Comparative Pharmacokinetics of Cyclacillin and Amoxicillin in Infants and Children

CHARLES M. GINSBURG, GEORGE H. MCCracken, JR., TERESA C. ZWEIGHAFT, AND JOAN C. CLAHSEN

Department of Pediatrics, University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas 75238

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Concentrations of cyclacillin in serum over a 6-h period were similar in fasted and milk-fed infants who received 25-mg/kg doses of cyclacillin suspension. Measured by the concentration in serum after oral administration of 15-mg/kg doses, cyclacillin was absorbed more rapidly, reached larger concentrations, and was cleared more promptly than was amoxicillin.

Cyclacillin is an aminoalicyclic semisynthetic penicillin that has been approved by the Food and Drug Administration for treatment of skin and soft tissue, respiratory, and genitourinary tract infections in infants and young children. However, there is only a single published report of efficacy and safety of this agent in pediatric patients, and this study did not present pharmacokinetic data (1). Accordingly, the present study was designed to evaluate the effects of concomitant drug and milk ingestion on the bioavailability of cyclacillin suspension, to compare the serum concentrations of cyclacillin and amoxicillin in infants receiving 15-mg/kg doses of the agents in a crossover pattern, and to measure the activities of cyclacillin and amoxicillin against Streptococcus pneumoniae and Haemophilus influenzae isolates to give perspective to the results of the serum concentration data.

The study was conducted in the outpatient clinic of Children's Medical Center, Dallas, Tex. Infants and young children with otitis media were eligible for the study. The decision to initiate antimicrobial therapy was made independent of the investigators. Before enrollment in the study, written parental consent was obtained for each patient. A total of 27 infants from 4 to 39 months of age (mean, 17.3 months) were studied. Of these, 15 were male, and 12 were female. Their weights ranged from 6.6 to 15.4 kg (mean, 11.2 kg), and their heights ranged from 64 to 96 cm (mean, 79.5 cm). The average body surface area was 0.53 m².

Each child received either cyclacillin or amoxicillin trihydrate oral suspension (125 or 250 mg/5 ml) administered four or three times daily, respectively, for 10 days. Most children were studied on two separate occasions; once while fasting and once when the antibiotic was administered with 4 oz. (ca. 118 ml) of milk or milk formula (Similac or Enfamil). Fifteen children received cyclacillin only, and 12 received both drugs in crossover fashion. There was a 4- to 5-day interval between studies in most children. None of the children was receiving any other medication before or at the time of the studies. A research nurse administered the drugs to all children. Blood samples were obtained immediately before and at 15, 30, 45, 60, 180, and 360 min after the dose.

Concentrations of cyclacillin and amoxicillin in body fluids were assayed by the agar disk diffusion micromethod, using Sarcina lutea (ATCC 9341) as the test organism (6). Body fluid specimens and reference samples were diluted identically in pooled serum for measurement of serum concentrations. The day-to-day variation in the assay was ±10%.

The equation for the regression line of the log serum concentrations of antibiotic against time was calculated by the method of least mean squares (5). The serum half-life was determined by dividing log₂ by the slope of the line (5). The curve of the area under the serum concentration time, expressed as micromgs per hour per milliliter, was formulated by successive trapezoidal approximation (5).

In vitro susceptibilities of 11 strains of H. influenzae type b and 6 strains of S. pneumoniae to cyclacillin and amoxicillin were determined by a tube-dilution technique, using Mueller-Hinton broth plus 1% Supplement C (Difco Laboratories) and Levinthal broth (4). All isolates were obtained from the cerebrospinal fluid of infants with meningitis. The inocula of H. influenzae ranged from 1 x 10⁴ to 7 x 10⁵ and those of S. pneumoniae ranged from 5 x 10⁴ to 2 x 10⁵.
colony-forming units per ml. The lowest concentration of drug that inhibited visible growth after 18 to 24 h of incubation at 37°C was taken as the minimal inhibitory concentration. The minimal bactericidal concentration was the lowest concentration of drug that killed 99.9% of the inoculum, as determined by subculturing 0.1-ml samples of broth cultures onto blood or chocolate agar.

Data were analyzed by the Student t test and Bartlett's test for equal variance (10). When significant differences between values were found, the two groups were compared by the Mann-Whitney U test (10). Differences in values were considered significant if the P value was ≤0.05.

