68 months (mean age, 33 months), and 11 children aged 7 years, 7 months to 12 years, 3 months (mean age, 11 years, 1 month). Mean peak plasma concentrations of cefuroxime occurred between 90 and 120 min in all study patients and were independent of the fasting or feeding status. The areas under the concentration-time curves were significantly higher in adult volunteers who received cefuroxime axetil with milk than in those who received the drug while fasting or with applesauce. The bioavailability of cefuroxime axetil was significantly enhanced in children by the concomitant ingestion of cefuroxime axetil and infant formula or whole milk. The areas under the concentration-time curves were 25 to 88% higher when cefuroxime axetil and milk were administered simultaneously than when the same dose was given to all fasting patients. The plasma bactericidal activities of cefuroxime against beta-lactamase-positive and -negative strains of *Haemophilus influenzae* and *Staphylococcus aureus* at the time of peak plasma concentrations were independent of feeding status and were similar in adults and in children. Against these strains, 52% of the children and 38% of the adults had peak bactericidal levels of 1:8 or greater.

Cefuroxime axetil is the acetoxyethyl ester of cefuroxime and is the prodrug of that compound. After oral administration, cefuroxime axetil is deesterified in the intestinal mucosa and absorbed into the bloodstream as cefuroxime, a drug that has activity against gram-positive cocci, certain members of the family *Enterobacteriaceae*, and beta-lactamase-positive and -negative strains of *Haemophilus influenzae* and *Staphylococcus aureus* (2).

Pharmacokinetic studies performed in adults have shown that cefuroxime axetil is well absorbed after oral administration; peak concentrations of cefuroxime occur in serum approximately 2 h after oral administration of tablets (2, 4). In adults the peak concentrations of cefuroxime in serum and the area under the time-concentration curve (AUC) after administration of cefuroxime axetil are significantly increased when the drug is administered with food (5). There are no comparable data on the pharmacokinetics of cefuroxime axetil in infants and children.

Because cefuroxime axetil has potential usefulness for the treatment of infants and children with acute otitis media, sinusitis, and, possibly, lower respiratory infections, the following investigation was undertaken.

MATERIALS AND METHODS

Study patients. Pharmacokinetic studies were conducted in the outpatient research laboratory of Children's Medical Center, Dallas, Tex. Healthy adult volunteers who were members of the pediatric house staff and infants and children with acute otitis media or skin and soft-tissue infections were studied after informed written consent was obtained.

A total of 10 adults aged 24 to 31 years (mean, 27 years) received 500-mg tablets of cefuroxime axetil while fasting, with 4 oz (113 g) of applesauce, or with 120 ml of milk. Their weights ranged from 51 to 94 kg (mean, 69.5 kg), and their heights ranged from 141 to 203 cm (mean, 176 cm). Of the 10 volunteers, 5 were male and 5 were female. The doses of

cefuroxime axetil ranged from 5.3 to 9.8 mg/kg of body weight (mean, 7.3 mg/kg).

The ages of the pediatric patients ranged from 11 months to 12 years, 3 months (mean, 15.7 months). Eleven older children (mean age, 11 years, 1 month) received 500 mg of cefuroxime in tablet form, and 22 children (mean age, 2 years, 9 months) received 15- or 20-mg/kg doses of the drug in the form of crushed tablets suspended in 85% sucrose. All children were studied while fasting and again when the drug was administered with 120 ml of milk formula. Each of the older children who received tablets was studied on a third occasion when the drug was administered with 120 ml of applesauce. Of the total number of children, 18 were male and 15 were female. Their weights ranged from 9.1 to 51.2 kg (mean, 22.8 kg), and their heights ranged from 73 to 155 cm (mean, 106 cm). The average body surface area was 0.53 m². There was a 6- to 7-day interval between studies in most patients. Blood samples were obtained from each patient through a heparin lock and a wing-tip needle inserted into a peripheral vein just before and at 0.5, 1, 1.5, 2, 3, 4, and 6 h after the dose was administered.

