

# BACK TO BASICS



A review of the scientific foundations of current clinical practice

## Author Disclosure

Drs Tetelbaum, Finkelstein, Nava-Ocampo, and Koren did not disclose any financial relationships relevant to this article.

## Understanding Drugs in Children: Pharmacokinetic Maturation

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**Objectives** After completing this article, readers should be able to:

1. Recognize age-related changes in pharmacokinetics and pharmacodynamics of drugs.
2. Describe the dynamics of rational drug dosing for neonates and children.
3. Identify areas of challenge where more drug research is needed during development.

### Introduction

Rapid age-related physiologic changes in the pediatric age group, especially during the first postnatal year, affect the absorption, distribution, metabolism, and elimination of drugs. This article reviews pharmacokinetic principles in neonates, infants, and children to help pediatricians understand the rationale for drug therapy and toxicity in these patients.

### Absorption

Drugs are administered through a wide range of routes (Table 1). General pharmacokinetic and pharmacodynamic principles can be defined by grouping them in two major routes: intravascular and extravascular. Extravascular administration entails ab-

sorption, distribution, metabolism, and excretion. Bioavailability is the fraction of drug reaching the systemic circulation following its administration by any route. Because drugs administered intravenously do not require an absorption process, their bioavailability is 100%.

### Oral Administration

Among the extravascular routes, oral administration commonly is used not only because it is painless, but also because technology involved in oral formulations is relatively less costly and requires fewer pharmaceutical processes. However, in some cases, the choice of administration route depends on the site of action, the desired plasma drug concentrations, and the time at which a certain drug concentration must be achieved. Bioavailability after oral administration naturally is less than after intravenous administration. The primary factors affecting oral bioavailability are listed in Table 2.

Gastric emptying is slow (6 to 8 h) in neonates and infants. Consequently, the rate at which most orally administered drugs are absorbed is slower in neonates and young infants, and the time to achieve the maximal

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## Table 1. Primary Routes of Drug Absorption in Children

### Intravascular

### Extravascular

- Oral
- Rectal
- Inhalational
- Subcutaneous
- Intramuscular
- Topical

### Less Common:

- Intranasal
- Intrathecal
- Sublingual
- Intraosseous
- Intra-articular

## Table 2. Factors Affecting Bioavailability of Oral Drugs

### Physicochemical Factors

- Molecular weight
- Molecular charge (pKa)
- Disintegration of the drug
- Dissolution characteristics in gastrointestinal fluid
- Lipophilicity

### Physiologic Factors

- Gastric content
- Gastric and duodenal pH
- Intestinal blood circulation
- Gut membrane permeability
- Hepatic first-pass metabolism
- Enterohepatic recirculation
- Biliary excretion
- Drug efflux in gut wall (eg, by P-glycoprotein)
- Gastrointestinal and hepatic diseases

plasma concentrations ( $T_{max}$ ) and, therefore, the therapeutic effect may be prolonged.

Gastric pH is neutral at birth and decreases to 1 to 3 within 24 hours. Hence, acid-labile drugs such as penicillin G, amoxicillin, nafcillin, and erythromycin are absorbed more efficiently in neonates and infants than in adults when administered orally. Oral absorption of drugs that are weak acids, such as phenobarbital, has been shown to be lower in infants than in older children and adults.

Food intake stimulates gastrointestinal secretions, hormones, and bile salts (which lower gastric pH), delays stomach emptying, and increases gastrointestinal transit time. Fluid volume and dietary fat in the meal appear to be the primary food-related factors affecting drug absorption. Meals can alter the absorption rate of sustained-release drugs such as theophylline, making it unpredictable. Iron absorption is facilitated by meat ingestion. Multivitamins containing iron and calcium interfere with the absorption of various medications, such as levothyroxine, tetracycline, fluoroquinolones, captopril, and folic acid.

