Physiological differences between children and adults result in age-related differences in pharmacokinetics and drug effect. In neonates and infants, decreased weight-adjusted doses are required because of decreased protein binding, renal excretion, and/or metabolism. For children older than 1 year of age, significantly higher weight-corrected doses compared with adults are needed for drugs eliminated by the cytochrome P450 (CYP) isozymes CYP1A2, CYP2C9, and CYP3A4. In contrast, weight-corrected doses for drugs eliminated by renal excretion or metabolism by CYP2C19, CYP2D6, N-Acetyl-transferase, and UDP glucuronosyltransferase in children are similar to those in adults. Ideally, pharmacokinetic and pharmacodynamic data should be available for all drugs used in children. Because many drugs are not approved for pediatric use, data are often limited, especially for older drugs. Understanding the effects of age on pharmacokinetics can help to determine appropriate pediatric dosing in situations in which there is limited information.

Semin Pediatr Neurol 17:208-213 © 2010 Published by Elsevier Inc.

Compared with older children and adults, there are many age-related differences between neonates and infants who can affect pharmacokinetic properties (summarized in Table 1 and described later). Pharmacokinetics is the study of the effect of the body on a drug. The pharmacokinetic parameters determine the relationship between an administered dose and the concentration of the drug in the body and include absorption, distribution, metabolism, and excretion. Pharmacodynamics describes the relationship between the concentration and pharmacologic effect of the drug and is dependent on biological receptors and their interactions with drugs. Even though receptors and their interactions play a significant role in the safety and efficacy of a drug, there is little known regarding age-dependent effects.

Absorption

Gastric pH is increased in neonates and infants and reaches adult values by 2 years of age. In contrast, gastrointestinal (GI) motility is decreased in neonates and reaches adult levels in older infants and children. The age at which these changes occur is unclear. The bioavailability of enterally administered drugs that are weak acids, like phenytoin and phenobarbital, may be decreased in infants and young children because of their higher gastric pH. One study reported the bioavailability of the enteral formulation of phenytoin in neonates and young infants (1-121 days old) to be only 75% of the nearly complete absorption seen in adults. Furthermore, after a single oral dose of phenobarbital, the time to peak concentrations in neonates was also significantly delayed.

Metabolism and active efflux transporters in the GI tract can also affect bioavailability. Immature intestinal cytochrome P450 3A4 metabolism of midazolam has been shown to reduce clearance in preterm infants. Gabapentin is eliminated by the renal excretion of the unchanged drug with dose-dependent bioavailability because of saturable transport by the L-amino acid transporter localized to the GI mucosa. The oral clearance (CL/F, where CL is total body clearance and F is the bioavailability) of gabapentin was 33% higher in children less than 5 years of age compared with children greater than 5 years and adults. Because renal clearance reaches adult levels by age 1 to 2 years and gabapentin is not protein bound, this suggests that the effect on oral clearance is not an effect on clearance per se but a decrease in bioavailability because of immature L-amino transporter activity-limiting absorption. The oral clearance of fexofenadine, an antihistamine, is dependent on the efflux transporters, P-glycoprotein, and organic anion transporting peptides in the GI tract. A population pharmacokinetic analysis of fexofenadine in children ages 6 months to 12 years found no significant effect of age on oral clearance, suggesting that the maturation of the efflux transporters has occurred by at least 6 months of age. Based on limited data, the bioavailability of drugs that are affected by pH, GI motility, efflux transporters, and/or intestinal metabolism should be close to adult values by age 5 years or possibly earlier for some drugs.
Distribution

After absorption, a drug is distributed to various body compartments depending on its physicochemical properties, such as molecular size, ionization constant, and relative aqueous and lipid solubility. The direction of the change, if any, (i.e., increase or decrease in volume of distribution \(V_d\)) will also depend on the drug’s physicochemical characteristics. In neonates and infants, the increased total body water-to-body fat ratio contributes to an increase in the \(V_d\) of hydrophilic drugs, such as phenobarbital,\textsuperscript{4} valproate,\textsuperscript{10} and propofol,\textsuperscript{11} requiring larger mg/kg loading doses to achieve therapeutic concentrations. In the case of propofol, a larger initial infusion as well as an initial loading dose is needed because of the larger \(V_d\) to achieve similar plasma concentrations.\textsuperscript{11} The \(V_d\) of the more lipophilic drugs, diazepam and lorazepam, are similar in infants and adults.\textsuperscript{12}

Renal Excretion

The elimination of antiepileptic drugs occurs through either renal excretion of the unchanged parent drug, hepatic biotransformation to metabolites (both active and inactive), or a combination of both. At birth, the glomerular filtration rate is approximately 40 mL/min/1.73 m\(^2\) in the full-term neonate. GFR increases steadily to 50% to 75% of adult function by 6 months. Tubular secretion lags behind maturation of glomerular filtration by 7 months to a year, leading to an imbalance in glomerular/tubular maturation.\textsuperscript{13} Full maturation of renal function is attained by approximately 1 year of age.\textsuperscript{14} Transporter proteins participate in active renal excretion and reabsorption of many drugs; however, knowledge regarding their maturation remains negligible.\textsuperscript{15} In general, weight-normalized doses of drugs excreted predominately unchanged by the kidneys need to be reduced only for neonates and infants.

