PEDIATRIC PHARMACOTHERAPY

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

Volume 13 Numbers 10 October 2007

Drug Metabolism via Cytochrome P450 2D6: Ontogeny and Variation in Children

Marcia L. Buck, Pharm.D., FCCP

Since the development of the field of pharmacogenomics (the study of the relationship between genetic variation and drug response) in the 1990's, there has been a number of significant advances in our understanding of developmental pharmacology and drug metabolism in infants and children. A key component of this research has been the study of the cytochrome P450 superfamily of metabolic enzymes.[1] Among these enzymes, the 2D6 group is responsible for the metabolism of a large number of drugs. This issue of *Pediatric Pharmacotherapy* will review several papers recently published in the pharmacy and pharmacology literature pertaining to the role of CYP2D6 ontogeny and variation in infants and children.

CYP2D6 Ontogeny

As with many of the CYP450 enzymes, expression of CYP2D6 is low to absent in fetal hepatic microsomes. Levels of CY2D6 activity begin to rise shortly after birth, with consistently measurable levels occurring within the first week of life.[2] The rate at which this increase in enzymatic activity occurs and the point at which adult levels are achieved are not well understood. Early *in vitro* studies conducted in fetal and neonatal microsomes suggested that infants slowly acquire CYP2D6 function over the first years of life.[2,3]

More recent studies, however, have revealed rapid attainment of CYP2D6 function. In the April 2007 issue of *Clinical Pharmacology and Therapeutics*, Blake and colleagues reported the results of their *in vivo* analysis of CYP2D6 activity in 193 infants.[4] A single 0.3 mg/kg oral dose of dextromethorphan was used as a probe substrate. Enzymatic activity was determined by the ratio of dextromethorphan to the dextrophan metabolite produced through CYP2D6 O-demethylation. In this sample population, enzymatic activity was detectable and predictable based on genotype by 2 weeks of age. The degree of activity was not correlated with gestational age and did not change over the first year of life.

Variations in CYP2D6 Activity

The CYP2D6 gene may undergo rearrangements of large sections of DNA, resulting in both deletions and duplication. Over 80 allele variations have been identified. As a result of this genetic polymorphism, CYP2D6 enzymatic activity may range from being entirely absent to a level substantially higher than average. The spectrum of enzymatic activity includes extensive metabolizers (EM), the predominant phenotype, intermediate metabolizers (IM), as well as poor metabolizers (PM) and utrarapid metabolizers (UM).[5-10]

Inheritance of two recessive non-functional alleles results in the absence of enzyme activity or the PM phenotype. This phenotype results in an inability to metabolize drugs through the CYP2D6 pathway and places patients at risk for toxicity from drug accumulation.[5] Patients with the PM phenotype may also experience a lack of efficacy when given drugs such as codeine or tramadol, since they cannot produce the active metabolite responsible for much of the drug's beneficial effect.[6]

Duplication of CYP2D6 can lead to significantly greater levels of enzymatic activity than observed in average patients, resulting in a UM phenotype. Pharmacogenomic studies have identified patients with over a dozen copies of the CYP2D6 gene. These patients may experience therapeutic failure resulting from an inability to maintain adequate serum concentrations after administration of standard drug doses. Conversely, these patients may be at risk for adverse effects associated with the accumulation of toxic metabolites formed through the CYP2D6 pathway.[5,7]

Rates of genetic polymorphisms appear to vary by ethnicity. Approximately 5-10% of whites have the PM phenotype, compared to only 1 to 2% of Asians and blacks. The UM phenotype is relatively infrequent in Asians or white Europeans, occurring in only 1-5% of the population, but has been found in up to 20-30% of Middle Eastern and North African populations.[8-10]

Drug Metabolism

It has been estimated that nearly a third of all drugs currently on the market undergo oxidative metabolism via CYP2D6.[1,11] Many cardiovascular agents, including most of the beta-adrenergic blocking agents and the Class I antiarrhythmics, are cleared through this pathway, as well as many antidepressants and antipsychotics.[1] The following table lists some examples of drugs metabolized, at least in part, by CYP2D6.

