

# Pediatric Pharmacotherapy

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## The Cytochrome P450 Enzyme System and Its Effect on Drug Metabolism (or Why all the fuss about Seldane®?)

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The cytochrome P450 (CYP) mixed-function monooxygenases are located on the smooth endoplasmic reticulum of cells throughout the body, primarily in liver and small intestine.<sup>1-3</sup> These enzymes are responsible for the oxidative (Phase I) metabolism of a wide number of compounds, including many medications. In recent years, interest in these enzymes has exploded as their role in drug interactions, drug toxicity, and the creation of carcinogenic by-products has become better understood. A search of the MEDLINE® database using the key term "cytochrome P450" revealed more than 5,000 publications since 1993 alone.

Drug interactions involving the CYP enzymes have received considerable attention this year as a result of the Food and Drug Administration (FDA) recommendation for the withdrawal of terfenadine (Seldane®) from the market. Terfenadine undergoes metabolism via a CYP pathway which may be inhibited by common medications, such as erythromycin or ketoconazole. Inhibition of terfenadine metabolism results in increased serum concentrations which may cause arrhythmias. According to figures released by the FDA, terfenadine toxicity has been linked to 396 deaths to date. There have been 39 reports of *torsades de pointes*, 145 reports of prolonged QT<sub>c</sub> interval, and 207 reports of cardiac arrest.<sup>4</sup>

Prescribing habits have slowly changed as knowledge of potential drug interactions involving CYP enzymes has become more widespread. According to a recent study by Burkhart and colleagues<sup>5</sup> using three databases (two from state Medicaid records and one from an HMO), prescriptions filled for terfenadine within two days of a ketoconazole or erythromycin prescription decreased by approximately 80% over the period from 1988 through 1994. This decline reflects both the

attempts by the FDA and pharmaceutical manufacturers to educate clinicians about the seriousness of these drug interactions and the availability of alternative medications which utilize different metabolic pathways.<sup>4,5</sup>

This brief review article will focus on the role of the CYP enzymes in drug interactions. Since not all of the known interactions can be discussed in this issue, a sample of drug interactions that might occur in pediatric practice will be highlighted. Standard nomenclature will be used throughout the article. The abbreviation "CYP" is followed by a number indicating the enzyme family, a letter indicating subfamily, and a number representing the specific enzyme isoform. The assignment of enzymes is based on the similarity of their amino acid sequences.<sup>1,6,7</sup>

### Substrates

A large number of commonly prescribed medications undergo metabolism via one or more CYP enzyme systems (Table 1).<sup>1-3,6,7,8</sup> As a result, their rate of metabolism is prone to alteration by other substances acting as enzyme inhibitors or inducers.

Drug interactions involving these substrates may result in mortality or significant morbidity. Families of children who are treated with one of these medications should be aware of the potential for drug interactions and the need to notify all health care providers of their child's medical history. Several case reports have described interactions resulting from medications prescribed by two different health care providers, often when an inducer or inhibitor is prescribed for a patient maintained on chronic therapy with a known CYP substrate.

Table 1. Substrates for CYP enzymes

CYP1A2	caffeine clozapine
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	R-warfarin tacrine theophylline
CYP2C9/10	phenytoin S-warfarin tolbutamide
CYP2C19	amitriptyline clomipramine diazepam imipramine omeprazole phenytoin propranolol
CYP2D6	amiodarone amitriptyline clomipramine codeine desipramine dextromethorphan encainide/flecainide fluvoxamine imipramine metoprolol mexilitine nortriptyline perphenazine propafenone propranolol thioridazine timolol
CYP2E1	chlorzoxazone halothane methoxyflurane
CYP3A3/4	astemizole carbamazepine cisapride cyclosporine dapson diltiazem erythromycin felodipine lidocaine lovastatin midazolam nifedipine quinidine tacrolimus tamoxifen terfenadine testosterone valproic acid verapamil

### Inducers and Inhibitors

Inducers are those substances which increase the rate of enzyme activity (Table 2). These agents typically affect more than one isoform.