| Table 1 Summary of the Effect of Age on Renal and Metabolic Elimination Pathways |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age                        | Neonate/Infants | Children 1-12   | Elderly         |
|----------------------------|-----------------|-----------------|-----------------|-----------------|
| Increased                  | CYP1A2          | CYP2C9          | CYP3A4          |
| Decreased                  | All CYPs*       | UGT*            | renal           |
|                            | UGT*            | renal elimination albumin | α\textsubscript{1}-AGP\textsuperscript{†} |
| No Change                  | CYP2C19         | CYP2D6          | UGT*            |
|                            | CYP2D6          | UGT*            | renal elimination albumin | α\textsubscript{1}-AGP\textsuperscript{†} |

\(\ast\) Cytochrome P450.

\(†\) Uridine diphosphate (UDP) glucuronosyltransferase.

\(\alpha\textsubscript{1}\) Acid glycoprotein.

By 1 year of age, dosing based on body weight is similar in children and adults.

Hepatic Metabolism

Metabolic reactions are primarily catalyzed by the cytochrome P450 (CYP) and uridine diphosphate glucuronosyltransferase (UGT) enzymes. The CYP system represents a widely heterogeneous family of enzymes, and individual isozymes belong to 1 of 3 major families (CYP1, CYP2, and CYP3). Seven primary isozymes are involved in the hepatic metabolism of most drugs: CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.\textsuperscript{16} The most abundant isozyme, CYP3A4, which accounts for approximately a third of the total hepatic CYP, has the broadest substrate specificity and is involved in the metabolism of more than 30% of all drugs. The UGTs are family of enzymes that catalyze the transfer of a glucuronic acid moiety from a donor cosubstrate UDPGA. The activity of the metabolic enzymes is dependent on genetic, physiological, and environmental effects. As shown in Table 2, renal excretion, CYP3A4, CY2D6, and CYP2C9/CYP2C19 represent the main sources of elimination of most drugs.\textsuperscript{17}

Genetic polymorphisms in the expression of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A5, UGT1A1, N-acetyltransferases (NAT2), and thiopurine S-methyltransferase have been identified.\textsuperscript{18} Poor metabolizers are homozygous for the mutant gene. Extensive metabolizers are either homozygous or heterozygous for the wild-type gene, with heterozygous carriers having intermediate metabolic activity. Ultrametabolizers have multiple copies of the gene; however, this has been described only for the CYP2D6 polymorphism. In addition, the predominant variant of CYP2D6 in Asians and blacks are alleles that reduce enzyme activity. There is a large interethnic variability in the proportion of poor metabolizers, intermediate metabolizers, and ultrametabolizers, a topic that is beyond the scope of this article. For those isozymes for which data are available, genotype is not related to phenotype at birth but develops upon maturation of the enzyme. After the initial development of the metabolic enzyme, there is no evidence to suggest that the phenotype of a child will be different from the adult.

In the past, there was a general assumption that all hepatic drug metabolism was increased in children compared with adults. There is now evidence that the influence of age on hepatic metabolism is dependent on the types of enzymes involved.\textsuperscript{1,2} CYP-dependent metabolism is low at birth, ap-
proximately 50% to 70% of adult levels. By 2 to 3 years of age, CYP enzymatic activity actually exceeds adult values for selected isozymes, including CYP1A2, CYP2C9, and CYP3A4. Therefore, infants less than 1 year of age generally have a decreased ability to eliminate drugs, whereas young children have an increased ability (relative to adults) to eliminate drugs metabolized by specific CYP isozymes.

Significantly higher weight-corrected doses are needed in children than adults for drugs metabolically eliminated solely by the specific cytochrome P450 (CYP) isozymes CYP1A2, CYP2C9, and CYP3A4. By puberty, the CYP activity decreases to adult levels. In contrast, weight-corrected doses for drugs eliminated by metabolism by CYP2C19, CYP2D6, NAT2, and UGT in children are similar to those in adults. UGT activity in neonates is deficient at birth and reaches adult levels by 2 to 4 years of age. Children appear to have slightly increased UGT activity compared with adult levels. However, the differences between activity in children and adults are significantly less than with the CYP isozymes. For drugs metabolized by non-CYP or UGT enzymes, the influence of age is not known. The effect of age on drugs eliminated by a combination of pathways, renal and hepatic, will be dependent on the fraction and age-dependent effects on each pathway. Maturation in both absorption (bioavailability or F) and elimination processes (clearance) will affect the relationship between the average steady-state concentrations obtained and the given dose (concentration/dose).

### Protein Binding

Albumin and α₁-acid glycoprotein (α₁-AGP) concentrations are decreased in the neonates and young infant. Although albumin is the primary binding protein, some drugs are bound to both albumin and α₁-AGP. For the majority of the drugs, protein binding is linear and the percentage unbound is a constant within the range of concentrations used clinically. Valproate is the 1 exception. Valproate is highly protein-bound and due to its high molar concentration, valproate saturates albumin binding sites within the therapeutic range. An increase in the percentage unbound as the dose increases results in total valproate concentrations increasing less than proportionately with increasing doses. Conversely, unbound valproate concentrations will increase linearly with increasing dose and total valproate concentrations will no longer reflect unbound or active concentrations.

