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Pharmacokinetics of Azithromycin in Pediatric Patients with Acute Otitis Media

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The objective of our study was to characterize the pharmacokinetics of azithromycin after the oral administration of multiple doses in suspension to children with acute otitis media. Thirteen children (ranging in age from 7.5 months to 5 years) received a single oral dose of 10 mg of azithromycin per kg of body weight on day 1 followed by single daily doses of 5 mg/kg on days 2 to 5. Each child fasted overnight before receiving the final dose on day 5. Multiple blood samples were collected after the last dose. Concentrations of azithromycin in serum were measured by a specific high-performance liquid chromatography–mass spectrometry method. The means and standard deviations for the maximum concentration of azithromycin in serum, the time to maximum concentration of azithromycin in serum, the area under the concentration-time curve (from 0 to 24 h), and the elimination half-life were 224 ± 120 ng/ml, 1.8 ± 0.4 h, 1,841 ± 651 ng · h/ml, and 31.6 ± 6.6 h, respectively. Concentrations in serum (means ± standard deviations) at 0 h (predose) and at 24, 48, and 72 h after the final dose were 51 ± 26, 47 ± 21, 27 ± 17, and 17 ± 13 ng/ml, respectively. Thus, the once-daily administration of azithromycin resulted in sustained systemic exposure to the drug. The drug dosage regimen used in this study should lead to tissue drug concentrations exceeding the MICs for common pathogens.

Azithromycin is an azalide antibiotic. It is active in vitro against a variety of microorganisms, including *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Legionella pneumophila*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Borrelia burgdorferi* (1, 4, 8, 10). Azithromycin has recently been approved by the U.S. Food and Drug Administration for use in adult patients but has not yet been approved for children.

On the basis of data for adults, azithromycin has a greater distribution in tissues, a longer elimination half-life, and a lower incidence of adverse effects than erythromycin (1, 3, 6, 9). These pharmacokinetic features allow once-daily dosing and a shorter duration of therapy.

Azithromycin may be effective in children with respiratory infections. The pharmacokinetics of azithromycin have been studied in children 6 to 15 years of age with the diagnosis of streptococcal pharyngitis. In these patients, a once-daily administration led to sustained systemic exposure to the drug (11). Little is known, however, about the pharmacokinetics of azithromycin in children between the ages of 7 months and 5 years. The purpose of our study was to determine the pharmacokinetics of azithromycin after the oral administration of multiple doses in suspension to young children with acute otitis media.

The study was approved by the Human Subjects Research Committee at the Children's Hospital, Columbus, Ohio. Written informed consent was obtained from a parent or legal guardian prior to the enrollment of each patient.

The criteria for inclusion of patients were as follows: an age of 6 months to 5 years; a weight of at least 4.5 kg; an intact eardrum; one or more signs of acute bacterial otitis media (fullness or bulging of the tympanic membrane landmarks, impaired mobility, and the presence of middle-ear fluid as determined by pneumatic otoscopy and/or tympanometry); and the presence of at least one symptom (pain in affected ear, fever, lethargy, or irritability).

The exclusion criteria included known hypersensitivity or intolerance to macrolide antibiotics; treatment with another antibiotic within the 72-h period prior to enrollment, including topical antibiotics in the external canal; treatment with a long-acting intramuscular penicillin (e.g., benzathine) or another investigational drug within the 6 weeks prior to enrollment; the concurrent use of ergotamine or digitalis glycoside; evidence of significant hematologic, renal, cardiovascular, or hepatic disease as indicated by a physical exam or laboratory tests (showing 1.5 to 3 times the upper or lower normal values); conditions which may affect drug absorption (e.g., malabsorption or short bowel syndrome); and otitis media that had persisted for more than 4 weeks.

Thirteen patients (seven males and six females 7.5 months to 5 years of age) were enrolled in the study. Baseline laboratory tests (complete blood counts with differential and platelet counts, serum chemistry, and urinalysis), physical exams, and clinical evaluations were performed. Five days of therapy with azithromycin (in a 20-mg/ml suspension) were begun, with a single dose of 10 mg of azithromycin per kg of body weight given on day 1 followed by single daily doses of 5 mg/kg on days 2 to 5. The actual doses administered may have differed slightly depending on the patient's weight (22 to 33 lb [ca. 9.98 to 14.97 kg], 34 to 44 lb [ca. 15.42 to 19.96 kg], or 45 to 55 lb [ca. 20.41 to 24.95 kg]), because fixed doses of 120, 180, and 220 mg were given for the first 10-mg/kg dose and fixed doses of 60, 80, and 120 mg were given for the 5-mg/kg doses. The first doses of azithromycin were measured and administered with a pediatric dosing syringe in the hospital, and the syringe with the appropriate dosing mark was given to parents for dosing at home.

