# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 11 Number 4 April 2005

## Pediatric Therapy Update: Azithromycin

**Marcia L. Buck, Pharm.D., FCCP**

Since its introduction in November 1991, azithromycin has become one of the most commonly prescribed antimicrobials in the United States. Azithromycin is currently approved by the Food and Drug Administration (FDA) for use in children 6 months of age and older with acute otitis media, acute bacterial sinusitis, community-acquired pneumonia, pharyngitis, or tonsillitis.[1-3] This issue of *Pediatric Pharmacotherapy* will describe the results of several recent clinical trials of azithromycin in children, as well as review the pharmacology, dosing and monitoring of this antimicrobial agent in the pediatric population.

Mechanism of Action/Antibacterial Spectrum

Azithromycin is an azalide antibiotic. It reversibly binds to the 50S ribosomal subunit of susceptible organisms, interfering with microbial protein synthesis. In both *in vitro* and clinical studies, azithromycin has been shown to be active against the following gram-positive organisms: *Staph. aureus*, *Strep. agalactiae*, *Strep. pneumoniae*,, and *Strep. pyogenes*. It is also active against several gram-negative organisms, including *Haemophilus influenzae*, *Haemophilus ducreyi*, *Moraxella catarrhalis*, and *Neisseria gonorrhoeae*, as well as other microorganisms such as *Chlamydia pneumoniae*, *Chlamydia trachomatis*, and *Mycoplasma pneumoniae*. In addition, azithromycin has shown *in vitro* activity against *Strep. viridans*, *Bordetella pertussis*, *Legionella pneumophilia*, *Prevotella bivius*, *Peptostreptococcus* sp., *Borrelia burgdoferi*, *Treponema pallidum*, *Ureaplasma urealyticum*, and *Mycoplasma homini*.[1-3]

Recent Papers

The approved pediatric indications for azithromycin are supported by a large number of clinical trials published over the past decade.[1] Recent clinical trials have focused primarily on alternative dosing regimens, with shorter treatment courses designed to improve patient compliance. The use of higher doses and shorter (1- and 3-day) treatment courses has been based on the extensive tissue penetration of azithromycin and its long half-life (>50 hours in children). Azithromycin has been shown to achieve high concentrations in neutrophils and macrophages. As these cells are recruited to the site of infection, drug is transported and released where it is most needed.[4]

Both the 1- and 3-day regimens have been studied in the treatment of otitis media. In 2003, the manufacturer sponsored a multi-center double-blind, randomized study comparing azithromycin 10 mg/kg/day for 3 days with amoxicillin-clavulanate 45 mg/kg/day for 10 days.[5] A total of 188 children between the ages of 6 months and 12 years were enrolled. At day 10, the clinical success (cure plus improvement) rate was 83% in the azithromycin group compared to 88% in the amoxicillin-clavulanate group. By day 28, the cure (resolution) rate was 74% in the azithromycin group, but only 68% in the amoxicillin-clavulanate group. The differences between groups at 10 and 28 days were not statistically significant. The authors suggested that short-course azithromycin was as effective as amoxicillin-clavulanate.

Later that year, the manufacturer sponsored two other studies. The first was an open-label study of a 30 mg/kg single-dose regimen in 242 children.[6] At day 28, the overall clinical cure rate was 85%, comparable to the rate achieved with the standard 5-day regimen. The other study was another multi-center double-blind trial comparing high-dose azithromycin versus high-dose amoxicillin-clavulanate in children with persistent or recurrent otitis media.[7] Three hundred children were randomized to receive either azithromycin 20 mg/kg/day for 3 days or amoxicillin-clavulanate 90 mg/kg/day for 10 days. At the first assessment (12 to 16 days), clinical success rates were comparable (86% for azithromycin compared to 84% for amoxicillin-clavulanate). Azithromycin success rates at the second assessment (28 to 32 days) were significantly higher than those in the amoxicillin-clavulanate group (72% and 61%, respectively).

Earlier this year, the manufacturer sponsored an additional trial of a 30 mg/kg single-dose regimen for acute otitis media.[8] In this multi-center randomized, double-blind trial, azithromycin was compared to the high-dose amoxicillin-clavulanate regimen described in the previous study. A total of 313 children between 3 and 30 months of age were enrolled. At the end of therapy, clinical success rates were 84% for both azithromycin and amoxicillin-clavulanate groups. Compliance with therapy was higher in the azithromycin group (100%) than in the amoxicillin-clavulanate group (90%).