Assay. Concentrations of cefuroxime in plasma were assayed by a microbiologic method, with *Sarcina lutea* (ATCC 9341; American Type Culture Collection, Rockville, Md.) as the test organism. Test and reference samples were diluted identically in pooled plasma. The accuracy of the procedure was $\pm 8\%$ as determined by analysis of zone diameters of the reference standards measured during the 6-month study period.

Plasma bactericidal activity. Plasma bactericidal titers in serum were determined by a standard microtiter technique with Mueller-Hinton broth plus supplement C (Difco Laboratories, Detroit, Mich.), beta-lactamase-negative and -positive strains of *H. influenzae* type b, and a penicillin-resistant strain of *S. aureus*. The MICs of cefuroxime were 0.31 and 0.62 $\mu\text{g/ml}$, respectively, for the negative and positive strains of *H. influenzae* and 0.62 $\mu\text{g/ml}$ for the *S. aureus* strain.

Analysis of data. The equation for the regression line of the

* Corresponding author.

TABLE 1. Plasma concentrations and pharmacokinetics of cefuroxime in adults and children given cefuroxime axetil

Dose	Feeding status	Plasma concn ($\mu\text{g/ml}$) at (min) following time after administration ^a :						Plasma half-life (h)	AUC ($\mu\text{g} \cdot \text{h/ml}$)	
		30	60	90	120	180	240			360
Adults (<i>n</i> = 10)	Fasting	1.3 \pm 0.89 (0.5-2.8)	2.6 \pm 1.4 (0.64-4.1)	3.6 \pm 1.1 (1.8-5.8)	3.4 \pm 1.4 (2.5-5.3)	2.6 \pm 1.1 (1.5-4.9)	1.9 \pm 1.09 (0.79-4.1)	<0.5 (0-1.3)	1.4 \pm 0.4 (0.96-2.2)	13.5 \pm 4.9 (6.7-23.3)
	Milk	1.5 \pm 0.76 (0.5-2.8)	3.1 \pm 1.6 (0.5-5.2)	4.2 \pm 2.2 (1.6-7.2)	4.5 \pm 1.0 (1.3-7.3)	3.5 \pm 1.0 (1.7-4.9)	2.5 \pm 0.93 (0.86-4.1)	0.71 \pm 0.3 (0-1.4)	1.4 \pm 0.5 (0.95-1.49)	16.9 \pm 4.4 (12.1-23.6)
	Applesauce	1.1 \pm 0.77 (0-2.4)	2.9 \pm 1.1 (0-4.4)	4.1 \pm 1.5 (0.71-5.7)	4.3 \pm 1.3 (1.9-6.2)	2.8 \pm 0.69 (1.4-3.8)	1.5 \pm 0.43 (0.89-2.3)	<0.5 (0-1.0)	1.1 \pm 0.12 (0.96-1.3)	13.6 \pm 3.7 (6.4-19.7)
Infants and children (<i>n</i> = 22)	Fasting	1.9 \pm 1.0 (0.85-3.3)	3.7 \pm 0.77 (2.4-4.9)	4.6 \pm 1.1 (3.4-6.2)	4.1 \pm 1.0 (2.6-6.2)	2.5 \pm 1.1 (1.2-4.8)	1.4 \pm 0.93 (0.65-3.2)	<0.5 (0-2.7)	1.3 \pm 0.2 (0.98-1.46)	12.6 \pm 2.9 (9.9-18.1)
	Milk	1.9 \pm 1.2 (0.53-3.9)	3.4 \pm 1.2 (1.8-5.8)	5.9 \pm 2.0 (3.1-10.5)	6.2 \pm 2.1 (3.3-10)	4.4 \pm 1.7 (2.3-6.4)	2.4 \pm 1.1 (0.92-4.4)	0.7 \pm 0.52 (0.9-1.9)	1.4 \pm 0.31 (0.95-1.54)	17.8 \pm 4.9 (13.2-22.3)
	Fasting	2.9 \pm 1.7 (0.5-4.3)	4.0 \pm 1.9 (0.77-7.0)	5.1 \pm 1.3 (3.3-7.3)	5.1 \pm 1.4 (3.1-6.9)	3.4 \pm 1.8 (1.1-6.0)	1.8 \pm 1.2 (0.5-3.8)	0.58 \pm 0.54 (0-4.7)	1.2 \pm 0.6 (0.76-1.8)	18.5 \pm 8.0 (9.9-30.4)
Older children (<i>n</i> = 11)	Milk	3.0 \pm 1.8 (1.3-4.4)	5.2 \pm 1.9 (2.1-8.1)	7.4 \pm 1.7 (2.7-10)	6.8 \pm 1.3 (2.5-8.9)	4.4 \pm 0.85 (2.1-6.8)	2.4 \pm 0.85 (1.3-3.5)	0.64 \pm 0.81 (0-2.5)	1.1 \pm 0.16 (0.85-1.26)	23.3 \pm 4.1 (15.1-27.4)
	Fasting	1.6 \pm 1.2 (0-3.2)	2.8 \pm 1.9 (0-5.4)	3.9 \pm 1.4 (0.84-5.6)	3.8 \pm 1.8 (0.79-7.3)	2.1 \pm 1.4 (0.5-3.9)	1.1 \pm 0.7 (0-2.2)	0.17 \pm 0.29 (0-0.82)	0.92 \pm 0.17 (0.72-1.3)	11.3 \pm 3.9 (7.2-19.1)
	Milk	1.1 \pm 1.1 (0-2.8)	2.4 \pm 1.9 (0-5.4)	4.3 \pm 2.8 (0-6.4)	4.5 \pm 2.8 (0-6.9)	3.2 \pm 2.1 (0-5.7)	2.2 \pm 1.6 (0-4.6)	0.69 \pm 0.89 (0-2.4)	1.4 \pm 0.41 (1.8-1.9)	22.3 \pm 7.9 (11.1-31.8)
500 mg	Applesauce	0.69 \pm 0.99 (0-2.7)	2.7 \pm 2.4 (0-6.2)	5.0 \pm 1.9 (1.2-7.4)	5.7 \pm 1.9 (2.7-9.4)	3.9 \pm 1.3 (2.4-5.5)	1.9 \pm 0.72 (0.65-2.8)	0.29 \pm 0.44 (0-0.98)	1.1 \pm 0.18 (0.9-1.2)	16.5 \pm 4.5 (11.6-22.4)