Patients were sent home with instructions to parents about azithromycin therapy, emphasizing that the drug should be given at least 1 h before or 2 h after meals. The once-daily doses were given at home for days 2 to 4. The medication

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TABLE 1. Summary of the pharmacokinetics of azithromycin following the administrations of doses of 10 mg/kg in suspension on day 1 and 5 mg/kg on days 2 through 5 to pediatric patients with acute otitis media

Patient	Age (yrs)	Dose[a] (mg)	Dose[a] (mg/kg)	C_{max} (ng/ml)	T_{max}[b] (h)	AUC_{0-24} (ng · h/ml)	$t_{1/2}$[c] (h)
1	2.3	60	4.7	244	1	2,587	48.1
2	2.1	60	4.7	241	2	2,390	27.1
3	2.3	60	4.3	191	2	1,736	28.9
4	5.0	80	4.2	91	2	1,077	25.7
5	3.9	80	5.2	425	2	2,220	29.1
6	1.9	60	4.6	237	2	1,541	29.7
7	2.0	60	4.1	197	2	1,209	—[d]
8	1.7	60	5.5	496	1	2,401	32.1
9	1.1	60	5.8	111	2	951	—[d]
10	1.4	60	5.2	201	2	—[e]	—[d]
11	1.5	60	5.8	198	2	2,285	36.1
12	0.5	40	5.1	210	2	2,646	40.3
13	2.4	80	4.8	65	1	1,048	30.3
Mean	2.2	63.1	4.9	224	1.8	1,841	31.6
SD	1.8	11.1	0.6	120	0.4	651	6.6

[a] Actual daily dose administered on day 5. The day 1 dose was approximately twice this value.
[b] T_{max}, time to C_{max}.
[c] $t_{1/2}$, half-life.
[d] Insufficient data to cover at least one half-life.
[e] Insufficient data to calculate AUC.

bottles were weighed before dispensing the first dose and after dispensing the last dose to assess patient compliance. Each child fasted overnight before receiving the final dose on day 5. This final dose was administered at the clinical study center of our hospital.

Blood samples were collected just before the fifth, i.e., the last, dose (0 h) and at 0.5, 1, 2, 4, 6, 8, and 12 h after the last dose. Patients returned to the hospital for the collection of blood samples at approximately 24, 48, and 72 h after the last dose. Concentrations of azithromycin in serum were measured by a specific high-performance liquid chromatography–mass spectrometry method (5). The drug concentrations in the linear range extended from 10 to 250 ng/ml. The assay's accuracy and precision over that range were 13% or better. This high-performance liquid chromatography–mass spectrometry method, which required only 50 μl of serum, had been validated by comparison with the standard high-performance liquid chromatographic method with electrochemical detection (12).

The physical exams and laboratory tests done at baseline were repeated on days 5, 8, and 30. Parents were also questioned about any adverse effects of azithromycin therapy.

Means and standard deviations (SD) were calculated for observed peak serum drug concentrations (C_{max}), the time required to achieve C_{max}, and the area under the serum concentration-time curve (AUC) as calculated by the linear trapezoidal method. The elimination rate constant was determined by a least-squares regression analysis of the terminal portion of the log serum concentration-time data. The elimination half-life was calculated by dividing 0.693 by the elimination rate constant.

The mean (± SD) C_{max}, time to C_{max} of azithromycin, and AUC from 0 to 24 h (AUC_{0-24}) in our 13 patients were 224 ± 120 ng/ml, 1.8 ± 0.4 h, and 1,841 ± 651 ng · h/ml, respectively. Data for individual patients are provided in Table 1. Figure 1 shows the mean serum drug concentration-time data for all patients.

