

Pharmacokinetic Considerations in the Treatment of Pediatric Behavioral Issues

Karen M. Theoktisto

Topic: A review of psychopharmacology and the genetic considerations with pharmacokinetics is followed through a case study to demonstrate the optimal clinical treatment of the child with pediatric behavioral issues.

Purpose: The knowledge of the pharmacokinetic and pharmacodynamic consequences of medications in clinical practice is of the utmost importance for all pediatric nurse practitioners. Drug interactions occur when the efficacy or toxicity of a medication is changed with the addition of another medication or dosage change.

Sources: An integrative literature review from nursing, medicine, psychology, and child psychiatry.

Conclusions: The current climate of a child psychiatric specialist shortage leaves the charge of this vulnerable population in the hands of the primary care provider. Pediatric primary care now requires a clear understanding of the psychostimulant and non-stimulant medications, thorough screening of each child, appropriate dosage regulation, and close monitoring of all outcomes. It is imperative that pediatric nurse practitioners understand the pharmacological interactions and safety in the treatment of children with behavioral issues.

Pharmacogenetics, the study of the effects of genetic differences on a person's response to medication, can assist in optimizing drug efficacy and minimizing adverse drug reactions in the treatment of behavioral issues in children (Rogers, Nafziger, & Bertino, 2002). Pharmacokinetic data are limited in the field of pediatrics, and the systematic study of the safety and efficacy of pharmaceutical treatment in the pediatric age group is scarce. Approximately 4.4 million children between 4 and 17 years of age have been diagnosed with attention deficit hyperactivity disorder (ADHD), and as of 2003, 2.7 million children are receiving medications for ADHD from a health care provider,

making it one of the most common behavioral disorders of childhood (Centers for Disease Control and Prevention [CDC], 2008). Epidemiologic studies have estimated the prevalence of ADHD in school-aged children to be anywhere between 1% to 20% (American Academy of Pediatrics, 2000; CDC, 2008).

Diagnosis of ADHD needs to be made carefully and thoughtfully, and should include physical examination, laboratory testing, psychological screening, and frequent follow up. A multitude of both free and low-cost psychological screening tools exist that can be used within the primary care home. Diagnosis should not be made without careful consideration of these factors. It is of paramount importance to make efficacious and well-tolerated drug treatment decisions to decrease the likelihood of drug interactions in this vulnerable population.

The current climate of a child psychiatric specialist shortage leaves the charge of this vulnerable population in the hands of the primary care provider. This makes the knowledge of the pharmacokinetic and pharmacodynamic consequences of clinical practice of the utmost importance. Drug interactions occur when the efficacy or toxicity of a medication is changed by the administration of another medication or substance (Dresser, Spence, & Bailey, 2000). Pharmacologically, children cannot be regarded as little adults because medications can intensify or become toxic from the differences in

the processes of drug disposition in the mature adult or in the receptor sensitivity that result from changes in receptor binding or strength. The phenotype expression of medications used in children should be of even greater interest due to the inability to monitor the effects and adverse reactions by objective methods (Rane, 1999).

Many stimulant medications used for the treatment of ADHD are metabolized through the Cytochrome P450 (CYP450) system, which is the major enzyme system for the oxidation of medications (Rane, 1999). Drug interactions occur as a result of the induction or inhibition of the CYP450 enzymes, which assists the metabolism of the medication by making it more water soluble and more readily excreted through the urine or bile (Cupp & Tracy, 1998). Individual genetic differences may make one child more susceptible to interactions than other children. Understanding the CYP450 enzyme interaction system will allow prescribers the ability to better anticipate and manage each individual child's response to a particular drug regimen.

Until genetic tests for CYP450 become more widely available, health care providers can anticipate drug interactions by becoming familiar with which medications inhibit or induce CYP450 enzyme reactions. In 2006, the United States Federal Department of Drug Administration (FDA) granted marketing approval for the first pharmacogenetic test using a DNA

Karen M. Theoktisto, DNP, ARNP, PNP-C, is a Pediatric Nurse Practitioner, the University of Florida/ Shands Eastside Community Practice, Gainesville, FL, and was a Doctorate of Nursing Practice Student, the University of Florida, at the time this article was written.

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The CNE Posttest
can be found
on pages 374-375.

microarray called the AmpliChip CYP450 (De Leon, 2006). This test can predict phenotypes and tests for genotypes CYP2D6 and CYP2C19, which allow the practitioner to choose specific medications for each specific patient. The test costs between \$600 (U.S.) and \$1300 (U.S.), and is currently not covered by third-party insurers (Xinmin et al., 2008).