Fifty pharmacokinetic studies were performed in 27 infants and children. Serum concentrations, half-life times, and values of area under the curve for cyclacillin and amoxicillin are shown in Table 1.

After administration of 25-mg/kg doses of cyclacillin, there were no statistically significant differences in serum concentrations throughout the 6-h observation between fasting and non-fasting patients. Peak concentrations of approximately 26 μg/ml were attained 30 min after dosage, were sustained near these concentrations for 1 h, and declined rapidly thereafter to levels of approximately 0.2 μg/ml at 6 h. At 6 h, the concentrations in 35% of the infants were below detectable levels.

The pharmacokinetics of cyclacillin and amoxicillin after 15-mg/kg doses were compared in 12 patients who received both drugs in crossover fashion (Table 1). The time to peak concentration was shorter in patients who received cyclacillin (30 min) than amoxicillin (60 min), and the mean peak serum concentration of cyclacillin (15.6 μg/ml) was significantly larger than that of amoxicillin (7.3 μg/ml). During the first 45 min, the serum concentrations of cyclacillin were significantly larger than those of amoxicillin, whereas the reverse was true at 3 and 6 h after the dose. Although the cumulative 6-h values of area under the curve were similar for both drugs, the values during the first 60 min were 10.4 and 3.9 μg/h per ml for cyclacillin and amoxicillin, respectively. By contrast, the values calculated for the time period from 1 to 6 h after the dose were 11.7 and 17.8 μg/h per ml for the two drugs, respectively. The mean half-life times were significantly larger for amoxicillin (mean, 1.2 h) than for cyclacillin (mean, 0.59 h).

The minimal inhibitory and minimal bactericidal concentration values for six S. pneumoniae strains were from 0.016 to 0.125 μg/ml (median, 0.016 μg/ml) and 0.016 to 0.125 μg/ml (median,
0.032 μg/ml), respectively, for amoxicillin and from 0.025 to 1.0 μg/ml (median, 0.25 μg/ml) and 0.25 to 2.0 μg/ml (median, 0.5 μg/ml), respectively, for cyclacillin. For beta-lactamase-negative \textit{H. influenzae} type b strains, the minimal inhibitory concentration of amoxicillin was 0.25 μg/ml, and the minimal bactericidal concentration ranged from 0.25 to 1.0 μg/ml (median, 0.5 μg/ml), whereas those of cyclacillin were 2 μg/ml and 4 μg/ml, respectively.

The results of these pharmacokinetic studies in infants and children are consistent with those reported in adult volunteers (2, 3, 8). Cyclacillin was rapidly absorbed from the gastrointestinal tract after ingestion of the suspension in fasting and nonfasting subjects, and its bioavailability was unaffected by the feeding status in this age group.

In fasting infants given 15-mg/kg doses of cyclacillin and amoxicillin in crossover fashion the peak serum concentrations of cyclacillin were approximately twice those of amoxicillin. At 6 h, antimicrobial activity was undetectable in all serum samples from cyclacillin-treated patients. By contrast, all patients who received amoxicillin had measurable antimicrobial activity in their 6-h specimens.

These pharmacological data would appear to favor cyclacillin for use in treating infections caused by susceptible bacteria. However, cyclacillin is substantially less active in vitro than amoxicillin against strains of \textit{S. pneumoniae} and \textit{H. influenzae} (9). In our laboratory, the median minimal bactericidal concentration values for \textit{S. pneumoniae} and \textit{H. influenzae} were 0.5 and 4.0 μg of cyclacillin per ml and 0.03 and 0.5 μg of amoxicillin per ml, respectively. Based on these in vitro data it is evident that the apparent pharmacokinetic advantage of cyclacillin over amoxicillin is offset by its inferior in vitro activity. In a double-blind controlled trial, the efficacy of cyclacillin was found to be comparable to that of ampicillin for therapy of otitis media (1). There are no comparative clinical studies of amoxicillin and cyclacillin in pediatric patients. Until results of such a study are reported, we prefer amoxicillin for therapy of illnesses like otitis media that require a broad-spectrum, orally administered antibiotic. Because of insufficient experience with cyclacillin in infants and children, we concur with the recommendation of The Medical Letter (7) that this agent should not be used routinely until there are data demonstrating its comparability to amoxicillin for the therapy of childhood infections.

\section*{Literature Cited}