Table 1. Examples of drugs metabolized via CYP2D6[1]

Amiodarone
Amphetamine salts
Amitriptyline
Atomoxetine
Bupropion
Carvedilol
Celecoxib
Chlorpromazine
Cimetidine
Citalopram
Clomipramine
Codeine
Desipramine
Dexamethasone
Dextromethorphan
Diphenhydramine
Doxepin
Doxorubicin
Flecainide
Fluoxetine
Haloperidol
Imipramine
Lidocaine
Methadone
Metoclopramide
Metoprolol
Mexiletine
Mirtazapine
Nortriptyline
Ondansetron
Paroxetine
Pimozide
Propafenone
Propranolol
Ranitidine
Risperidone
Ritonavir
Terbinafine
Thioridazine
Timolol
Tramadol
Venlafaxine
Vinblastine
Vincristine

Examples in Pediatrics

The application of pharmacogenomic information to clinical trial design is becoming an accepted part of the drug development process. Cytochrome P450 enzyme activity is often evaluated in patients participating in pharmacokinetic studies of new drugs known to be metabolized through this system. Knowledge of metabolic phenotype (e.g. the percentage of UM or PM subjects in a clinical trial) can also aid in evaluating differences in clinical response. Investigation of metabolic phenotype can also be done on an individual basis to aid in evaluating patients who fail to respond to treatment or develop toxicity with standard drug regimens. While not yet routine, due to both cost and availability, testing for CYP2D6 function in specific settings may provide useful information for patient management.

Atomoxetine

Earlier this year, Michelson and colleagues evaluated the effects of different CYP2D6 phenotypes on the response to atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder.[12] Five hundred eighty-nine patients between 6 and 18 years of age who were participating in premarketing clinical trials with atomoxetine were included in this evaluation. Overall, patients with the PM phenotype required lower atomoxetine doses to achieve symptom control. In the patients enrolled in the atomoxetine efficacy trial, the final dose in the subjects with a PM phenotype was 1.28+0.36 mg/kg/day, compared to 1.37+0.33 mg/kg/day for the EM group ($p=0.12$). The discrepancy between the phenotypes was more apparent in the open-label trials, where the final dose was 1.33+0.44 mg/kg/day in the PM group versus 1.50+0.36 mg/kg/day in the EM group ($p<0.001$).

As a group, children with the PM phenotype had significantly greater reductions in their mean symptom severity scores compared to the extensive metabolizers (-20.9$\pm$15.2 versus - 14.1 $\pm$13.4, $p=0.002$, using the ADHD Rating Scale-IV Parent Version: Investigator-Administered and Scored assessment tool). More patients in the EM group discontinued therapy due to lack of efficacy. The PM group also had greater

increases in heart rate and diastolic blood pressure than the EM group (9.7±13.9 bpm versus 5.8±12.9 bpm, $p<0.001$ and 4.2±9.5 mmHg versus 2.6±9.6 mmHg, $p=0.014$, respectively), possibly reflecting drug accumulation. Based on the results of their analysis, the authors concluded that differences in CYP2D6 phenotypes can affect response to atomoxetine and may suggest a need for dosage adjustment. Patients with the PM phenotype required lower doses, but experienced greater clinical benefit and the potential for increased adverse effects.[12]

