

# PEDIATRIC PHARMACOTHERAPY

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## **Doxycycline for Pediatric Infections** **Marcia L. Buck, Pharm.D., FCCP**

The use of tetracycline antibiotics has traditionally been limited in young children because of their ability to cause permanent staining of developing teeth. However, the increasing incidence of tick-borne diseases, such as Rocky Mountain spotted fever (RMSF), ehrlichiosis, and Lyme disease, as well as bioterrorism attacks involving anthrax, has led to a renewed interest in this class. Doxycycline, a synthetic derivative of tetracycline, is now considered the drug of choice in several pediatric infections. It offers a similar antimicrobial spectrum to tetracycline, but has greater bioavailability, a longer half-life, and a more favorable adverse effect profile.<sup>1,2</sup> This issue of *Pediatric Pharmacotherapy* will review the basic pharmacology, pharmacokinetics, and dosing of doxycycline in pediatric patients.

### Mechanism of Action

Tetracycline antibiotics, including doxycycline, are bacteriostatic. They inhibit protein synthesis by reversibly binding to the 30S ribosomal subunit of susceptible organisms. As a result, they prevent the binding of aminoacyl transfer RNA, thus inhibiting protein synthesis and bacterial cell growth.<sup>3,4</sup>

### Antimicrobial Spectrum

Tetracyclines have a broad spectrum of activity; but bacterial resistance, particularly among Gram positive organisms, is common. Doxycycline is currently the drug of choice for all rickettsial infections, including RMSF, ehrlichiosis, and murine typhus. It is also used for *Bacillus anthracis* (the cause of anthrax), *Bartonella henselae* (cat-scratch disease), *Borrelia burgdorferi* (Lyme disease), *Brucella* sp., *Chlamydia* sp., *Clostridium* sp., *Mycobacterium* sp., *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, and *Vibrio* sp. infections. In addition, doxycycline may be used as prophylaxis for malaria in areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains of *Plasmodium falciparum*.<sup>2-7</sup>

### Examples of Use in Children

#### *Rocky Mountain Spotted Fever*

Doxycycline is considered the antibiotic of choice in the treatment of RMSF and all other rickettsial diseases in children and adults by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC).<sup>1,5,8,9</sup> Until 1991, chloramphenicol was recommended for children less than 8 years of age, but the lack of an oral liquid dosage formulation, the potential for chloramphenicol-associated blood dyscrasias, and new research suggesting minimal staining of dental enamel with doxycycline has changed this standard.

Doxycycline has been shown to be highly effective in the treatment of RMSF.<sup>10-12</sup> In a retrospective review by Dalton and colleagues, doxycycline was associated with improved survival compared to chloramphenicol. The success of treatment was also directly related to the rapidity of diagnosis and initiation of antibiotics. Mortality rose from 2% in children treated within four days of the onset of symptoms to 6% in patients who did not receive treatment until after the fourth day of illness.<sup>10</sup> A second study published the same year showed an increase in mortality from 6.5% to 22.9% when comparing patients treated within the first five days of illness to those whose therapy began later.<sup>12</sup>

Despite the need for prompt initiation of therapy, there is often reluctance to begin doxycycline. In a retrospective review of 35 children presenting with signs and symptoms of rickettsial disease at Texas Children's Hospital between 1987 and 1999, only one child was started on doxycycline at admission. Fifty-four percent were eventually treated with an antirickettsial agent. The authors hypothesized that reluctance to consider rickettsial disease and hesitancy to use a tetracycline led to these low numbers.<sup>1</sup>

### Lyme Disease

Doxycycline is also the drug of choice for the treatment of early localized Lyme disease. In addition, it is often used in the treatment of early disseminated and late disease. At this time, the recommendation for treatment with doxycycline is restricted to adults and children greater than 8 years of age because of the risk for dental staining. Amoxicillin is still considered the drug of choice for the treatment of younger children.<sup>7,13,14</sup>

### Anthrax

In response to bioterrorist activity in 2001, the CDC published new recommendations for postexposure prophylaxis and treatment of anthrax infections in children and adults.<sup>15-17</sup> In these guidelines, ciprofloxacin and doxycycline are considered equivalent agents of choice, regardless of patient age. The choice of agent may be based on availability and tolerability; there is not enough clinical data available in children to determine the ideal treatment regimen. In patients with systemic or inhalational exposure, additional agents may also be used. Because of reports of beta-lactam resistance, penicillins, including amoxicillin, are no longer recommended as initial therapy, but may be used when the specific isolate of *B. anthracis* implicated is determined to be susceptible.<sup>15,16</sup>

