

# Pediatric Pharmacotherapy

## A Monthly Review for Health Care Professionals of the Children's Medical Center

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### Formulary Update

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The macrolide antibiotics have recently come to the forefront of pediatric infectious disease literature with the release of oral liquid dosage forms of both clarithromycin and azithromycin. Many health care professionals are already familiar with the newly marketed azithromycin liquid, due to the extensive marketing this product has received as an alternative to penicillins and cephalosporins for the treatment of acute otitis media and pharyngitis. While these agents expand our choices for treatment and provide some distinct advantages, these factors must be balanced by the growing concern over the role of newer antibacterial agents in the development of bacterial resistance as well as the increasing cost of therapy.

### Antibacterial Spectrum

Macrolide antibiotics act by binding to the P site of the 50S ribosomal subunit of susceptible organisms and inhibiting bacterial RNA-dependent protein synthesis. They may be either bacteriostatic or bactericidal, depending on drug concentration and bacterial susceptibility.<sup>1,2</sup> There are currently five macrolide antibiotics on the market in the United States: erythromycin, clarithromycin, azithromycin, troleandomycin, and dirithromycin.<sup>3</sup> Erythromycin (when combined with a sulfonamide), clarithromycin, and azithromycin provide adequate antibacterial coverage of the organisms commonly associated with childhood infections, including: *Strep. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. These agents also are useful in treating pertussis, legionella, chlamydia, and mycoplasma infections.<sup>1,2</sup> Clarithromycin appears to have a spectrum of activity very similar to erythromycin, but is more potent. It also is useful in treating *Mycobacterium avium* complex (MAC) infections in immunocompromised patients.<sup>4,5</sup> Azithromycin is considered less potent against gram positive organisms than erythromycin, but more active against gram negative organisms.<sup>2</sup>

Troleandomycin, although structurally related to the others, does not possess their spectrum of activity. It is limited to the treatment of infections due to *Strep. pyogenes* and *Strep. pneumoniae*. Dirithromycin received FDA approval in June 1995, but only for patients greater than 12 years of age. It does not provide adequate coverage against *H. influenzae*; and as a result, it was not targeted at the pediatric population.<sup>3</sup> These latter two agents will not be discussed in the remaining sections of this brief review.

## **Comparison to Other Antibiotics**

Clarithromycin was the first of the new macrolides to become available in a liquid dosage form for use in children. It currently carries FDA-approved indications for use in children with pharyngitis, tonsillitis, acute maxillary sinusitis, acute otitis media, uncomplicated skin and suture infections, as well as the treatment and prevention of *M. avium*. A number of studies are available which compare the efficacy and safety of clarithromycin to standard therapies for the treatment of otitis media and pharyngitis.<sup>1,6</sup> The rate of clinical cure or improvement is typically greater than 95% with a recurrence of infection rate of 5-10%. In addition, clarithromycin has been found to be as effective as erythromycin for the treatment of pediatric community-acquired pneumonia in children greater than two years of age.<sup>7</sup> The incidence of adverse effects with clarithromycin is similar to that associated with the use of amoxicillin/clavulanate or cefaclor. Azithromycin suspension became available in October 1995, making it another choice for treating young children. At this time, it is indicated only for primary treatment in children with acute otitis media and as a second-line therapy for children with pharyngitis or tonsillitis. The average clinical cure rate from the otitis media trials conducted in the United States was 87.5% with a recurrence rate of 5-15%. In comparative trials with amoxicillin/clavulanate, azithromycin

has been found to be equally efficacious with a lower incidence of adverse effects.<sup>8</sup> Clinicians reviewing these trials, however, should keep in mind that differences in study methodology and the definitions of clinical cure and adverse effects will affect study outcomes.

## Pharmacokinetics

The bioavailability of the macrolide antibiotics is uniformly poor. At best, approximately 40-50% of a given dose is absorbed through the gastrointestinal tract. Food significantly reduces the absorption of azithromycin capsules as well as the stearate and some base forms of erythromycin. If tolerated by the patient, these products should be taken one hour prior to or two hours after a meal. Clarithromycin, azithromycin suspension, and erythromycin in the estolate, ethylsuccinate, and delayed-release base (enteric-coated) forms can be taken without regard to meals.<sup>1-3,5</sup>

The macrolides penetrate well into the respiratory, genital, and gastrointestinal tracts as well as skin and soft tissues. They are only moderately (40-50%) protein bound. Azithromycin is slowly released from tissue stores, prolonging its elimination.<sup>1,8</sup>

