



What does azithromycin study mean for pediatric prescribing?

by **Mary Anne Jackson, M.D., FAAP,**
and **William M. McDonnell, M.D., J.D., FAAP**

A recent study identified a small increase in the risk of cardiovascular death in adults (ages 30-74 years) treated with a five-day course of azithromycin (Ray WA, et al. *N Engl J Med.* 2012;366:1881-1890). This macrolide antibiotic previously had been identified as having potential for provoking ventricular arrhythmia by producing QT interval prolongation. Torsades de pointes and polymorphic ventricular tachycardia also had been described without QT prolongation.

The investigators retrospectively compared patients treated with azithromycin (n=347,795) to those treated with amoxicillin (n=1,348,672), ciprofloxacin (n=264,626), levofloxacin (n=193,906) or no antibiotic treatment (n=1,391,180). The risk of cardiovascular death was increased with azithromycin and levofloxacin (a drug with known pro-arrhythmic potential) but not in those given amoxicillin (primary control antibiotic), ciprofloxacin (a drug with limited pro-arrhythmic potential) or no antibiotic.

The authors noted that the risk of death was higher among patients with a higher baseline risk of cardiovascular disease, and the risk persisted only during the five days of treatment. The risk converts to 47 excess deaths per 1 million prescriptions and increases to 245 per 1 million prescriptions for those with the highest cardiovascular risk profile.

What is the message for pediatricians?

First, in the interest of judicious antibiotic use, practitioners should bear in mind that neither azithromycin nor any other antibiotic should be given for the common cold or bronchitis. Before any antibiotic is prescribed, physicians should ensure that the drug is appropriate for the indication and the diagnosis has been secured.

While Food and Drug Administration indications for azithromycin include acute bacterial sinusitis, community-acquired pneumonia (CAP), pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections, azithromycin is not recommended to treat otitis media or sinusitis due to the lack of coverage for the most common pathogens, *Streptococcus pneumoniae* or *Haemophilus influenzae*. Similarly, for skin and soft tissue infection caused by *Staphylococcus aureus*, azithromycin is not an appropriate choice.

Even for treatment of CAP due to mycoplasma, the role of antibiotics has been questioned. In at least two studies, patients who received a non-mycoplasma regimen fared equally well to those receiving a macrolide or fluoroquinolone. Macrolide-resistant group A streptococcus (GAS) has been increasingly noted, and alternatives to azithromycin are readily available for treatment of GAS pharyngitis.

Azithromycin is considered the drug of choice for treatment of sexually transmitted infections (STIs). The Centers for Disease Control and Prevention has recommended that practitioners do not modify treatment regimens for patients who require azithromycin for chlamydia or gonorrhea, especially as the use involves a single dose of azithromycin.

Azithromycin also remains the drug of choice for treatment and chemo-

prophylaxis for pertussis. Since outbreaks of pertussis continue to occur throughout the United States, physicians should be alert to the signs and symptoms of pertussis, use appropriate diagnostic tools, treat the index case and provide chemoprophylaxis for household contacts.

The Ray study should serve as a reminder for pediatricians to use azithromycin or any other medication in an appropriate manner. However, it should not alter the pediatrician's use of azithromycin when it is clearly the most appropriate antibiotic, e.g. STIs and pertussis.

Practitioners should remember that treatment is effective when initiated early in the course, which is potentially feasible when provided to a household contact of someone with pertussis. It is additionally a public health recommendation as treatment will limit the spread of infection. Providing azithromycin, similar to immunization, would benefit the adult household contacts as well as the children to whom they provide care.

In light of this study's new data, it would be prudent to consider an alternate antibiotic when available for those patients with known cardiovascular disease, especially those with long QT syndrome, those who are receiving medications that can prolong the QT interval, those with low potassium levels or those with other ventricular arrhythmias, and in adult patients. Alternatives to azithromycin for pertussis treatment or chemoprophylaxis include ciprofloxacin or trimethoprim-sulfamethoxazole. As always, discussion of risks/benefits and appropriate documentation should occur.

Liability concerns

Some pediatricians are questioning whether they should avoid prescribing azithromycin to their pediatric patients due to liability concerns. Pediatricians should recall that malpractice liability arises from medical care that fails to meet prevailing practice standards. It seems unlikely that this single study, which included no pediatric patients, will be considered to have significantly changed the standard of care for pediatric practice.

Another risk management issue is whether prescribing azithromycin to parents and other household contacts of pediatric patients poses a significant liability risk.

On a related issue, the Academy has published a policy supporting immunization of parents or other adult family contacts in the pediatric office setting as a potential benefit to themselves and pediatric patients. With immunizations, physicians are protected by the National Childhood Vaccine Injury Act (NCVIA). Treating adult parents with azithromycin likely creates a physician-patient relationship between the pediatrician and the adult patient and imposes legal requirements to provide care consistent with prevailing medical standards. Such medical care would not carry the liability protections of the NCVIA.

Therefore, when pediatricians prescribe azithromycin for chemoprophylaxis for their patients' household contacts, they should consider the indications, contraindications, risks and benefits and should document these considerations in a distinct medical record for each adult patient.

Pediatricians also should remember that when azithromycin remains the most appropriate alternative for their patients (e.g., STIs, pertussis), failing to prescribe this medication may well carry greater liability risks than prescribing the medication.



Dr. Jackson



Dr. McDonnell

Dr. Jackson is a member of the AAP Committee on Infectious Diseases. Dr. McDonnell is chair of the AAP Committee on Medical Liability and Risk Management.