^a Mean \pm standard deviation. Values in parentheses show the range.

log plasma concentrations of cefuroxime against time were calculated by the method of least mean squares. The plasma half-life was determined by dividing the $\ln 2$ by the slope of the regression line. The AUC, expressed as micrograms \times hours per milliliter, was formulated by successive trapezoidal approximation. Data were analyzed by a two-way analysis of variance. When significant differences between values were found, the groups were compared by Newman-Keuls multiple-comparison testing. Differences in values were considered significant as $P \leq 0.05$.

RESULTS

Pharmacokinetic data. The pharmacokinetics of cefuroxime axetil in adults and after 500-mg and 15- or 20-mg/kg doses in infants and children are shown in Table 1. The mean peak plasma concentrations of cefuroxime occurred between 90 and 120 min in all groups of study patients and were independent of fasting or feeding status. In adults who received cefuroxime axetil with milk and with applesauce, the mean peak plasma concentrations of cefuroxime were 25 and 19% higher, respectively, than those in volunteers who received the drug in the fasting state. The AUCs were significantly higher in volunteers who received cefuroxime axetil with milk than in those who received the drug while fasting or with applesauce.

With the exception of the 30- and 60-min intervals in children who ingested 15-mg/kg doses, the mean plasma concentrations after 15- and 20-mg/kg doses of cefuroxime axetil suspension were substantially higher at all time intervals in patients who ingested the drug with milk formula than in those who received the drug while fasting. In children who received 15- and 20-mg/kg doses of cefuroxime axetil the 90- and 120-min plasma concentrations were significantly higher in nonfasting than in fasting patients. These results are reflected in the higher AUCs obtained in both groups of nonfasting children. In older children who received 500-mg doses of cefuroxime axetil the plasma concentrations were lower at all time intervals than were those in younger children who received either 15- or 20-mg/kg doses. When calculated on the basis of weight, the doses in the older group of children ranged from 7 to 17.6 mg/kg (mean, 12.4 mg/kg).