### Pharmacokinetics

Doxycycline is well absorbed after oral administration, with peak serum concentrations averaging 3 to 4 mcg/ml within 2 hours of a 200 mg oral dose. It is widely distributed throughout the body, and is 80 to 95% protein bound. Doxycycline is primarily concentrated in the bile. It is eliminated through the feces and via renal excretion as unchanged drug. The average rate of clearance in adults is approximately 75 ml/min with an elimination half-life of 18 to 22 hours after multiple dosing. No dosage adjustment is required in patients with renal dysfunction.<sup>2-4</sup>

### Drug Interactions

The bioavailability of doxycycline may be reduced by concomitant administration with calcium, aluminum, or magnesium supplements or antacids. Absorption may also be impaired by administration with cholestyramine, colestipol, kaolin, pectin, zinc, iron, or bismuth salicylate. The rate of clearance of doxycycline may be increased by concurrent use of carbamazepine, phenytoin, phenobarbital, or rifampin. Doxycycline may increase the effect of warfarin or theophylline, and decrease the effectiveness of oral contraceptives.<sup>2-4</sup>

### Adverse Effects

Doxycycline is generally well tolerated. The most frequently reported adverse effects in children and adults include: nausea, diarrhea, rash, and photosensitivity.<sup>2-4</sup> Sun exposure may also result in photoonycholysis, separation of the nail plate from the bed after exposure to ultraviolet light.<sup>18</sup> Parenteral use has been associated with phlebitis and pain at the site of infusion. Although rare, cases of elevated intracranial pressure and pseudotumor cerebri have been reported in patients receiving doxycycline. Other rare adverse effects include hypersensitivity reactions, eosinophilia, neutropenia, hypoglycemia, hepatotoxicity, and esophageal ulceration.<sup>2-4,19</sup>

The primary adverse effect of tetracyclines which limits their use in children is deposition in teeth and bone. The mechanism for this effect is believed to be deposition of the complex formed from chelation of tetracyclines to calcium. Staining of the teeth is permanent and appears to be the result of enamel hypoplasia. Patients are at risk at any time during dental development, from the second half of pregnancy through the first seven years of life. Growth retardation from deposition in bone has been less widely reported, but appears to be most significant when the tetracycline is administered during pregnancy or in the neonatal period. Unlike the staining of teeth, the effect on bone appears to be transient, with a gradual reversal after discontinuation of therapy.<sup>1-4</sup>

The chelation of calcium is common to all of the agents in the class, and has resulted in a general contraindication for their use in children less than 8 years of age since the 1970's. In cases where a tetracycline antibiotic is indicated, doxycycline is generally preferred over other tetracyclines because it is less strongly bound to calcium and may produce fewer adverse effects.<sup>16</sup>

Although several investigators have attempted to correlate the frequency and severity of dental staining with the duration and/or dose of tetracycline antibiotics, their conclusions have been limited by the length of time needed for assessment and the lack of adequate controls. In the May 1998 issue of *The Pediatric Infectious Disease Journal*, Lochary and colleagues described the results of a retrospective study of children given doxycycline for RMSF over a 7 year period.<sup>20</sup> Each of the 10 treated children who participated in the study were matched with two controls. The mean age of the patients who had been treated was 13.7 years (range 11 to 19 years), and their average age at the time of treatment was 5.1 years. In four of

the 10 cases, the median tooth color score was higher than that of the controls, indicating more staining. In three cases, the controls had more staining; and in each of the remaining three cases, there was no difference between the controls and the study subject. Using the combined data, the authors concluded that there was no significant difference in tooth enamel staining in children who received a single course of doxycycline compared to matched controls.

#### Dosing and Drug Availability

Doxycycline is available in a wide variety of dosage formulations, including 50, 75, and 100 mg tablets and capsules. There are two commercially-available oral liquid dosage formulations, a 25 mg/ 5 ml oral suspension and a 50 mg/ 5 ml syrup. Doxycycline injection is available in 100 mg and 200 mg vials.<sup>3,4</sup>

In adolescents and adults, the recommend oral or parenteral dose for doxycycline is 100 mg given every 12 hours. For children, the recommended dose is 2 to 4 mg/kg/day (up to 200 mg/day) divided and given every 12 hours. Some references list the dose as 2.2 to 4.4 mg/kg/day, based on a conversion from the original 1 to 2 mg/pound/day recommendation. Treatment should be continued for a minimum of 1 week for RMSF and 2 to 3 weeks for Lyme disease.<sup>3-7,21</sup>