The developmental aspects of drug metabolism is often overlooked in clinical practice, and it should be carefully considered because of the increasing research on the number and isosymes of the CYP450 and other enzymes systems in adults (Benedetti & Baltes, 2003). The potential for drug-to-drug interactions in psychopharmacotherapy is very high, especially in children or adolescents who may be treated for multiple concomitant medical diagnoses (Sproule, Naranjo, Brenner, & Hassan, 1997). Multiple factors, including dietary, environmental, and behavioral factors, affect the metabolism of medication, which can significantly modify both the pharmacokinetics and metabolism of action in the pediatric population. A case study of an adolescent followed in primary care who is on multiple medications that could trigger a CYP450 reaction is presented here.

Case Study

Melissa is an 18-year-old high school senior who is the captain of the varsity volleyball team. Melissa was diagnosed with ADHD at age 8 and has been on low doses of methylphenidate since that time. Recently, Melissa has complained of an increase in difficulty keeping up with her school load and sports schedule, and is totally unable to focus at the end of the day. A trial dose of 30mg of lisdexamfetamine, a new prodrug amphetamine stimulant, was written. Melissa is a typical high school student with a full academic and sports load, and she sleeps very little at night. She is on oral contraceptives, fenofexodine for allergy treatment, and multiple supplemental vitamins.

After two days of taking the new medication, Melissa experienced an episode of tachycardia, chest pain, and syncope while competing in a volleyball game. The new dose of stimulant was stopped, and the symptoms have not reoccurred. Not only was this episode frightening, but an extensive cardiac work up was performed per National Collegiate Athletic Association (NCAA) rules to ensure her ability to play volleyball at the college level and

not lose her future college sports scholarship. This case represents the importance of careful and slow titration of stimulant medications in adolescents who may be on multiple medications or be consuming supplements and other substances without knowledge of a parent.

ADHD Treatment in Pediatric Primary Care

The primary treatment for ADHD is stimulant medication; however, a wide variety of longer-acting pharmaceutical options with various lengths of duration is now available. Although pharmaceutical treatment provides quick, short-term benefits with a wide margin of safety, a child's response to each medication is highly individual with regard to both choice and dose (Stevens, 2006; Wolraich, 2006). Due to the shortage of child psychiatric providers in most communities, increasing numbers of children with ADHD are receiving treatment with medication from the primary provider.

Genetic endowment and other factors related to temperament can underlie a child's response to pain or medication side effects as they develop (Walco & Goldschneider, 2008). Children do not report side effects of medications in the same manner or description method as adults. Reactions to medication treatment in children are dependent on individual differences, such as temperament, genetics, developmental variations in maturation, and central procession of information. Children do not develop logical response to stimulus until after age 11 (Walco & Goldschneider, 2008). Therefore, side effects from medications need to be closely monitored via parent interview and teacher observation both prior to and after treatment begins or any changes are made. Treatment recommendations for side effects from medications in the treatment of ADHD can be found in Table 1.

Primary care is an opportune location to closely monitor individual reactions to medications, such as heart rate and blood pressure. This is especially important because many children are diagnosed with co-morbid disorders, such as depression or oppositional defiant disorder, and many are now prescribed multiple medications (Tosyali & Greenhill, 1998). The phenotypic expression of pharmaceutical reaction is of even greater importance in children because the drug effect and side effect are often difficult to monitor by objective means (Vitiello, 2001).

New reports of drug-to-drug interactions are released daily, and with limited research available concerning the unique vulnerabilities of children, caution should be exercised when prescribing concomitant medications. Many of these new ADHD medications have new formulations that allow methylphenidate to be released over an extended period of time. Several of these newer medications use a microbead technology and may last anywhere from 8 to 12 hours (Wolraich, McGuinn, & Doffing, 2007).

Cytochrome P450 in Pediatric Behavioral Treatment

Current research indicates that an increase in the use of psychotropic and psychostimulant, such as stimulants, antidepressants, and clonidine, is occurring in children as young as 2 years old (Vitiello, 2001). This raises many concerns as these medications are not approved for use in children under the age of 6, nor have these medications been tested for efficacy or safety in this age group. Methylphenidate is approved by the FDA for treating ADHD only in children over the age of 6. Antidepressants, such as sertraline and fluvoxamine, are approved only in school-age children for the treatment of obsessive-compulsive disorder and not for depression. Use of any pediatric behavioral medications increases the chance of any number of CYP450 drug-inhibitor interactions occurring, including life-threatening events (Dresser et al., 2000).