Table 2. Inducers of CYP enzymes

All	phenobarbital phenytoin
CYP2E1	isoniazid
CYP3A1	spironolactone
CYP3A4	carbamazepine rifampin

Inhibitors decrease the metabolic rate of a given enzyme. Their ability to block metabolism of other compounds may range from minimal to nearly complete, with considerable interpatient variability. With decreased metabolism, the substrate accumulates and may reach toxic serum or tissue concentrations. The following table lists several examples of medications known to inhibit metabolic activity through one or more CYP enzymes.<sup>1,8</sup>

Table 3. Inhibitors of CYP enzymes

CYP1A2	cimetidine ciprofloxacin enoxacin erythromycin fluvoxamine grapefruit juice ritonavir
CYP2C9/10	fluconazole
CYP2C19	fluoxetine fluvoxamine omeprazole
CYP2D6	cimetidine fluoxetine haloperidol paroxetine quinidine ritonavir
CYP3A3/4	cimetidine clarithromycin diltiazem erythromycin fluconazole fluoxetine fluvoxamine grapefruit juice indinavir itraconazole ketoconazole miconazole ritonavir

### Examples of Drug Interactions

#### **Carbamazepine and Erythromycin**

The inhibition of carbamazepine by erythromycin was first reported in the late 1970's. Erythromycin acts as a potent inhibitor of CYP3A4, the primary enzyme responsible for carbamazepine metabolism, and can increase serum carbamazepine levels to the toxic range.<sup>6</sup>

Numerous cases of this interaction have been reported in children, typically occurring when children stabilized on carbamazepine for a seizure disorder are given erythromycin for otitis media or pharyngitis. Signs of toxicity reported as a result of this drug interaction in children have ranged from mild nystagmus and ataxia to an increase in vasopressin (leading to water intoxication), acute renal necrosis, and atrioventricular block with cardiac arrest.<sup>9-12</sup>

Inhibition of carbamazepine metabolism has recently been described with clarithromycin, a macrolide antibiotic similar to erythromycin which also inhibits CYP3A4 activity.<sup>13</sup>

### **Cisapride and Fluconazole**

Cisapride has become a popular alternative to metoclopramide in the treatment of gastrointestinal reflux in children. At therapeutic dosages, cisapride is relatively free of adverse effects; however, in higher concentrations it may cause severe disturbances of cardiac conduction. Cisapride is extensively metabolized via CYP3A4. Inhibitors of this isoform, such as fluconazole, block metabolism and increase serum concentrations to create toxicity.<sup>14-16</sup> Children with leukemia are often at risk of this interaction, when cisapride has been prescribed to stimulate gut motility following opioid use and fluconazole is added for prevention or treatment of fungal infections.

Within the first three years following approval, the FDA had received 34 accounts of *torsade de pointes* and 23 reports of prolonged QT<sub>c</sub> interval occurring in patients treated with cisapride. Four of those reports involved children. Over half of the patients reported were also taking a drug known to inhibit cisapride metabolism. The FDA has responded by requiring the manufacturer to include a black box warning on product labeling. In addition, letters describing these drug interactions were sent to physicians throughout the U.S. in 1995.<sup>15,16</sup>

### **Phenytoin and Valproic Acid**

The induction of valproic acid metabolism by phenytoin may or may not result in a significant decrease in valproic acid serum concentrations. Perhaps of greater concern, phenytoin has the potential to significantly increase the production of 4-ene-valproate, an intermediate step in the metabolic process. Increased concentrations of this metabolite have been linked to the hepatotoxicity associated with valproic acid use. Use of this combination, particularly in children less than 2 years of age, should be avoided whenever possible.<sup>17</sup>

### Patient Variation

Many of the enzymes of the CYP family have been shown to exhibit genetic polymorphism. Three classes of metabolic rates have been associated with specific CYP enzymes: poor metabolizers, extensive metabolizers, and ultraextensive metabolizers. The rate of enzyme activity appears to be transmitted as an autosomal recessive trait.<sup>7,18</sup>