Codeine

On August 17, 2007, the Food and Drug Administration (FDA) released a Safety Alert regarding the use of codeine in breastfeeding women.[13] The alert was prompted by the August 2006 report in *The Lancet* describing the death of a 13-day-old infant whose mother was taking codeine for postpartum pain.[14] The mother was taking a combination product with codeine 30 mg and acetaminophen 500 mg, initially at a dose of 2 tablets every 12 hours for two days, then one tablet every 12 hours for approximately 2 weeks. On day 7 of life, the infant developed lethargy and difficulty feeding. He continued to decline, and was found dead six days later. Post-mortem analysis revealed a blood concentration of morphine (the active metabolite of codeine) to be 70 ng/mL. For comparison, the average morphine concentration of babies whose mothers were receiving codeine at doses of 60 mg every 6 hours is typically between 2 and 20 ng/mL. Genotypic analysis of the mother revealed a CYP2D6*2x2 duplication, classifying her as a UM phenotype. The phenotype was consistent with an increased rate of codeine metabolism and a resulting increase in production of morphine. The infant's death was attributed to the high concentrations of morphine present in the breastmilk, in conjunction with a reduced ability to metabolize morphine.

As a result of this case, the FDA has urged health care providers to be aware of the risks of administering codeine to breastfeeding women. The use of other analgesics should be considered; if codeine is selected as the best alternative, the nursing infant should be closely monitored. Parents should be aware of the potential risk to infants and be alert for signs of excessive sedation or difficulty breathing.[13]

Two other papers published earlier this year confirm the potential for CYP2D6 genetic polymorphism to lead to an altered response to codeine.[15,16] Voronov and colleagues described severe apnea occurring in a 29-month-old child receiving standard doses of a combination acetaminophen/codeine product following tonsillectomy.[15] Genotyping revealed the presence of a CYP2D6*1/*2P heterozygous variant associated with the UM phenotype. The authors speculated that accumulation of the morphine metabolite resulted in respiratory depression and led to the patient's apnea and resulting need for mechanical ventilation.

Brousseau and colleagues conducted CYP2D6 genotyping in a group of children being treated for sickle cell crisis.[16] The authors found that the children with genotypes associated with reduced enzymatic function (a PM phenotype) were less likely to respond to codeine, suggesting that they were not producing adequate serum concentrations of the morphine metabolite to produce the desired level of analgesia.

Summary

Research on the development of CYP2D6 function, as well as the presence of genetic polymorphisms, is providing valuable information on the metabolism of a variety of drugs used in infants and children. Combining pharmacogenomics and developmental pharmacology can aid in dose optimization, producing the desired pharmacologic effects while minimizing adverse effects.

References

1. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005;352:2211-21.
2. Blake MJ, Castro J, Leeder JS. Ontogeny of drug metabolizing enzymes in the neonate. Sem Fetal Neonatal Med 2005;10:123-38.
3. Jacqz-Aigrain E, Cresteil T. Cytochrome P450-dependent metabolism of dextromethorphan: fetal and adult studies. Develop Pharmacol Ther 1992;18:161-8.
4. Blake MJ, Gaedigk A, Pearce RE, et al. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther 2007;81:510-6.
5. Court MH. A pharmacogenomics primer. J Clin Pharmacol 2007;47:1087-103.
6. Stamer UM, Musshoff F, Kobilay M, et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007;82:41-7.
7. Dalen P, Dahl ML, Benal Ruiz ML, et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functions CYP2D6 genes. Clin Pharmacol Ther 1998;63:444-52.
8. Aklillu E, Persson I, Bertilsson L, et al. Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and mutliduplicated functional CYP2D6 alleles. J Pharmacol Exp Ther 1996;278:441-6.
9. McLellan RA, Oscarson M, Seidegard J, et al. Frequent occurrence of CYP2D6 gene duplication in Saudi Arabians. Pharmacogenetics 1997;7:187-91.
10. Shen H, He MM, Liu H, et al. Comparative metabolic capabilities and inhibitory profiles of CYP2D6.1, CYP2D6.10, and CYP2D6.17. Drug Metab Dispos 2007;35:1292-300.