The activity of gastrointestinal enzymes (eg, pancreatic enzymes) is low in infants younger than 4 months of age. Absorption of lipid-soluble drugs is decreased in neonates due to low production of lipase and bile acids. Peristalsis also may affect drug absorption. Prokinetic agents, such as cisapride, have been shown to increase the absorption of morphine, diazepam, and cyclosporin. In the neonate, peristalsis is irregular, making the absorption of drugs in the small intestine highly variable. Diarrhea shortens intestinal transit time and may decrease the absorption of sustained-release formulations.

Rectal administration of drugs that have a large first-pass effect, such

as diazepam, have been used effectively in children. Diazepam bioavailability is higher following rectal than oral administration by circumventing the portal system. Midazolam also is more effective when administered rectally compared with intramuscular injection. The absorption time of rectal acetaminophen suppositories is greater among infants younger than 3 months of age versus older infants.

### Intramuscular Administration

Absorption following intramuscular administration depends on various factors inherent to the drug (eg, lipophilicity versus water solubility), the site of administration, and blood supply to and from the injected site. The latter may be compromised in newborns whose peripheral perfusion is poor. Muscular mass and activity also are decreased in neonates compared with older children.

### Topical Administration

For certain dermatologic conditions, the topical route of administration is easier, faster, and safer, minimizing systemic adverse effects. Transdermal absorption and systemic exposure to drugs, such as corticosteroids, antihistamines, and antiseptics, may be increased in children, particularly in neonates and infants, due to increased body surface area and thinner epidermis and stratum corneum.

### Inhalational Administration

Administration of drugs via inhalation is used commonly in children. The primary goal is to achieve a localized pulmonary effect, although systemic exposure occurs (eg, inhaled corticosteroid therapy for asthma).

### Distribution

Independent of the route of administration, once the drug enters the bloodstream, it is distributed into var-

ious compartments of the body. Drug distribution varies significantly with age due to developmental changes in body composition, protein binding, hemodynamic factors (cardiac output, tissue perfusion), and membrane permeability.

The preterm neonate has more total body water (80% of total body weight) compared with a term neonate (70% to 75%) and the adult (50% to 60%). The extracellular water compartment is about 40% of total body weight in the neonate compared with 20% in the adult. These changes result in a relatively higher volume of distribution and lower concentration of water-soluble drugs at receptor sites in neonates and infants compared with adults. For example, the volume of distribution of gentamicin is 0.5 to 1.2 L/kg in neonates and infants and 0.2 to 0.3 L/kg in adults. This effect translates to a need for larger doses in younger infants.

Total body fat in preterm neonates may be as low as 1% of total body weight compared with about 15% in term neonates, about 25% in 4-months-old babies, and about 20% in adults. Therefore, the volume of distribution of lipid-soluble drugs, such as diazepam and flunitrazepam, is less in preterm neonates compared with those in other age groups.

Drug distribution may be limited by certain permanent natural barriers (eg, blood brain barrier [BBB] and placenta). The BBB, however, may be altered by infectious diseases, traumatic lesions, or surgical procedures. Certain drugs (eg, morphine) evidence higher permeability through the BBB in neonates.

### Protein Binding

Plasma protein binding indicates how much of the total amount of a drug in plasma is bound to plasma proteins. Because only the unbound

fraction of the drug reaches the receptors to exert the therapeutic or toxic effects, the extent of protein binding is important. Albumin and alpha<sub>1</sub>-acid glycoprotein are the two major drug-binding proteins in plasma. Albumin has higher binding affinity for acidic compounds and alpha<sub>1</sub>-acid glycoprotein for basic compounds. Lipoproteins are other plasma proteins whose primary physiologic role is to synthesize and transport endogenous fatty acids such as triglycerides, phospholipids, and cholesterol. These proteins also are important in the binding of very lipophilic or basic compounds. Other specific proteins contribute to plasma binding and transport of certain endogenous compounds, including hormones. The red and white blood cells and platelets also can bind drugs, especially basic compounds.

