ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1993, p. 314–316
0066-4804/93/020314-03$02.00/0

Vol. 37, No. 2

Pharmacokinetics of Azithromycin in Pediatric Patients after Oral Administration of Multiple Doses of Suspension

MILAP C. NAHATA,[1,2]* KATALIN I. KORANYI,[1,2] SHRIKANT D. GADGIL,[3] DONALD M. HILLIGOSS,[3] HASSAN G. FOUDA,[3] AND MARK J. GARDNER[3]

Colleges of Pharmacy and Medicine, The Ohio State University, 500 West 12th Avenue, Columbus, Ohio 43210[1]; Wexner Institute for Pediatric Research, Children's Hospital, Columbus, Ohio 43205[2]; and Central Research, Pfizer Inc., Groton, Connecticut 06340[3]*

Received 29 May 1992/Accepted 2 December 1992

Azithromycin is an azalide antibiotic. On the basis of data in adults, azithromycin appears to have a greater distribution into tissues, a longer elimination half-life, and a lower incidence of adverse effects than the macrolide antibiotic erythromycin. However, little about the pharmacokinetics of azithromycin in children is known. The objective of our study was to characterize the pharmacokinetics of azithromycin after oral administration of multiple doses of suspension to children with streptococcal pharyngitis. Fourteen children (6 to 15 years of age) 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. Blood samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 h after this last dose. Concentrations of azithromycin in serum were measured by a specific high-performance liquid chromatography–mass spectrometry method. The mean ± standard deviation for maximum concentration of drug in serum, time to maximum concentration of drug in serum, and area under the curve (0 to 24 h) were 383 ± 142 ng/ml, 2.4 ± 1.1 h, and 3,109 ± 1,033 ng · h/ml, respectively. Concentrations in serum at 0 h (predose) and at 24, 48, and 72 h after the final dose were 67 ± 31, 64 ± 24, 41 ± 17, and 29 ± 14 ng/ml, respectively. Thus, once-daily administration of azithromycin resulted in sustained systemic exposure to the drug.

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, 7, 9). Azithromycin has been recently approved by the U.S. Food and Drug Administration for use in adult patients. For the treatment of streptococcal pharyngitis in adults, a 500-mg dose on the first day is recommended followed by 250 mg once daily for the next 4 days (3).

On the basis of data in adults, azithromycin has a greater distribution into tissues, a longer elimination half-life, and lower incidence of adverse effects than erythromycin (1, 3, 6, 8). These pharmacokinetic features allow administration of once-daily doses and shorter duration of therapy for various infections including streptococcal pharyngitis.

Azithromycin may be effective in children with respiratory infections. Little is known, however, about the pharmacokinetics of azithromycin in children. The purpose of our study was to determine the pharmacokinetics of azithromycin after oral administration of multiple doses of suspension in children with streptococcal pharyngitis.

MATERIALS AND METHODS

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

The inclusion criteria of patients were age of 2 to 15 years, signs and symptoms of streptococcal pharyngitis, and a positive result by a rapid immunoassay test for group A streptococcal antigen.

The exclusion criteria included known hypersensitivity or intolerance to macrolide antibiotics; history of rheumatic fever; presence of infection that may require treatment with any other antibiotic(s); use of any other antibiotic within 72 h prior to enrollment; treatment with long-acting penicillin injections within the preceding 6 weeks; evidence or history of significant hepatic, renal, cardiovascular, or hematologic abnormalities; malabsorption or other conditions affecting drug absorption; treatment with any other drug(s) under investigation within 4 weeks prior to enrollment; and being pregnant or lactating.

Fourteen patients (5 male, 9 female, 6 to 15 years of age) were enrolled in the study. Baseline laboratory tests (complete blood count with differential and platelet count, serum chemistry, and urinalysis), a physical exam, and clinical evaluation were performed. Five days of therapy with azithromycin (40-mg/ml suspension) were begun, with a single dose of 10 mg/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, because fixed doses of 220, 300, 400, and 500 mg were given for the first 10-mg/kg dose and fixed doses of 120, 160, 200, and 250 mg were given for the 5-mg/kg doses. The first doses of azithromycin were measured and administered by using a pediatric dosing syringe in the hospital, and the syringe with the appropriate dosing mark was given to parents for giving doses 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 through 4. The medication 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

* Corresponding author.