The 3-day regimen has also been proposed for the treatment of community-acquired pneumonia. In 2003, Kogan and colleagues published the results of a randomized trial of azithromycin 10 mg/kg/day for 3 days versus amoxicillin 75 mg/kg/day for 7 days for classic pneumonia or erythromycin 50 mg/kg/day for 14 days for atypical pneumonia.[9] A total of 110 children were enrolled. Chest x-rays were considered normal in more of the azithromycin patients than in either of the other groups by the end of therapy. Children with atypical pneumonia who were treated with azithromycin also had a shorter duration of cough than those given erythromycin (3.6±1.9 days compared to 5.5±3.6 days).

In addition to its use in these FDA-approved indications, several papers published within the last year support expanded uses for azithromycin. Langley and colleagues found that oral azithromycin (10 mg/kg on day 1 followed by 5 mg/kg on days 2-5) was as effective as erythromycin estolate (40 mg/kg/day for 10 days) in the treatment of pertussis.[10] A total of 477 children (6 months to 16 years) were enrolled in this multicenter, randomized trial. All patients had bacterial eradication at the end of therapy, with no reports of recurrence. Compliance was significantly better in the azithromycin group (90%) compared to the erythromycin group (55%).

Frenck and colleagues studied 149 children (3-17 years of age) with uncomplicated typhoid fever who were treated with either oral azithromycin at a dose of 20 mg/kg/day or standard therapy with ceftriaxone 75 mg/kg/day IV for 5 days.[11] Cure was achieved in 94% of the azithromycin group compared to 97% of the ceftriaxone group. Miron et al studied the efficacy of oral azithromycin as an alternative to nalidixic acid for children with *Shigella* gastroenteritis.[12] All of the 61 children studied initially received nalidixic acid (55 mg/kg/day), but 25 were switched to azithromycin (10 mg/kg/day) because of persistent diarrhea. All of the azithromycin-treated patients had resolution of diarrhea within 48 hours of initiation of therapy, versus 65% of the nalidixic acid-only group. Other publications have documented the effectiveness of both oral azithromycin (500 mg three times weekly) and an extemporaneous 2% topical preparation in the treatment of acne vulgaris.[13,14]

Pharmacokinetics

The bioavailability of azithromycin after oral administration is approximately 40%. Administration with food, particularly a high fat meal, increases the maximum concentration, but does not affect the overall absorption of the drug. In a study of adults receiving a standard regimen of 500 mg on day 1 followed by 250 mg on days 2-5, the maximum concentration was 0.24 mcg/ml, with a time to achieve maximum concentration of 3.2 hours and an average area under the concentration curve (AUC) of 2.1 mcg·hr/ml. Azithromycin is widely distributed throughout the body, with a volume of distribution in adults of 31.1 L/kg. Protein binding is concentration dependent, ranging from 7 to 51%. Azithromycin penetrates well into the lungs, tonsils, and middle ear fluid, with concentrations exceeding those in the blood. Although azithromycin has extensive tissue distribution, only minimal concentrations have been measured in cerebrospinal fluid.[2,3]

The primary route of elimination of azithromycin is through biliary excretion, as unchanged drug. Only 6-14% of a dose is excreted unchanged in the urine. Azithromycin has an apparent clearance of 630 ml/min in adults, with a terminal elimination half-life of 68 hours. [2,3]

The pharmacokinetic profile of oral azithromycin in children has been evaluated in two clinical trials using the first dosing regimen approved (10 mg/kg on day 1, followed by 5 mg/kg on days 2-5).[15,16] Patients were divided by age, with a group between 0.6 and 5 years of age and another group of children 6 to 15 years of age. On day 5, the average maximum concentration was 0.224 mcg/ml in the younger patients, compared to a maximum concentration of 0.383 mcg/ml in the older children. The AUC was also lower in the younger children (1.8 mcg·hr/ml compared to 3.1 mcg·hr/ml). A similar effect of age on AUC was shown in a third trial of 9 children, using a dose of 12 mg/kg. Clearance in this study was 5.4 L/hr/kg, with an elimination half-life of 55 hours after a 5-day course of treatment.[17]

Earlier this year, Jacobs and colleagues reported the results of a pharmacokinetic study of a single

10 mg/kg intravenous (IV) dose of azithromycin in 32 children between 0.5 and 16 years of age.[18] The average maximum concentration was 2.4 mcg/ml, with an AUC of 8.2 mcg·hr/ml, a volume of distribution of 44.1 L/kg, a clearance of 15.3 ml/min/kg, and an elimination half-life of 65.2 hours. Unlike the studies conducted with oral therapy, none of the pharmacokinetic parameters varied significantly with age.