Protein binding usually is reversible, although covalent binding may occur occasionally (eg, with alkylating compounds). The fraction of the total drug in plasma that is bound to proteins is determined by the drug concentration, its affinity for the binding sites, and the number of available binding sites. Protein binding is a saturable and nonlinear process. However, for most drugs, the therapeutic range of plasma concentrations is limited, and the ratio between bound and unbound fraction of the drug is relatively constant. Hypoalbuminemia due to severe liver or kidney disease, malnutrition, or cystic fibrosis may result in reduced drug binding, increasing the unbound fraction of plasma drug concentration. Burns, surgery, trauma, inflammatory processes, and malignancy may increase alpha<sub>1</sub>-acid glycoprotein serum concentrations, enhancing the binding of basic drugs. Plasma protein levels are decreased in neonates and during the course of nephrotic syndrome.

Several endogenous substances may compete for plasma protein binding sites, reducing the bound fraction of a compound in neonates. Hyperbilirubinemia, for example, reduces the protein binding for ampicillin, penicillin, phenobarbital, and phenytoin, whereas some drugs such as sulfonamides can displace bilirubin from albumin binding sites, leading to more profound neonatal jaundice.

### Drug Elimination

Drugs may be eliminated unchanged from the plasma by renal and bile excretion or following hepatic metabolism. After liver biotransformation, metabolites, which may be pharmacologically active or inactive, can be eliminated by either renal or biliary excretion or both. Some drugs exhibit enterohepatic recirculation, which involves drug excretion in bile into the small bowel and subsequent reabsorption by the portal system into the liver. Certain drugs are metabolized by enzymatic systems that may be saturated at certain serum concentrations. This form of elimination is known as Michaelis-Menten elimination kinetics. However, most plasma drug concentrations typically decay at a constant rate. The half-life of any drug is the time at which a certain plasma concentration decays by 50%. This elimination process is known as first-order elimination kinetics, and the half-life of each drug is constant until the drug is completely eliminated from the systemic circulation.

Clearance rate is the measure of the body's ability to eliminate a drug from plasma and is defined as the unit of blood volume (mL) cleared of the drug per unit of time (hour). Changes in clearance rate affect half-life inversely. If a drug undergoes hepatic clearance, a patient who has liver disease exhibits a lower clearance rate and longer half-life of cer-

tain drugs. Drug accumulation may become a problem in certain cases. Similar conclusions can be derived for a drug that is cleared renally in a patient who has renal failure. However, pharmacokinetics in a patient who has hepatic failure and receives a drug that is primarily cleared renally are not significantly affected unless other systemic changes affect the renal function directly or indirectly. Similar conclusions apply to a patient who has renal failure and is receiving a drug cleared mainly by the liver. Biotransformation and renal elimination of drugs often exhibit differences between newborns and older children due to immature systems, and differences may be more evident when immaturity is combined with disease.

### Hepatic Metabolism

In general, metabolism transforms lipophilic parent drugs to more hydrophilic metabolites, which can be excreted readily into bile or urine. Drug metabolism can be divided into two different types of reactions: phase I and phase II metabolism. Phase I metabolism generally results in either the introduction of a functional group into the parent compound (eg, by oxidation, reduction, or methylation) or the exposure of new functional groups of the parent drug. Phase I metabolism reaches maximal maturity by 1 year of age. Phase II metabolism involves conjugation of functional groups of molecules with hydrophilic endogenous substrates (eg, glutathione conjugation, glucuronidation, sulfation, acetylation). In neonates, these processes progress at a substantially lower rate than in adults (50% to 70%).

Glucuronidation reaches its full maturity by 3 to 4 years of age. Cytochrome P450 (CYP) mono-oxygenases play a role in the metabolism of various endogenous com-

pounds, such as steroid hormones, bile acids, fat-soluble vitamins, and fatty acids, and are responsible for the metabolism of more than 85% of the drugs available for clinical use. The CYP mono-oxygenases are classified according to the extent of amino acid sequence identity of different enzymes rather than catalytic activities or substrate specificity. CYP3A4 is responsible for the metabolism of about 50% of drugs on the market, followed by CYP2D6 (25%), CYP2C9 (15%), and CYP1A2 (5%). Other classes are involved in the metabolism of about 5% of drugs. These processes mature at different ages. CYP1A2 is not available in fetal or in early neonatal microsomes. It is the last hepatic CYP to develop, and its concentrations rise progressively and reach 50% of the adult value at 1 year of age or older.