TABLE 1. Summary of azithromycin pharmacokinetic parameters determined on the final day of a 5-day oral regimen[a]

Subject	Sex	Wt (kg)	Age (yr)	Dose (mg/kg)[b]	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-24} (ng · h/ml)[c]
1	M	21.8	7	5.5	247	2.0	2,858
2	F	25.4	7	6.3	460	2.0	3,310
3	F	31.8	8	5.0	366	4.0	3,373
4	F	52.5	12	4.8	325	2.0	3,245
5	F	27.4	7	5.8	514	2.0	2,229
6	M	79.8	15	3.1	623	1.0	3,393
7	F	49.0	7	5.1	305	4.0	3,809
8	F	35.8	9	5.6	240	4.0	3,276
9	M	38.8	11	5.1	238	4.0	2,167
10	F	48.6	15	5.1	600	2.0	4,615
11	F	24.5	6	4.9	474	2.0	2,844
12	M	58.6	8	4.3	467	2.0	5,134
13	M	38.6	12	5.2	165	1.0	1,062
14	F	33.6	11	4.8	340	2.0	2,217
Mean ± SD		40.4 ± 16.0	10 ± 3	5.0 ± 0.7	383 ± 142	2.4 ± 1.1	3,109 ± 1,033

[a] A dose of 10 mg/kg was given on day 1 followed by single 5-mg/kg doses on days 2 to 5.
[b] Actual daily dose administered on day 5. Approximately twice this amount was administered on day 1.
[c] Values are based on estimated concentration at 24 h as determined by linear regression, because actual sampling did not always occur exactly at 24 h.

final dose on day 5. This final dose was administered at the clinical study center.

Blood samples were collected just before the fifth (i.e., last [0 h]) dose and at 0.5, 1, 2, 4, 6, 8, and 12 h after the last dose. Patients returned to the hospital for 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, has been validated by comparison with the standard high-performance liquid chromatography method with electrochemical detection (10).

The physical exam and laboratory tests done at baseline were repeated on day 6. Parents were also questioned about any adverse effects of azithromycin therapy.

Mean and standard deviations were calculated for the observed peak concentrations in serum (C_{max}), time to achieve peak concentrations in serum (T_{max}), and area under the concentration (in serum)-time curve from 0 to 24 h (AUC_{0-24}) as calculated by the linear trapezoidal method.

RESULTS

The mean ± standard deviation C_{max}, T_{max}, and AUC_{0-24} in our 14 patients were 383 ± 142 ng/ml, 2.4 ± 1.1 h, and 3,109 ± 1,033 ng · h/ml, respectively. Data for individual patients are provided in Table 1. Figure 1 shows the mean concentration (in serum)-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 67 ± 31 and 64 ± 24 ng/ml, respectively, suggesting that a steady state may have been achieved after 4 days of therapy. Concentrations in serum at 48 and 72 h were 41 ± 17 and 29 ± 14 ng/ml, indicating that the dosage regimen used in the study provided a systemic exposure to azithromycin for at least 72 h after the final dose.

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

DISCUSSION

Our results demonstrate that the concentrations of azithromycin in serum achieved in children with streptococcal pharyngitis were similar to those reported for adults (2). Furthermore, detectable concentrations of azithromycin were present in the sera of all patients not only throughout the 24-h dosage interval but also at 72 h after the last dose given on day 5 of therapy.

These data indicate that once-daily administration of azithromycin resulted in sustained systemic exposure to the drug and was well tolerated in pediatric patients. Exposure was comparable to that seen in adult, healthy volunteers after treatment with a similar regimen (2). However, specific dosage recommendations for the treatment of streptococcal pharyngitis should await completion of the ongoing multicenter efficacy studies. On the basis of our experience, however, azithromycin appears to offer both the ease of once-daily drug administration and a favorable safety profile.

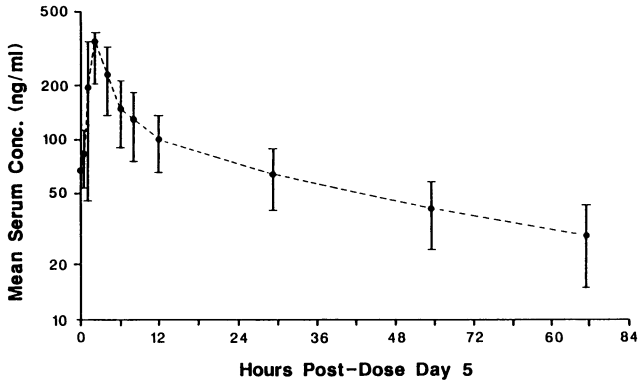

FIG. 1. Concentrations of azithromycin in sera from pediatric patients.

ACKNOWLEDGMENT

This work was supported by Pfizer Central Research, Groton, Conn.

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