Psychostimulants

Methylphenidate is the most widely prescribed of the psychostimulants for the childhood disorder ADHD. Neuropharmacologically, it is viewed as a dopamine uptake inhibitor and facilitates a therapeutic effect by facilitating a dopaminergic neurotransmission by eliciting a cocaine-like action at the site of the dopamine transporter (Markowitz & Patrick, 2001). Methylphenidate and dopamine both compete for the uptake binding site, thus impeding clearance of dopamine in the synapse area. Methylphenidate appears to be implicated in pharmacokinetic interactions that are more indicative of metabolic inhibition, although the true mechanism remains unclear (Wolraich & Doffing, 2004). Amphetamines are more often implicated in metabolic interactions and could potentially be influenced by the cytochrome P450 (CYP) 2D6 pathway. Any medication that is a CYP2D6

Table 1.
Stimulant Medication Side Effects

| Type | Symptom | Action | |
|-----------------|--------------------------|--|---|
| Expected | Reduced appetite | Check weight every 3 months Adjust dose as needed | |
| | Sleep difficulty | Check timing of doses Review sleep hygiene | |
| Possible | Over-focused | Monitor dose Taper increase slowly Consider reducing dose | |
| | Anxiety | Consider reducing dose | |
| | Nervousness | May be rebound Consider adding afternoon dose or changing agent | |
| | Irritability | May be rebound Consider adding afternoon dose or changing agent | |
| | Tearfulness | May be rebound Consider adding afternoon dose or changing agent | |
| | Headache | Provide reassurance Monitor Consider dose change | |
| | Dizziness | Check blood sugar Give medication with food | |
| | Drowsiness | Reduce dose | |
| | Tics/twitches | Consider reducing dose Add another medication to control tics | |
| | Gastrointestinal upset | Consider change of medication type Give medication with meals | |
| | Staring spells | Reduce dose | |
| | Increased blood pressure | Reduce dose Check other medication intake Monitor closely | |
| | Increased heart rate | Reduce dose Monitor closely | |
| | Rare | Blood sugar changes | Review nutritional intake Check labs |
| | | Psychosis | Stop medication Refer to psychiatry |
| Paranoia | | Stop medication Refer to psychiatry | |

inhibitor may increase the levels or effects of a stimulant in a susceptible individual's system, thereby increasing the cardiac risk.

Methylphenidate causes a small but significant increase in blood pressure approximately 45 minutes after administration (Bhat, Grizenko, Sanche, & Joobar, 2008). Children often have poor adherence with taking medications and following medication regimes, for suboptimal outcomes in

the treatment of children with ADHD (Gau et al., 2008). It is important for health care providers to ensure adherence prior to adjusting dosage or changing medication in the treatment of ADHD.

A new amphetamine derivative, lisdexamfetamine, is now being marketed to provide longer duration with less likelihood of abuse. This new amphetamine derivative is reported to have less probability for a CYP2D6 reaction;

however, reports of chest pain, hypertension, and other cardiac side effects continue to be reported, as in Melissa's case. Although lisdexamfetamine has been designed as a therapeutically inactive d-amphetamine prodrug with a probability of less adverse reactions, long-term trials reported that 74% of the patients reported treatment emergent adverse reactions (Blick & Keating, 2007). However, it is important to note that many side effects clas-

sified as emergent were mild and transient in nature. Further detailed investigation of the pharmacokinetic properties of lisdexamfetamine in children with ADHD is needed to clarify the safety and impact of this issue in children (Bany & Clarke, 2007).

Psychotropics

Pharmacogenomics played a crucial role in the development of a new non-stimulant medication for ADHD called atomoxetine. Atomoxetine is a substrate for hepatic cytochrome (CYP) 450 isozymes and specifically inhibits CYP2D6 and CYP 3A4 *in vitro* (McGough et al., 2003). The metabolism of atomoxetine by CYP2D6 raises concern for patient safety, especially because 5% to 10% of Caucasians and 0% to 19% of African Americans have polymorphisms at CYP2D6 that can lead to slow metabolism and concomitant use increases drug plasma levels (Stevens, 2006). Many other psychotropic medications that may be used in conjunction with atomoxetine, such as selective serotonin reuptake inhibitors, may strongly inhibit CYP2D6 activity. This inhibition can lead to the possibility of adverse medication reactions.

Clinically significant drug-to-drug interactions occur, and the majority of psychotropic medications used with pediatric patients are metabolized through the CYP450 system (Francis, 2002). Recent reports of death in pediatric patients taking psychotropic medications have raised the possibility of ventricular dysfunction with the use of these drugs. This has raised concerns about the appropriateness of this therapy, as well as advising baseline and electrocardiographic (EKG) monitoring of any patient receiving clonidine (Gutgesell et al., 1999). Pediatric patients experience many different factors that may make the young heart susceptible to ventricular dysfunction, sudden ventricular dysrhythmias, or even death.