Other enzymatic systems also are relevant in newborns, especially among preterm infants. About 85% of theophylline is metabolized in adults, and its plasma elimination half-life is approximately 9 hours. Approximately 95% of caffeine is metabolized, and its plasma half-life ranges from 3 to 7 hours. By comparison, the half-lives for these two compounds in the preterm infant are 50 hours and 20 to 36 hours, respectively. In neonates, only 10% of theophylline is methylated to caffeine, with 50% of the drug excreted unchanged in urine.

As the hydroxylation and acetylation activities of hepatic enzymes mature in infants and young children, the clearance rate of theophylline increases, and the half-life decreases to 3 to 5 hours (compared with 9 h in adults).

Some drugs may increase hepatic metabolism by inducing CYP sub-families or other enzymatic systems, decreasing the half-life of many drugs. This effect is evident among

the older antiepileptic drugs. Phenobarbital competitively interferes with the biotransformation of other drugs as well as endogenous substrates, such as steroid hormones, cholesterol, bile salts, and vitamins K and D. Carbamazepine induces hepatic metabolism and may lower concentrations of phenytoin, valproic acid, lamotrigine, and topiramate administered concurrently and induces the conversion of primidone to phenobarbital. Inversely, phenobarbital, phenytoin, and valproate may increase the metabolism of carbamazepine.

Among neonates born to mothers who received phenobarbital during pregnancy, the ability of the neonate to metabolize certain drugs is greater than expected due to enzyme induction, leading to subtherapeutic plasma drug concentrations because of early maturation of fetal hepatic enzymes.

### Renal Excretion

Two major pathways of renal elimination of drugs and their metabolites are apparent: glomerular filtration and tubular secretion. As blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. Although glomerular filtration begins around the ninth week of fetal life, this function is not necessary for normal intrauterine homeostasis because the placenta serves as the major excretory organ. After birth, the glomerular filtration rate (GFR) increases. The GFR is approximately 2 to 4 mL/min per 1.73 m<sup>2</sup> in term newborns and only 0.6 to 0.8 mL/min per 1.73 m<sup>2</sup> in preterm newborns. It increases rapidly during the first postnatal week to reach 40 mL/min per 1.73 m<sup>2</sup> in term neonates and 15 mL/min per 1.73 m<sup>2</sup> in preterm neonates. By the end of the third postnatal week, the GFR is 50%

to 60% of the adult value. At 3 to 6 years of age, the GFR exceeds adult values (per kg).

In general, filtration of molecules that have a molecular weight of up to 5,000 is not restricted. As molecular size increases, filtration decreases and approaches almost zero for compounds that have a molecular weight of 68,000, such as albumin. Another important mechanism that limits protein filtration is ionic charge. Endothelial cells, basement membrane cells, and epithelial cells of the glomerular capillary wall have strong negative ionic charges. Proteins have a net negative charge and, consequently, are repelled, thereby restricting their filtration.

Aminoglycosides are excreted almost entirely by glomerular filtration, and although excretion of these antimicrobials is similar in adults and children older than 6 months of age, elimination half-lives of the drugs may be prolonged significantly in the newborn. Tubular function capacities also are decreased in neonates due to a reduced GFR, tubular cell immaturity, reduced nephron length, reduced medullary solute gradient, and diminished tubular responsiveness to antidiuretic hormone.