Concentrations of azithromycin in serum just before the last dose (0 h) and at 24 h after the last dose were 51 ± 26 and 47 ± 21 ng/ml, respectively, suggesting that a steady state may have been achieved after 4 days of therapy including a loading dose. The mean concentrations in serum at 48 and 72 h were 27 ± 17 and 17 ± 13 ng/ml, indicating that the dosage regimen used in the study provided a sustained systemic exposure to azithromycin for at least 72 h after the final dose. The drug was detectable (≥10 ng/ml) in 10 of 12 patients at 72 h after the last dose.

The measurement of bottle weights indicated that the patients had used the drug amounts as expected. Azithromycin was well tolerated. No significant laboratory abnormalities or adverse effects due to azithromycin therapy occurred in any patients.

Our results demonstrate that once-daily administrations of azithromycin resulted in a sustained systemic exposure to the drug and that azithromycin was well tolerated in children between the ages of 7 months and 5 years. Interestingly, the C_{max} and AUC_{0-24} values in these patients were lower than the C_{max} of 383 ng/ml and the AUC_{0-24} of 3,109 ng · h/ml reported for 6- to 15-year-old patients with streptococcal pharyngitis after

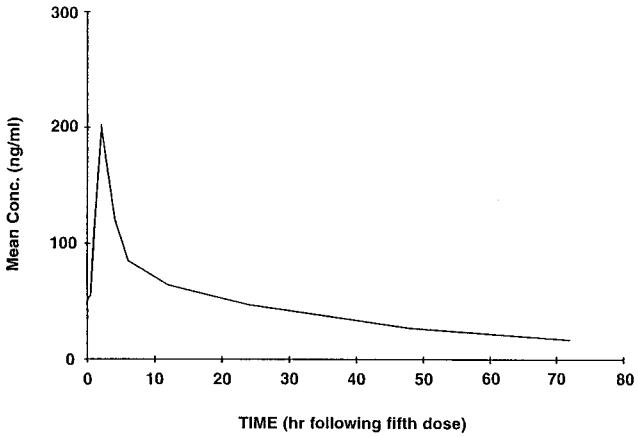

FIG. 1. Mean concentrations in serum of azithromycin on day 5 after oral administrations of 10 mg/kg in suspension on day 1 and 5 mg/kg on days 2 through 5 to pediatric patients with acute otitis media.

the administration of similar dosages (11). However, mean concentrations in serum for the two studies show similar rates of decline following peak concentrations, suggesting that the distribution and elimination rates for the two populations were similar. The values for C_{max} and AUC_{0-24} overlapped broadly for the patients in the two studies, suggesting that the pharmacokinetics for children ≤5 years old were not greatly different from those for children >5 years old.

Since this is the first report of the pharmacokinetics of azithromycin in children below the age of 2 years, the data from this study were also analyzed with respect to the difference(s), if any, in the pharmacokinetics of azithromycin administered to children above and to children below the age of 2 years. The mean (± SD) values for C_{max} were 242 ± 131 ng/ml ($n = 6$) for children <2.0 years old and 207 ± 118 ng/ml ($n = 7$) for children 2 to 5 years old. The mean (± SD) values for AUC_{0-24} were 1,965 ± 701 ng · h/ml ($n = 5$) for children <2.0 years old and 1,752 ± 654 ng · h/ml ($n = 7$) for children 2 to 5 years old. The mean values for the elimination rate constant were similar in children <2 years old (0.0203 h^{-1}) and 2 to 5 years old (0.0230 h^{-1}). Thus, azithromycin pharmacokinetics appear to be similar for children <2 years old and for those 2 to 5 years old.

The mean AUC_{0-24} for pediatric patients in this study was also somewhat lower than the AUC_{0-24} of 2,100 ng · h/ml determined for young adults after the oral administration of azithromycin at a dosage of 500 mg on day 1 followed by 250 mg on days two to five (2). The mean half-life of 31.6 h (range, 25.7 to 48.1 h) in our 10 patients was shorter than the approximately 2- to 3-day terminal-phase half-life in healthy adults (6, 7).

Specific dosage recommendations for the treatment of acute otitis media should await completion of the ongoing multicenter efficacy studies. On the basis of our experience, however, azithromycin appears to offer the ease of once-daily drug administration and a favorable safety profile. Finally, the dosage regimen utilized in this study should lead to tissue drug concentrations exceeding the MICs for common pathogens (6).

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