Erythromycin and clarithromycin are extensively metabolized by the liver. The metabolites of erythromycin are excreted in the bile, and the urine to a small extent. The elimination half-life of erythromycin in adults is 1-2 hours. Clarithromycin is metabolized to a pharmacologically active compound, 14-OH clarithromycin, which undergoes renal elimination. This metabolite may be responsible for giving clarithromycin its greater efficacy against *H. influenzae* compared to erythromycin. The elimination half-life of clarithromycin is 3-7 hours in adults. Azithromycin is predominately excreted as unchanged drug in the bile. Its long half-life, 60-70 hours in adults and 30-40 hours in children, and greater tissue penetration allow for less frequent dosing.<sup>2,9</sup>

## Adverse Effects

Most adverse reactions associated with the use of macrolide antibiotics are mild and resolve with the discontinuation of therapy. In children, the most frequently reported adverse effects with erythromycin are diarrhea, vomiting (6% each), abdominal pain, rash (3% each), nausea (1-2%), and headache (2%).<sup>3</sup> The experience with clarithromycin has been similar. In Phase III trials involving 1,676 children, the reported incidence of diarrhea was 7%, vomiting 6%, and abdominal pain 2%.<sup>10</sup> The combined results of Phase II/III trials with azithromycin in children demonstrated a lower incidence of gastrointestinal effects. Of the 1,928 children between the ages of 6 months and 15 years enrolled in the United States, the overall incidence of diarrhea was 3.1%, vomiting 2.5%, and abdominal pain 1.9%.<sup>11</sup>

Less frequent but more severe adverse effects include: anaphylaxis, Stevens-Johnson syndrome, reversible hearing loss, and hepatocellular cholestatic hepatitis.<sup>1-3</sup> Pseudomembranous colitis, resulting from the overgrowth of *Clostridium difficile*, has long been associated with erythromycin. It now appears that this adverse effect is possible with the newer macrolides as well. Clarithromycin was recently linked to the development of pseudomembranous colitis in a 26 month-old child being treated for otitis media.<sup>12</sup> Erythromycin, clarithromycin, and azithromycin have been associated with the development of ventricular arrhythmias, including torsade de pointes and ventricular tachycardia, in patients with prolonged QT<sub>c</sub> interval.<sup>3</sup> In many of the reported cases, these patients were also receiving a medication which interacts with macrolides.

## Drug Interactions

Both erythromycin and clarithromycin inhibit the activity of the hepatic cytochrome P450 enzyme system. As a result, these agents reduce the metabolism and increase the serum concentration of other drugs eliminated through the P450 pathway.<sup>1-3,13</sup> Azithromycin, due to differences in its chemical structure, does not cause these interactions. The following medications are known to be affected by erythromycin or clarithromycin:

1. anticoagulants
2. astemizole
3. bromocriptine
4. carbamazepine
5. cisapride
6. cyclosporine
7. digoxin
8. disopyramide
9. ergot alkaloids
10. methylprednisolone
11. terfenadine
12. theophylline and related compounds
13. triazolam

## Dosing Recommendations

All three macrolide antibiotics approved for use in children are available in tablet and liquid (suspension) dosage forms. Erythromycin ethylsuccinate is commonly used in conjunction with sulfisoxazole (Pediazole®) in young children to extend its antibacterial spectrum. This combination is only available in a liquid dosage form.

Due to their longer elimination half-lives, the newer macrolides offer the advantage of once or twice daily dosing. This can significantly improve

compliance, especially for patients in day-care or school. Unlike erythromycin-sulfisoxazole, clarithromycin and azithromycin do not require refrigeration, another potential advantage to consider for some families.<sup>3,14</sup>

### **Erythromycin**

- base or stearate
  - 20-50 mg/kg/day divided q 6 hrs for 10 days
- estolate
  - 20-50 mg/kg/day divided q 8 hrs for 10 days
- ethylsuccinate
  - 32-80 mg/kg/day divided q 8 hrs for 10 days

### **Clarithromycin**

- 7.5 mg/kg/dose every 12 hrs for 10 days

### **Azithromycin**

- otitis media: 10 mg/kg on the first day, then 5 mg/kg once daily on days 2-5
- pharyngitis/tonsillitis: 12 mg/kg/dose every 24 hours for 5 days

### **Cost Comparison**

For comparison, the cost of a typical treatment course for a 25 kg child with otitis media is provided below. These figures represent an average from several local pharmacies.