The ability to concentrate urine in infants is reduced compared with older children and adults—600 to 700 mOsm/kg H<sub>2</sub>O versus 1,000 mOsm/kg H<sub>2</sub>O, respectively. Tubular drug secretion in children and adolescents, however, can be greater than in adults. Drugs may be secreted at the proximal tubule by active transport through the tubular membranes. Organic anions and cations are secreted into proximal tubules by separate transport processes. Some drugs, such as quinidine and amiodarone, may inhibit tubular secretion of digoxin by the P-glycoprotein transporter, producing a rapid increase in serum digoxin con-

centration, resulting in drug-related toxicity.

Two mechanisms are responsible for neonatal chloramphenicol toxicity: 1) failure of the drug to be conjugated with glucuronic acid due to inadequate activity of glucuronyl transferase in the liver (characteristic of the first postnatal month), and 2) inadequate renal excretion of unconjugated drug by the newborn. Excessive plasma concentrations of chloramphenicol accumulate because its tubular secretion is decreased in the immature neonatal kidney.

### Multiple-dose Pharmacokinetics

During the administration of multiple doses, the pharmacokinetics of any drug differ from those observed after a single dose. Drug administration may be repeated at intervals equal to its elimination half-life. During each dose interval, drug concentration rises and falls. However, after about five half-lives, drug elimination equals drug intake, and the rate of change in the amount of the drug in the body becomes zero. This equilibrium is known as “the steady state,” and the time to reach it depends only on the drug’s half-life. It is independent of the dose. The concentrations observed at steady state are proportional to the dose interval and to the ratio between drug in plasma and clearance rate. The loading dose for different drugs (eg, anticonvulsants such as phenobarbital and phenytoin) aims at reaching the therapeutic range (but not the steady state) faster. The maintenance dose varies in terms of the child’s age (Table 3). Although volume of distribution also may affect dose, age-specific differences are due primarily to the maturation level of liver enzymatic systems.

### Therapeutic Drug Monitoring (TDM)

Determination of serum drug concentrations is appropriate when the correlation between drug concentration and response is good, a surrogate marker of response is not available, the drug has a narrow therapeutic range with significant toxicity, the duration of therapy is sufficient to benefit from TDM, the interpatient variability in drug disposition is substantial, and a small inpatient variation is desired. TDM focuses on achieving and maintaining a drug concentration within a therapeutic range. Even within the therapeutic range, however, some patients do not achieve the expected pharmacologic effect, and others experience toxic adverse effects. In general, TDM samples should be drawn at “steady state” serum concentrations (usually after three to five doses). In specific cases, the time to first TDM sample may differ.

TDM of theophylline is recommended due to its high toxicity. Adverse reactions may appear after repeated administration. Seizures are relatively rare at concentrations below 40 mcg/mL, but convulsions and death have occurred at plasma concentrations as low as 25 mcg/mL. Although scarcely detectable in adults, the conversion of theophylline to caffeine is an important metabolic pathway in infants, and substantial amounts of caffeine may be accumulated after multiple doses of theophylline.

TDM also is recommended for aminoglycosides. For twice- or thrice-daily dosing regimens, a trough level measured just prior to a dose and a peak level measured 30 minutes after intramuscular or intravenous administration are recommended at steady state. The peak concentration is used to document the dose having achieved therapeutic concentration