Clonidine, an alpha-adrenergic agonist, is increasingly being used for the treatment of ADHD. Clonidine is reported to affect hyperactivity and roused aggressive behavior that may not be completely managed by stimulant use alone (Cantwell, Swanson, & Connor, 1997). The majority of psychotropic medications are metabolized through the cytochrome P450 system, which can cause significant adverse reactions or even sudden death when this system is inhibited. This leads to elevated levels of medications that prolong the QT interval and can produce ventricular tachycardia (torsade de

pointes) (Gutgesell et al., 1999). These complex reactions require genetic predisposition, structural cardiac disease, drug-to-drug interactions, drug dosage concerns, and drug metabolism and clearance. Before any cardiac medication is added to children also taking other psychotropic medications, special attention should be given to the potential for drug-to-drug interactions, QTc prolongation, or even sudden death (Francis, 2002).

Many atypical antipsychotic medications are being added to stimulant therapy by child psychiatrists and some pediatric health care providers for a newer approach to obsessive-compulsive disorder, tic disorders, aggressive disorders, and some cases of developmental disorders (such as autism, Rett Syndrome, childhood disintegrative disorder, Asperger's, and eating disorders) (Dubois, 2005). The atypical antipsychotics are well absorbed from the gastrointestinal track, but they also undergo a significant first-pass metabolism. These medications are highly lipophilic and protein bound, and accumulate in the brain, heart, lung, and other tissues. Thus, the medication has a large volume of distribution in the body, and children tend to metabolize antipsychotics more rapidly. This is of particular concern because antipsychotic medications are primarily metabolized by the cytochrome P450 system in the liver (DuBois, 2005).

Considerations for Pediatric Practice

The American Academy of Pediatrics (2001) lists the following recommendations in the treatment and diagnosis of a child with ADHD in the primary care setting:

- Establish a treatment plan program that recognizes ADHD as a chronic condition.
- Establish a collaborative relationship with the clinician, parents, child, and school personnel with specific targets.
- Recommend medication and/or behavioral treatment based on specific individual targets.
- Schedule routine visits to address target outcomes, evaluate diagnosis, use all appropriate treatments, review adherence to treatment plan, and examine for coexisting conditions.
- Provide systematic follow-up is essential to monitor adverse side effects, target outcomes, and gather information from parents, teachers, and the child.

Prescribing ADHD medication in pediatrics requires careful consideration in regard to the safety and screening of each individual child, especially because each year in the United States, an estimated 3% of children age 3 to 18 years receive pharmacological treatment for ADHD (Olfson, 2004). Data reviewed by the FDA Committee in 2006 revealed that the annual incidence of sudden death in children and adolescents using psychotropic medications is low. The FDA's Adverse Event reporting system revealed that between 1999 and 2003, there were 25 reports of sudden death in children using stimulant medications, 8 using methylphenidate, and 17 using amphetamines (Gephart & Leslie, 2006).