Several drugs are known to have significant variability in pharmacokinetics, efficacy, and

adverse effects as a result of these differences in enzymatic function. For example, the tricyclic antidepressants structurally related to amitriptyline, such as imipramine and nortriptyline, all undergo 2-hydroxylation by CYP2D6 enzymes to form inactive metabolites. Genetic differences in the rate of metabolism results in the wide ranges of elimination half-lives reported for these compounds (e.g. 18 to 93 hours for nortriptyline in adults) and may, in part, explain the variation in patient response and likelihood of developing adverse effects.<sup>2,3,7</sup>

In a similar manner, genetic differences may explain variation among patients in response to codeine. The enzyme CYP2D6 converts codeine to morphine. Patients who fail to achieve pain relief with codeine may be poor metabolizers, incapable of forming the more potent metabolic by-product.<sup>1</sup>

Other factors known to affect CYP enzymes include cigarette smoking, which induces metabolism of compounds through the CYP1A2 pathway, and alcohol ingestion, which induces CYP2E activity.<sup>2</sup> Conversely, grapefruit juice has been shown to inhibit CYP3A4 activity in gut wall mucosa. Ingestion of grapefruit or grapefruit juice may cause a significant increase in the serum concentrations of drugs normally metabolized by the CYP3A4 pathway, such as felodipine, cyclosporine, and terfenadine.<sup>19,20</sup>

### Summary

The process of isolating and classifying members of the CYP enzyme system is proceeding at a rapid pace. Research on genetic differences and the effects of gender and age on enzyme function is also being conducted.<sup>21</sup> This work will play a significant role in our understanding of drug interactions and drug toxicity, as well as help to explain individual differences in therapeutic response.

At this time, it is vital that health care providers understand the importance of CYP enzymes and inform patients and their families of potential drug interactions and signs of toxicity when using medications affected by the CYP family.

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## **Pharmacology Literature Review**

### **Amiloride Pharmacokinetics**

Nine adolescent and 10 adult patients with mild to moderate cystic fibrosis participated in this open-label study of amiloride pharmacokinetics. Single doses of nebulized amiloride (4.5 mg) were compared to a standard oral dose of 10 mg. As anticipated, peak and area under the concentration curve values were lower for the nebulized group, demonstrating little systemic exposure. Jones KM, Liao E, Hohneker K et al. Pharmacokinetics of amiloride after inhalation and oral administration in adolescents and adults

with cystic fibrosis. **Pharmacotherapy 1997;17:263-70.**

### **Heparin Pharmacodynamics**

This study describes the pharmacodynamics of heparin in 23 neonates, ranging from 26 to 40 weeks gestation, using activated clotting times (ACT) as a measure of response. Increased heparin sensitivity was noted in several patients, putting them at increased risk for intraventricular hemorrhage. The authors recommend monitoring ACT values in all neonates for the first five days of life to establish individual response. Gal P, Childress C, Ransom JL et al. Heparin pharmacodynamics in premature infants. **J Pediatr Pharm Pract 1997;2:79-81.**

### **Management of Croup**

The authors present a brief risk-benefit assessment of using corticosteroids in children with croup. They cite the studies published to date demonstrating the benefit of steroid therapy in reducing frequency of hospitalization for mild cases and the need for intubation in more severe cases. The authors also address the risks of steroid use and compare systemic and inhaled routes. Yates RW, Doull IJM. A risk-benefit assessment of corticosteroids in the management of croup. **Drug Safety 1997;16:48-55.**

### **Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/25/97:

1. Topiramate (Topamax®) was added to the formulary for treatment of partial onset seizures.
2. Latanoprost ophthalmic solution (Xalatan®), a prostaglandin F<sub>2α</sub> analog, was added for use in treating glaucoma.
3. Liposomal daunorubicin (DaunoXome®) was added to the formulary, restricted to use in patients with Kaposi's sarcoma.
4. The medicated urethral system for erection (MUSE®) was also added to the formulary.

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