**Table 3. Examples of Age-specific Doses of Medications Commonly Prescribed to Children**

Drug	Neonates	Infants	Children
Phenytoin	Loading dose: 20 mg/kg IV Maintenance dose: 2.5 to 4.0 mg/kg per day IV bid or 4 to 8 mg/kg per day PO qd or bid	Loading dose: 20 mg/kg IV Maintenance dose: 2 to 3 mg/kg per day IV tid or 7 to 9 mg/kg per day PO tid or bid	Loading dose: 20 mg/kg IV Maintenance dose: 2.3 to 2.6 mg/kg per day IV tid or 3 to 5 mg/kg per day PO tid or bid
Phenobarbital	Loading dose: 10 to 20 mg/kg IV up to maximum total dose of 30 mg/kg Maintenance dose: 3 to 4 mg/kg per day IV qd or 4 to 6 mg/kg per day PO qd	Loading dose: 20 mg/kg IV Maintenance dose: 2.5 to 3.0 mg/kg per day IV bid or 5 to 6 mg/kg per day PO qd or bid	Loading dose: 20 mg/kg IV Maintenance dose: 2 to 4 mg/kg per day IV bid or 3 to 5 mg/kg per day PO qd or bid
Digoxin	Digitalization (three doses): 17 mcg/kg per dose PO or 12 mcg/kg per dose IV Maintenance dose: 10 mcg/kg per day	Digitalization (three doses): 17 mcg/kg per dose PO or 12 mcg/kg per dose IV Maintenance dose: 10 mcg/kg per day 10 mg/kg per day qd	Digitalization (three doses): 13 mcg/kg per dose PO or 10 mcg/kg per dose IV Maintenance dose: 8 mcg/kg per day 6 to 8 mg/kg per day qd
Gentamicin (For oncology patients who have fever and neutropenia)			

Doses from Taketomo CK, Hodding JH, Kraus DM. *Pediatric Dosage Handbook*. 6th ed. Hudson, Ohio: Lexi-Comp, 2000; and The Hospital for Sick Children, 2004–2005 Formulary. Toronto, Ontario, Canada.

for optimal bacterial killing. Higher-than-therapeutic peak levels have been associated with a high risk of oto- and nephrotoxicity. The trough concentration is measured to avoid nephrotoxicity by drug accumulation. Trough levels alone are recommended for aminoglycosides administered once daily.

TDM should be used when the desired therapeutic effects are not observed after administration of a standard dose of digoxin, when an unknown amount of digoxin has been administered or accidentally ingested, when renal function is impaired, if drug interactions are possible, and when a toxic response is suspected. A sample of blood should be obtained immediately prior to administering a dose but at least 4 hours after the last dose.

Not all drugs can be monitored by plasma concentrations. For example, diazepam metabolites manifest a large proportion of the desired phar-

macologic effect but cannot be monitored effectively by measuring the parent drug. Similar problems are encountered with drugs that are comprised of a mixture of enantiomers, one of which is significantly more active. For many other drugs (eg, antidepressants, certain sedatives), there is no direct correlation between serum concentrations and effect.

### Drug Interactions

Drug interactions consist of modification of the magnitude or duration of action of one drug (index drug) caused by prior or concomitant administration of another drug. These interactions can occur at every pharmacokinetic stage. Only limited data are available regarding the influence of immature enzyme systems on drug interactions in infants and young children, due partly to obvious ethical and practical issues. Also, it rarely is feasible to distinguish drug interactions from other coexisting factors,

such as disease processes and environmental factors (eg, diet).

Drug interactions in the gastrointestinal tract may decrease the oral bioavailability of the index drug. The rate and extent of oral absorption of many drugs such as cephalosporins and fluoroquinolones can be impaired significantly by concomitant oral administration of calcium, magnesium, iron, or aluminum compounds. Change in the rate of gastric emptying by certain drugs alters the rate of absorption of the index drug. Drug interactions also may result from displacement of high plasma protein-bound drugs by other drugs that have a higher affinity for the same protein binding sites (see protein binding). The most common drug interactions are those affecting hepatic biotransformation. Some of these differences have been attributed to differences in the maturation of different enzymatic systems, primarily of the CYP system.

Commonly prescribed medications in children, such as erythromycin, ciprofloxacin, cimetidine, and omeprazole, have inhibitory effects on hepatic enzymatic systems, reducing the metabolism of drugs such as theophylline, codeine, beta blockers, antidepressants, corticosteroids, warfarin, and metronidazole. In such cases, toxicity may occur. In contrast, rifampin, phenobarbital, carbamazepine, and phenytoin are potent enzymatic inducers that increase the metabolism of other drugs metabolized by the liver, decreasing their plasma concentration and effect. In this case, the dose of the index drug may need to be increased.