Adverse Effects

Azithromycin is generally well tolerated. In pediatric clinical trials, the most frequently reported adverse effects were diarrhea (1-6%), abdominal pain (1-4%), nausea (0.5-2%), vomiting (1-6%), headache (1-2%), and rash (0.4-2%). Less common adverse effects included dizziness, agitation, insomnia, fatigue, fever, constipation, loss of appetite, chest pain, and pruritus. Transient neutropenia was also reported. Discontinuation due to treatment-related adverse effects in pediatric clinical trials was approximately 1%.[2,3,19]

Severe allergic reactions have been reported with azithromycin use, including anaphylaxis, angioedema, Stevens Johnson Syndrome, and toxic epidermal necrolysis. Severe cases of cholestatic jaundice have also been associated with azithromycin.[2,3] Nephritis has been reported with azithromycin use, most recently in a case involving a 14 year old girl.[20] The patient had a serum creatinine concentration of 2.2 mg/dl two weeks after treatment, but slowly recovered. Serum creatinine declined to 0.8 mg/dl. A second course of azithromycin 3 months later produced more significant renal impairment. She recovered without sequelae, and serum creatinine one year after the second episode was 1.2 mg/dl. Azithromycin should be used with caution in patients with known renal or hepatic dysfunction. In addition, as with other antimicrobial agents, pseudomembraneous colitis may result from azithromycin use.[2,3]

Drug Interactions

The concurrent use of antacids with azithromycin may reduce peak serum concentrations, but does not appear to affect overall absorption. Administration of azithromycin with nelfinavir has resulted in increased azithromycin serum concentrations. There is a case report suggesting that azithromycin may increase serum concentrations of cyclosporine when the two drugs are given together. Patients receiving this combination should be closely monitored. Use of azithromycin in patients receiving HMG-CoA reductase inhibitors may be at increased risk for myopathy or rhabdomyolysis.[2,3]

Administration of any macrolide antibiotic with pimozide is contraindicated. Two cases of sudden death have been reported when clarithromycin was added to chronic pimozide therapy.[2]

Dosing and Administration

For children 6 months of age and older with acute otitis media, there are three accepted oral dosing regimens: 1) the original regimen of 10 mg/kg as a single dose on the first day, followed by 5 mg/kg on days 2 through 5, 2) 10 mg/kg given once daily for 3 days, or 3) 30 mg/kg given as a single dose. For children with acute bacterial sinusitis, the recommended dose is 10 mg/kg given once daily for 3 days.[1-3]

In children with community-acquired pneumonia, the traditional regimen of 10 mg/kg on the first day followed by 5 mg/kg on days 2 through 5 is recommended.[1-3] An alternative dosing regimen of 10 mg/kg/day for 3 days has also been studied.[9] For the treatment of pharyngitis or tonsillitis in children 2 years of age and older, a dose of 12 mg/kg should be given once daily for 5 days.[1-3] An alternative dose of 20 mg/kg/day for 3 days has also been demonstrated to be effective, but has not yet been added to the product labeling.[4]

For children with chlamydial infections who are over 8 years of age or weigh more than 45 kg, the Centers for Disease Control and Prevention (CDC) recommends an azithromycin dose of 1 gram given orally as a single dose.[2]

In adults, the IV dose of azithromycin is 500 mg given once daily. Although not currently approved by the FDA, the IV preparation has been studied in children using a dose of 10 mg/kg administered over 1 hour once daily.[18]

Availability

Azithromycin is available as Zithromax® (Pfizer, Inc.) in 250 and 500 mg tablets, 600 mg capsules, 100 mg/5 ml and 200 mg/5 ml oral suspensions, a 1 gram dry powder (to be mixed with 60 ml water for use in adults), and a 500 mg/10 ml injection. The oral suspension formulations are provided as powder for reconstitution. Once prepared, the suspension may be stored at room temperature for up to 10 days.[3]

Cost

A Z-pak® (6 of the 250 mg Zithromax tablets) typically costs $49.00 to $55.00 in most retail pharmacies. The average cost of 15 ml of either the 100 mg/5 ml or 200 mg/5 ml suspensions is

$30.00 to $38.00. The injection is approximately $26.00 to $30.00 per 500 mg vial.[21]

Summary

Azithromycin has become a frequent choice for many common pediatric infections, including otitis media and pharyngitis. It appears to be as effective as traditional therapies, and offers the advantage of a shorter treatment course. Research continues with this drug, as new dosing regimens are proposed and additional patient populations are studied.