Protein binding effects are only clinically significant for 2 different types of highly protein-bound drugs that are predominantly eliminated by hepatic elimination.19 For low ex-
traction ratio (ER) drugs in which clearance of the drug is dependent on protein binding and the activity of the metabolic enzymes, total concentrations will underestimate unbound or active concentrations. This has been shown for both phenytoin and valproate in the elderly and in pregnant women with low albumin; however, the same holds true for neonates and infants with decreased albumin concentrations. Total concentrations decrease significantly more than unbound concentrations with decreased albumin concentrations. Adjusting doses based on total concentrations will result in higher doses of valproate and phenytoin than needed to maintain therapeutic unbound concentrations.

For high ER drugs, whose clearance is dependent on hepatic blood flow and administered by nonoral routes, the concentration of unbound drug can be significantly increased and results in increased pharmacologic effects for drugs in neonates and infants with low albumin and/or AGP. Recommended doses (in mg/kg) should be lower in neonates and infants with low albumin because of both decreased protein binding as well as decreased elimination by renal and/or hepatic metabolism. Examples of high ER drugs that are highly protein bound (ie, >70%) with narrow therapeutic windows include alfentanil, diphenhydramine, fentanyl, lidocaine, midazolam, and propofol.

### Excretion into Breast Milk

Pharmacologic exposure to neonates and infants can also occur during lactation. The dose of a drug received during breastfeeding is dependent on the amount excreted into the breast milk, the daily volume of milk ingested, and the average plasma concentrations of the mother. The physicochemical properties of a drug will determine how much of the drug will be excreted into the breast milk, including its lipophilicity, protein binding, and ionization properties. The milk-to-plasma concentration ratio has large inter- and intrasubject variability and is often not known. In contrast, protein binding is usually known and knowledge of the protein-binding properties of a drug can provide a quick and easy tool to estimate exposure of an infant to medication from breastfeeding. Based on an extensive literature review of case reports that included infant concentrations from breastfed infants exposed to maternal drugs, measurable concentrations of the drug in the infant did not occur for drugs that were at least 85% protein bound if there was no placental exposure immediately before or during delivery.

### Consideration of Drugs Commonly Used in Pediatric Neurology

Decreased maintenance doses of the large majority of drugs used in neonates and infants are needed because of decreased protein binding, renal excretion, and metabolism. The effect of age on loading or bolus doses is dependent on the effect of age on the volume of distribution and is dependent on physicochemical properties, which can be difficult to predict. For
children greater than 1 to 2 years old, the enzyme-specific maturation of the cytochrome P450 isozymes, UGT, and other enzymes will result in a need for an increase, decrease, or no change in the weight-adjusted dose depending on the primary biotransformation of the drug. The presence of an active metabolite with similar potency can normalize the effect of age by increasing the ratio of metabolite to parent for those drugs in which cytochrome P450 activity is increased in children.

Ideally, pharmacokinetic and pharmacodynamic data should be available for all drugs used in neonates, infants, children, and adolescents; however, this is rarely the case. Because many drugs used by neurologists in children are not approved for pediatric use, data remain limited. Understanding the effects of age on pharmacokinetics can help to establish efficacious and safe dosing in the pediatric patient population in situations in which scant data exist. The pharmacokinetics and the need for age-related dosing compared with the adult population are given in Tables 3 to 5 for drugs used in the treatment of epilepsy, sleep disorders, attention deficient disorders, and spasticity.

Most of the drugs used clinically undergo elimination by renal excretion of the unchanged drug or metabolism by CYP or UGT. Available maturational data are available in Tables 1 and 2. Drugs are also metabolized by non-UGT and CYP enzymes in which less is known regarding maturation. For example, the triptans used in the acute treatment of migraine are extensively metabolized by monoamine oxidase A, one of the 2 primary enzymes responsible for numerous endogenous bioactive amines, including serotonin, adrenaline, and noradrenaline. Monoamine oxidase A activity in the neonatal liver is approximately 50% of the adult. Unfortunately, further development of this enzyme system has not been studied in humans.

There are also many drugs that are eliminated by a combination of the various pathways as well as metabolism by non-UGT or CYP isozymes. In this scenario involving multiple pathways, an initial estimation of the effect of age may be possible. For drugs that have been on the market for a long time, information on the pathways of elimination and the specific metabolic enzymes involved is often not known. In general, for many new drugs, there is significantly more phar-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal %</th>
<th>Hepatic Isozymes Involved %</th>
<th>Active Metabolite</th>
<th>Protein Binding % Bound</th>
<th>Age-Related Dose (mg/kg) in Children 2 Years and Older Compared With Adult</th>
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macokinetic information available before marketing in adults, and such data can be useful for predicting pediatric doses in cases in which sufficient pediatric data do not exist.

References