It is expected that as enzymatic systems mature metabolically, specific drug interactions that are common in adults may occur. For example, topiramate pharmacokinetics vary with age, and combinations that include enzyme-inducing drugs (such as phenytoin, carbamazepine, phenobarbital, and oxcarbazepine) significantly lower topiramate plasma concentrations.

CYP enzymes also are involved in the metabolism of endobiotics and may regulate growth, morphogenesis, and homeostasis, especially in early embryogenesis. However, the metabolism mediated by CYP enzymes is more complex, considering that fetal tissues can metabolize different drugs and that exposure to those in utero may result in enhanced abilities to metabolize drugs in extrauterine life. Renal elimination may be decreased by concomitant administration of medications, especially for drugs that are actively excreted by the tubule. For example, salicylates can inhibit tubular secretion of methotrexate, leading to toxicity.

## Adverse Drug Reactions

Type A adverse drug reactions, which are predictable and dose-related, are characterized by exaggeration of the pharmacologic effect. Type B reactions are represented by more rare allergic, pseudoallergic, and idiosyncratic reactions.

Compared with adults, children are at higher risk of idiosyncratic reactions. Age-related changes in pharmacokinetics may play a role in some cases. Fetuses and newborns may be phenotypically poor metabolizers for certain metabolizing pathways but may acquire a phenotype consistent with their genotype later in the developmental process. For example, immature CYP2D6 may contribute to symptoms consistent with serotonin toxicity in the first 4 postnatal weeks among neonates exposed in utero to fluoxetine or paroxetine.

The risk of fatal hepatotoxicity due to valproic acid is highest (1/500) in children younger than 2 years of age who are receiving concurrent anticonvulsant therapy. This effect suggests that increased vulnerability to adverse drug reactions may occur at certain developmental stages. The mechanism of valproic acid hepatotoxicity appears to be related to its hepatotoxic metabolite 4-ene-VPA and to inhibition of beta-oxidation. It appears that CYP2C9 may be responsible for most of the 4-ene-VPA formation, whereas CYP2D6 plays a greater role during polypharmacy with anticonvulsants. Beyond the neonatal stage, CYP-catalyzed metabolism is increased, so increased formation of toxic metabolites of different drugs (eg, valproic acid, lamotrigine) may be responsible for idiosyncratic reactions such as hepatotoxicity from valproic acid and rash from lamotrigine.

## Conclusions

Although growth and development are most rapid during the first several years after birth, pharmacokinetic maturation may continue at a slower pace throughout childhood. This dynamic process of growth, differentiation, and maturation may have an important impact on drug pharmacokinetics, influencing drug response, including toxicity and dosing regimens.

## Suggested Reading

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## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

5. Among the following, the factor defining bioavailability of drugs administered by any route is:
  - A. Absorption into the circulatory system.
  - B. Binding to protein.
  - C. Distribution throughout the body.
  - D. Excretion in the urine.
  - E. Metabolism in the liver.
  
6. Which of the following drugs displaces bilirubin from albumin binding sites?
  - A. Ampicillin.
  - B. Penicillin.
  - C. Phenobarbital.
  - D. Phenytoin.
  - E. Sulfisoxazole.
  
7. In multiple-dose pharmacokinetics, the typical number of half-lives to achieve a "steady state" is:
  - A. 3.
  - B. 5.
  - C. 7.
  - D. 9.
  - E. 11.
  
8. For which of the following patients would obtaining serum drug concentrations be *least* useful?
  - A. A 2-day-old boy who has presumed sepsis and is receiving gentamicin.
  - B. An 18-month-old girl who has asthma and is receiving theophylline.
  - C. A 4-year-old girl who ingested her grandmother's digoxin tablets.
  - D. A 14-year-old boy who ingested acetaminophen tablets in a suicide attempt.
  - E. A 16-year-old girl who is receiving diazepam for anxiety.
  
9. Which of the following drugs is *most* likely to cause theophylline toxicity if taken concurrently?
  - A. Carbamazepine.
  - B. Erythromycin.
  - C. Phenobarbital.
  - D. Phenytoin.
  - E. Rifampin.