- Eryth./Sulf. (Pediazole®) \$ 40.39
- Eryth./Sulf. generic \$ 31.99
- Clarithromycin (Biaxin®) \$ 62.99
- Azithromycin (Zithromax®) \$ 57.98

The newer macrolide antibiotics offer some distinct advantages for treating common childhood infections. While maintaining the high rate of bacterial eradication associated with penicillins and cephalosporins, these agents have fewer adverse effects, allow once or twice daily dosing, and do not require special storage conditions. Azithromycin also has a shorter treatment course. However, they are considerably more expensive than common first-line therapies, and their effect on the emergence of bacterial resistance is unknown.

### **References**

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## **Pharmacology Literature Review**

### **ACE Inhibitor Review**

Angiotensin-converting enzyme (ACE) inhibitors have become an important therapy in several neonatal and pediatric disease states. Although not specific to pediatrics, this concise review provides information on the incidence, predisposing factors, and management of the most common ACE inhibitor-related adverse effects. The author also has included a brief section on the adverse effects of maternal therapy on the developing fetus. Alderman CP.

Adverse effects of the angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1996;30:55-61.

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### **Imipenem/Cilastatin**

The authors present a thorough review of this unique antibiotic. While imipenem is not routinely used in children due to concerns over adverse effects and the development of bacterial resistance, the article does include a discussion of its use in febrile, neutropenic children receiving chemotherapy. Balfour JA, Bryson HM, Brogden RN. Imipenem/cilastatin: An update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 1996;51:99-136.

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### **Ceftazidime in Infants**

Multiple-dose pharmacokinetics were evaluated in 136 preterm infants to determine the effect of gestational age on drug clearance. The mean volume of distribution (with standard deviation) was  $0.35 \pm 0.09$  L/kg and the mean elimination half-life was  $6.95 \pm 2.32$  hours. Within the study population, volume of distribution increased with increasing gestational age, while elimination half-life decreased. The authors recommend a dosage of 10 mg/kg given every 12 hours for infants with gestational ages < 28 weeks, a dosage of 15 mg/kg twice daily in infants between 28 and 32 weeks, and a dosage of 25 mg/kg twice daily in infants born at greater than 32 weeks. Prenatal exposure to indomethacin was associated with a reduction in ceftazidime clearance. In infants born to mothers receiving indomethacin, the authors recommend a dosage of 7.5 mg/kg every 12 hours for infants < 28 weeks gestational age and a dosage of 10 mg/kg every 12 hours for infants between 28 and 32 weeks. van den Anker JD, Schoemaker RC, Hop WCJ et al. Ceftazidime pharmacokinetics in preterm infants: Effects of renal function and gestational age. *Clin Pharmacol Ther* 1995;58:650-9.

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### **Midazolam Plasma Concentrations**

The authors of this study obtained steady-state midazolam concentrations from 38 infants and children to calculate an estimate of clearance. As a group, the children less than 3 years of age had a significantly slower clearance than older children (2-3 ml/min/kg vs. 13 ml/min/kg). While this paper presents some interesting findings, readers should be aware of the limitations in evaluations based on a single serum sample. Hughes J, Gill AM, Mulhearn H et al. Steady-state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother* 1996;30:27-30.

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## Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/26/96:

1. Acarbose (Precose®) was added to the formulary. This agent is an antihyperglycemic for use in controlling Type II diabetes.
2. Lamivudine (Epivir®, 3TC) was added to the formulary for use in patients with HIV infection. This antiviral is designed for use in combination with zidovudine. To date, there have been limited studies performed in children. The primary adverse reactions associated with lamivudine use in children include neutropenia, pancreatitis, and peripheral neuropathies. Lamivudine is available as both a tablet and as an oral solution. Lamivudine is restricted to the Infectious Disease Service.
3. Saquinavir (Invirase®), a protease inhibitor for use in patients with HIV infection, also was added to the formulary. Due to the development of resistance, this agent is being used in combination with other HIV therapies. Saquinavir has been approved by the FDA through an expedited review process, using surrogate makers. For more information on this process, please refer to *Pediatric Pharmacotherapy* vol.1 no. 11. Saquinavir use is restricted to the Infectious Disease Service.
4. Four new dosage forms of drugs already in use were placed on the formulary: transdermal testosterone (Androderm®), azithromycin suspension (Zithromax®), nasal calcitonin (Miacalcin®), and oral granisetron (Kytril®). Valacyclovir, another antiviral for use in the treatment of herpes zoster, was rejected.

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