**References**


1. Langtry HD, Balfour JA. Azithromycin: a review of its use in paediatric infectious diseases. Drugs 1998;56:273-97.
2. Azithromycin. *Drug Facts and Comparisons*. Efacts [online]. 2005. Available from Wolters Kluwer Health, Inc. Accessed 3/16/05.
3. Zithromax® prescribing information. Pfizer Inc., January 2004.
4. Gordon EM, Blumer JL. Rationale for single and high dose treatment regimens with azithromycin. Pediatr Infect Dis J 2004;23:S102-7.
5. Dunne MW, Latiolais T, Lewis B, et al. Randomized, double-blind study of the clinical efficacy of 3 days of azithromycin compared with co-amoxiclav for the treatment of acute otitis media. J Antimicrob Chemother 2003;52:469-72.
6. Dunne MW, Khurana C, Mohs AA, et al. Efficacy of single-dose azithromycin in treatment of acute otitis media in children after a baseline tympanocentesis. Antimicrob Agent Chemother 2003;47:2663-5.
7. Arrieta A, Arguedas A, Fernandez P, et al. High-dose azithromycin versus high-dose amoxicillin-clavulanate for treatment of children with recurrent or persistent acute otitis media. Antimicrob Agent Chemother 2003;47:3179-86.
8. Arguedas A, Emparazna P, Schwartz RH, et al. A randomized, multicenter, double blind, double dummy trial of single dose azithromycin versus high dose amoxicillin for treatment of uncomplicated acute otitis media. Pediatr Infect Dis J 2005;24:153-61.
9. Kogan R, Martinez MA, Rubilar L, et al. Comparative randomized trial of azithromycin versus erythromycin and amoxicillin for treatment of community-acquired pneumonia in children. Pediatr Pulmonol 2003;35:91-8.
10. Langley JM, Halperin SA, Boucher FD, et al. Azithromycin is as effective as and better tolerated than erythromycin estolate for the treatment of pertussis. Pediatrics 2004;114:96-101.
11. Frenck RW, Mansour A, Nakhla I, et al. Short-course azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. Clin Infect Dis 2004;38:951-7.
12. Miron D, Torem M, Merom R, et al. Azithromycin as an alternative to nalidixic acid in the therapy of childhood shigellosis. Pediatr Infect Dis J 2004;23:367-8.
13. Kapadia N, Talib A. Acne treated successfully with azithromycin. Int J Dermatol 2004;43:766-7.
14. McHugh RC, Rice A, Sangha ND, et al. A topical azithromycin preparation for the treatment of acne vulgaris and rosacea. J Dermatol Treat 2004;15:295-302.
15. Nahata MC, Koranyi KI, Gadgil SD, et al. Pharmacokinetics of azithromycin in pediatric patients after oral administration of multiple doses of suspension. Antimicrob Agents Chemother 1993;37:314-6.
16. Nahata MC, Koranyi KI, Luke DR, et al. Pharmacokinetics of azithromycin in pediatric patients with acute otitis media. Antimicrob Agents Chemother 1995;39:1875-7.
17. Stevens RC, Reed MD, Shenep JL, et al. Pharmacokinetics of azithromycin after single- and multiple-doses in children. Pharmacotherapy 1997;17:874-80.
18. Jacobs RF, Maples HD, Aranda JV, et al. Pharmacokinetics of intravenously administered azithromycin in pediatric patients. Pediatr Infec Dis J 2005;24:34-9.
19. Ruuskanen O. Safety and tolerability of azithromycin in pediatric infectious diseases: 2003 update. Pediatr Infect Dis J 2004;23:S135-9.
20. Soni N, Harrington JW, Weiss R, et al. Recurrent acute interstitial nephritis induced by azithromycin. Pediatr Infect Dis J 2004;23:965-6.
21. Sifton DW, ed. 2002 Drug Topics Red Book. 106th ed. Montvale, NJ: Thomson Medical Economics, 2002:598.


**Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/25/05:

1. Pegaptanib (Macugen®) was added to both the Inpatient and Outpatient Formularies for the treatment of neovascular (wet) age-related macular degeneration.
2. An intravenous formulation of sodium phenylacetate 10% and sodium benzoate 10% (Ammonul®) was added to the Inpatient Formulary for the treatment of acute hyperammonemia in patients with urea cycle disorders. It is restricted to this indication, with approval of applicable intensive care medical directors and Genetics.
3. A request for the addition of amlodipine/atorvastatin (Caduet®) was rejected.
4. The restriction for aripiprazole (Abilify®) limiting its use to patients under the care of a psychiatrist was removed.
5. As a result of the annual Formulary review, the following agents were deleted from the Inpatient Formulary: salsalate tablets, oxaprozin tablets, meperidine tablets, butorphanol injection and nasal spray, nalmefene injection, ethosuximide capsules and syrup, felbamate tablets and suspension, desipramine tablets, perphenazine tablets, thiothixene capsules and liquid, thioridazine tablets and liquid, and trifluoroperazine tablets. Agents removed from the Outpatient Formulary included: butorphanol nasal spray, perphenazine tablets, thiothixene capsules and liquid, and thioridazine tablets.


*Contributing Editor:Marcia L. Buck, Pharm.D.*
*Editorial Board: Kristi N. Hofer, Pharm.D.*
*Michelle W. McCarthy, Pharm.D.*
*If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to mlb3u@virginia.edu. This newsletter is also available at www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/home.cfm*