11. Gardiner SJ, Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. Pharmacol Rev 2006;58:521-90.
12. Michelson D, Read HA, Ruff DD, et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 2007;46:242-51.
13. U.S. Food and Drug Administration. FDA Alert: Use of codeine products in nursing mothers. Available at: www.fda.gov/cder/drug/infopage/codeine/default.htm (accessed 10/5/07).
14. Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006;368:704.
15. Voronov P, Przybylo H, Jagannathan N. Apnea in a child after oral codeine: a genetic variant- an ultra-rapid metabolizer. Pediatr Anaesth 2007;17:684-7.
16. Brousseau DC, McCarver DG, Drendel AL, et al. The effect of CYP2D6 polymorphisms on the response to pain treatment for pediatric sickle cell pain crisis. J Pediatr 2007;150:623-6.

Pharmacology Literature Review

Guanfacine pharmacokinetics

The pharmacokinetic profile of a new extended-release formulation of the alpha-2 agonist guanfacine was evaluated in this study. Twenty-eight children participated in the study: 14 between 6 and 12 years of age and 14 between 13 and 17 years of age. All patients received a 2 mg dose on day 1, followed by daily 2 mg doses on days 9-15, 3 mg doses on days 16-22, and 4 mg on days 23-39. The extended-release guanfacine demonstrated linear kinetics. Average maximum plasma concentration was 2.55±1.03 ng/mL and 1.69±0.43 ng/mL in the two groups after the initial dose, with values approximately doubling after repeated dosing. Mean half-life values were 14.4±2.39 hours in the younger children and 17.9±5.77 hours in the teens. The most commonly reported adverse effects were somnolence, insomnia, headache, blurred vision, and altered mood. Blood pressure and heart rate were unchanged, and all electrocardiogram results were within normal limits. Boellner SW, Pennick M, Fiske K, et al. Pharmacokinetics of a guanfacine extended-release formulation in children and adolescents with attention-deficit-hyperactivity disorder. **Pharmacotherapy 2007;27:1253-62.**

Hypertonic saline in CF

The use of inhaled hypertonic saline (5-8% sodium chloride) has emerged over the last decade as a useful adjuvant treatment in patients with cystic fibrosis. The authors of this brief review describe the studies conducted with hypertonic saline to date, including those conducted with a normal saline (placebo) control group and those using dornase alfa (rhDNase) as a comparator. Based on their review of the literature, the authors conclude that although hypertonic saline appears to improve mucociliary clearance and lung function compared to normal saline, it has not been found to be as effective as dornase alfa. Condren ME, Donald DV, Dunehew KL. The emerging role of hypertonic saline in cystic fibrosis-related pulmonary disease. **J Pediatr Pharmacol Ther 2007;12:23-30.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/28/07:

1. A metered dose inhaler containing the combination of fluticasone propionate, a corticosteroid, and salmeterol, a long-acting $beta_2$ adrenergic agonist, (Advair® HFA) was added to the Inpatient Formulary. The usual dose for patients with asthma is 2 inhalations twice daily.
2. Cytarabine liposomal injection (Depocyt®), a sustained-release formulation of cytarabine, was added for the intrathecal treatment of lymphomatous meningitis.
3. The restriction on paclitaxel protein-bound particles for injectable suspension (Abraxane™) was changed to its FDA-approved indication for treatment of breast cancer after failure of combination therapy for metastatic disease or in patients with relapse within 6 months.
4. Aminolevulinic acid for topical solution 20% (Levulan® Kerastick®) was added to the Formulary for use in the Dermatology clinic. This product is indicated in patients with stage 1 or 2 actinic keratoses of the face and scalp, in combination with photodynamic therapy.
5. Zoledronic acid injection (Reclast®) was added to the Formulary for use in the Endocrinology clinic. It is a bisphosphonate used in the treatment of adults with Paget's disease or postmenopausal osteoporosis.
6. A request for the addition of carvedilol phosphate extended-release (Coreg CR™) was rejected. Generic immediate release carvedilol will remain on the Formulary.

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