Bactericidal titers. The plasma bactericidal activity against beta-lactamase-positive and -negative strains of *H. influenzae* type b and against *S. aureus* was determined in most study patients after the peak plasma concentrations had been determined (Table 2). Median peak plasma bactericidal titers in the plasma of fasting and nonfasting adult volunteers were 1:4 against *S. aureus* and 1:8 against *H. influenzae*. In fasting and nonfasting children the median titers were 1:4 and 1:8, respectively, against each strain. Of the 106 plasma samples tested against beta-lactamase-positive strains of *H. influenzae*, 6 (6%) had 1:2, 32 (30%) had 1:4, 56 (53%) had 1:8, and 12 (11%) had 1:16 titers after cefuroxime axetil administration.

DISCUSSION

These data extend pharmacokinetic observations on cefuroxime axetil in adults. Like other investigators who have studied the pharmacokinetics of cefuroxime axetil, we were able to demonstrate significantly enhanced absorption of the drug in adults when it was coadministered with food (5). Although the plasma concentrations of cefuroxime tended to be higher at most time intervals in adult volunteers who

TABLE 2. Bactericidal titers of cefuroxime at time of peak plasma concentration

Bactericidal titer	No. (%) of subjects with designated titer			
	Children		Adults	
	<i>S. aureus</i>	<i>H. influenzae</i>	<i>S. aureus</i>	<i>H. influenzae</i>
$\leq 1:2$	5 (6)	6 (6)	5 (17)	1 (3)
1:4	50 (57)	32 (30)	19 (63)	6 (10)
1:8	32 (37)	56 (53)	5 (17)	15 (50)
$> 1:16$		12 (11)	1 (3)	8 (27)

received the drug with milk or applesauce, the AUCs were significantly different only between subjects who fasted and those who received the drug with milk. The concentrations of cefuroxime in plasma at all time intervals were, however, substantially lower than were those reported by Sommers and co-workers (4). In the latter study, a mean peak concentration of 8.6 $\mu\text{g/ml}$ was attained at 3 h after postprandial ingestion of a 500-mg dose of cefuroxime axetil tablets. In the present study, mean peak plasma concentrations of 4.5 and 4.3 $\mu\text{g/ml}$ occurred at 2 h in volunteers who ingested a 500-mg dose of cefuroxime with milk and with applesauce, respectively. Although the assay methods in the two studies were different, it seems unlikely that this alone could account for the differences in mean peak plasma concentrations. It is conceivable, however, that the amounts and types of food ingested or the differences in the timing of feedings in relation to drug ingestion in the two studies are responsible for the variations. In the previous study, the type of food administered to the adult volunteers was quite different from the applesauce and milk that were used in this study.

The bioavailability of cefuroxime in children was significantly enhanced by concomitant ingestion of cefuroxime axetil and infant formula or whole milk. The mean peak plasma concentrations were 33 to 51% higher and the AUCs were 25 to 88% higher when cefuroxime axetil and milk were administered simultaneously than when the same dose was given to fasting patients. In this regard, cefuroxime axetil differs from cephalexin and cephadrine, the bioavailability of which is significantly reduced when coadministered with milk or infant formula (1, 3).

When calculated on the basis of weight, the mean dose of cefuroxime axetil administered to older children was 18 and 38% smaller than those administered to infants and children, respectively. These results were reflected in the lower plasma concentrations and AUCs obtained in this group compared with those obtained in infants and children who received the drug in sucrose suspension. The AUCs and plasma concentrations in the older children were similar to those in adults.

The plasma bactericidal activities of cefuroxime against beta-lactamase-positive and -negative strains of *H. influenzae* and against *S. aureus* at the time of peak plasma concentrations were independent of feeding status and were similar in adults and in children. Against these strains, 52% of the children and 38% of the adults had peak bactericidal titers of 1:8 or greater.

These pharmacokinetic data and the results of efficacy data with the parenteral form of cefuroxime suggest that cefuroxime axetil in a dose of 20 mg/kg of body weight given three or four times daily may be useful for treatment of otitis media, sinusitis, and, possibly, lower respiratory tract infections in infants and children. The lack of a liquid formulation of the drug, however, precludes its use in infants and

children who are unable to swallow the solid form of the drug.

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