After exposure to anthrax, the CDC recommends treatment with either ciprofloxacin or doxycycline for a period of 60 days. Children receiving doxycycline should be treated according to the following schedule:

- ≤ 8 years: 2.2 mg/kg/dose given twice daily
- > 8 years and ≤ 45 kg: 2.2 mg/kg/dose given twice daily
- > 8 years and > 45 kg: 100 mg given twice daily.<sup>15-17</sup>

It is typically recommended that oral doxycycline doses be administered with water or juice. Antacids, milk or other dairy products, infant formula, and iron supplements should be given 1 hour before or at least 2 hours after a dose to allow optimal absorption. Doxycycline may be given with other foods to reduce gastric upset.

The Food and Drug Administration (FDA) has recently published information on the stability of crushed doxycycline tablets mixed with food or drinks.<sup>22-24</sup> For ease of storage, the government stockpile of drugs to avert a bioterrorism attack includes doxycycline in tablet form. The FDA has prepared information for emergency preparation of the tablet form into a liquid for younger children. This information is also useful

for clinics with limited access to liquid dosage forms due to availability or cost.

Because the bitterness of doxycycline is not masked by water, the FDA recommends crushing doxycycline tablets and mixing them with a soft food or drink. Researchers at the FDA have conducted stability and palatability studies of several common combinations.<sup>23,24</sup> Despite the potential for chelation by calcium, the doxycycline/milk mixtures were stable for 24 hours at room temperature, without significant loss of drug. The doxycycline/chocolate milk mixture was found to be stable for at least six days when refrigerated.

#### Summary

Doxycycline is the antibiotic of choice for RMSF, ehrlichiosis, and Lyme disease in children. It is also one of the antibiotics recommended for older children and adults who have been exposed to anthrax. Compared to its parent compound tetracycline, doxycycline has a greater bioavailability, allowing administration with food or milk. In addition, doxycycline has a more favorable adverse effect profile, with less tendency to stain dental enamel. While not without drawbacks, doxycycline has a unique role in the treatment of pediatric infections.

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### **Pharmacology Literature Review**

#### **Cisapride and Cytochrome P450 Development**

Cisapride, a prokinetic agent, was widely used in the treatment of gastroesophageal reflux in infants and children prior to reports of its association with arrhythmias. This study was conducted to define the basic pharmacokinetic profile of the drug in infants and to use the drug as a means of studying the development of the cytochrome P450 3A4 enzyme system. The authors found that cisapride absorption and metabolism were related to developmental stage, with a reduced clearance in infants compared to older children and adults. Using cisapride as a marker, a rapid increase in cytochrome P450 3A4 activity was seen during the first three months of life. Kearns GL, Robinson PK, Wilson JT, et al. Cisapride disposition in neonates and infants: *in vivo* reflection of cytochrome P450 3A4 ontogeny. ***Clin Pharmacol Ther* 2003;74:312-25.**

### **Methylphenidate Review**

The authors of this review focus on the role of the newer once-daily methylphenidate products in the management of attention deficit/hyperactivity disorder (ADHD). In addition to a comparison of these products, the article is also a useful tool for those needing a basic review of methylphenidate pharmacology. The pharmacokinetic section is very thorough, and includes a discussion of possible gender-based differences. Markowitz JS, Straughn AB, Patrick KS. Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: focus on methylphenidate formulations.

**Pharmacotherapy 2003;23:1281-99.**

### **Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 9/26/03:

1. Hepatitis A inactivated and hepatitis B recombinant vaccine (Twinrix<sup>®</sup>) was approved for both the Inpatient and Outpatient Formularies. This combination vaccine is indicated for immunization of adults ages 18 years and older.
2. Atazanavir (Reyataz<sup>®</sup>), an azapeptide HIV-1 protease inhibitor, was added for use in combination with other antiretroviral agents for HIV infection.
3. Emtricitabine (Emtriva<sup>®</sup>), a deoxycytidine analog nucleoside reverse transcriptase inhibitor, was added for the treatment of patients with HIV. It is also under investigation for the treatment of chronic hepatitis B infection.
4. The restrictions on the use of drotrecogin alfa (activated protein C, Xigris<sup>®</sup>) were amended to allow use in either patients with sepsis-induced dysfunction of two or more organ systems or in patients with APACHE II scores greater than 25. The contraindication of chronic renal failure was removed and restated as a caution.
5. The influenza virus live vaccine, intranasal (FluMist<sup>®</sup>) was tabled pending further economic analyses.

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