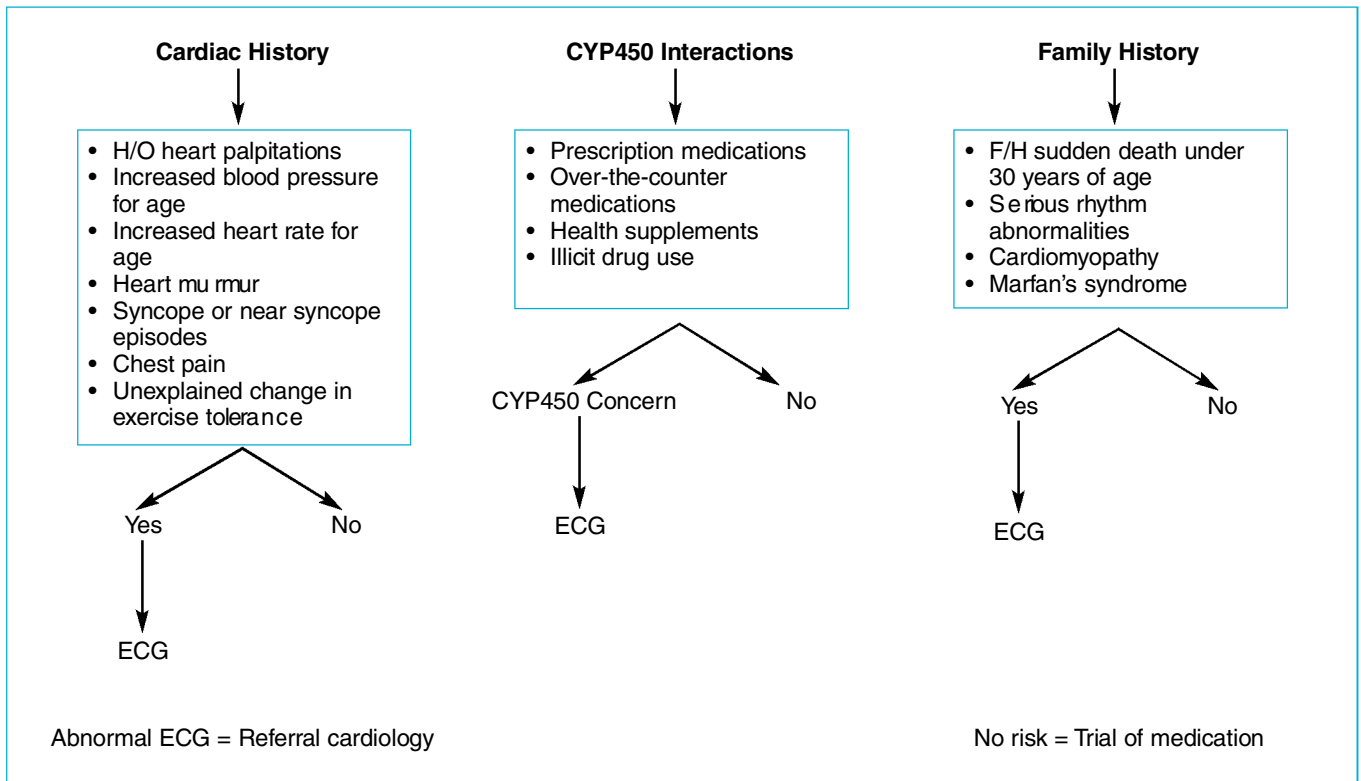
Careful screening prior to prescribing should include consideration of any underlying cardiac abnormalities, family history of ventricular tachycardia, and any other medical condition (see Figure 1). Reviews of family response to medications and their side effects may lead to recognition of genetic variants and potential clinical significance in treatment choices (McGough et al., 2003). This type of pharmacogenomic history may provide an opportunity to increase knowledge of stimulant activity in a specific individual and identify risks for adverse reactions. A patient history should include any past history of syncope, near syncope, palpitations, family history of deafness, sudden unexplained cardiac death, or tachycardic episodes. Physical examinations should be scheduled at least every three months to document the presence or absence of a normal cardiovascular exam, monitor vital signs, and check neurological status.

Health care providers are obligated to be cognizant of drug interactions that may alter drug absorption and clearance. It is also imperative to educate and warn parents and families about the potentially lethal consequences of using multiple medications metabolized by the cytochrome P450 system (Francis, 2002). Additions of new medications, changes in clinical status, and increases or decreases in doses should be carefully considered in the decision to treat and monitor ADHD.

The choice of which medication to use in the treatment of ADHD should be individualized, based on the child's age, desired duration of effect, and cost. Methylphenidate is only about half as strong as amphetamine, and should be considered first line for easier fine tuning and to minimize possible adverse reactions.

Health care providers, such as nurse

Figure 1.
Screening Questions Prior to Implementation of Pharmaceutical Treatment of the ADHD Child



practitioners, are often the first health care professionals that parents encounter when they suspect their child may have ADHD. The majority of these children will be diagnosed and treated in a primary care setting. Each primary care health care provider must remain abreast of likely changes and diagnostic criteria for ADHD, current clinical guidelines, and advances in the assessment and treatment of children and adolescents with ADHD and other co-morbidities.

Medicine is still far from being totally explained by science, as in the case of pediatric psychopharmacology. Children are different not just in age but in developmental stages, and sometimes it can be difficult to discern the difference. Therefore, the treatment of children and adolescents can sometimes require trial and error, an open mind, a vigilant clinical assessment, and a flexible treatment plan (Tosyali & Greenhill, 1998). The key to optimal clinical treatment of the child with ADHD is a clear understanding of the psychostimulant and non-stimulant medications, thorough screening of each child, appropriate dosage regulation, and close monitoring of all outcomes.

Clinical genetic research is now providing the opportunity to incorporate

pharmacokinetics into drug development (Rogers et al., 2002). This research may soon lead health care providers toward anticipating how a child with a defined genotype or phenotype might respond to a particular drug for a particular diagnosis. It may also better explain and avoid drug toxicities and therapeutic failures that might occur with a cytochrome P450 reaction, as with Melissa. Pharmacogenetics can assist health care providers in the notion that one dose is not right for all, and newer is not necessarily safer, especially in the very young.

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