Pediatric Pharmacokinetics
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Educational Gaps

1. A basic understanding of pharmacokinetics and drug disposition will help clinicians select appropriate drugs and dosing. For example, the fraction of the administered dose that makes it into the blood as “intact” drug defines bioavailability. This is clinically relevant because it allows us to understand that comorbidities (e.g., diarrheal disease and psoriasis), dietary changes, formulation manipulation (e.g., crushing tablets and preparing oral liquids), and other factors can alter the dose-exposure relationship.

2. Anatomical and physiologic developmental changes should remind clinicians to recognize when drug dosing and intervals must be tailored to individual patient needs. For example, for acid-labile β-lactam penicillin given orally, the elevated gastric pH in neonates and the relative frequency of feedings will result in serum concentrations that are 5 to 6 times higher in neonates versus older children because the drug is relatively protected from degradation during the time spent in the stomach.

Objectives

After reading this article, the reader should be able to

1. Realize that volume of distribution, elimination clearance, and elimination half-life are crucial parameters of pharmacokinetics that must be understood to determine clinical pharmacologic decisions.

2. Know that drug disposition is a complicated process of absorption, distribution, metabolism, and excretion.

3. Understand that any abnormality in absorption, distribution, metabolism, and/or excretion can potentially affect the efficacy or toxicity of a drug.

4. Understand that the anatomical and physiologic changes during development must be considered in predicting age-dependent changes in drug disposition.

Introduction

For many clinicians, the term pharmacokinetics conjures images of algebraic equations and differential calculus long forgotten since the days of training. As a result, pharmacokinetic concepts tend to be perceived as somewhat esoteric by the general health care clinician. What often goes unappreciated is that clinicians are uniquely primed to understand pharmacokinetics because pharmacokinetics are merely the mathematical characterization of anatomical and physiologic processes that determine how drugs get into the body (absorption), where they go (distribution), and how they are removed (metabolism/excretion). Knowledge of anatomy and physiology enhances our understanding of pharmacokinetics in much the same way that knowledge of
patient-specific factors (eg, age, genetics, diet, and end-organ function) influences our understanding of disease risk and drug response. It is important to realize that the application of pharmacokinetic-related knowledge is bidirectional in that pharmacokinetic studies can broaden our understanding of biology in areas where this knowledge is incomplete.

This article is designed to reintroduce the reader to fundamental pharmacokinetic concepts and frame them in the context of the pediatric patient. Integral to beginning this discussion is a review of some basic pharmacokinetic terms that collectively drive decisions related to selecting the most appropriate dosing regimens for our patients.

Volume of Distribution

Like any volume, volume of distribution (Vd) represents a quantitative measure of size or space. In theory, Vd reflects the combined volume of the various compartments and tissues wherein a drug can be found after it enters the body. Factors that influence the extent to which a drug distributes into various tissues include the drugs’ octanol-water partition coefficient, acid dissociation constant, and affinity for plasma and tissue proteins.

In practice, Vd represents a mathematical variable that relates the amount of drug administered (ie, the dose) to the resulting plasma concentration (equation 1). In essence, Vd reflects the size of a compartment necessary to account for the concentration that is measured after the total amount of drug has been administered.

Imagine a jar of maraschino cherries that has been emptied into a large bowl of punch. If we know that the jar contains 100 cherries (dose) and we observe that every cup of punch in the bowl contains 2 cherries (concentration), we can estimate the volume of the punch bowl:

\[
\text{concentration} = \frac{\text{dose}}{\text{Vd}} \quad \text{equation 1.0}
\]

\[
\text{Vd} = \frac{\text{dose}}{\text{concentration}} \quad \text{equation 1.1}
\]

\[
\text{Vd} = \frac{100 \text{ cherries}}{2 \text{ cherries/cup}} = 50 \text{ cups}
\]

For some drugs, the Vd is small and corresponds to a true biological space (eg, intravascular compartment, extracellular fluid stores, and total body water space). For other drugs that concentrate in tissues, the calculated Vd can be quite large. A Vd that exceeds the total volume of the body may seem nonsensical in a biological context; however, we simply need to recognize that Vd estimates are based on the measurement of drug concentrations in the blood. When tissue concentrations go up and blood concentrations go down, the denominator in equation 1.1 becomes smaller and the value of Vd increases.

Irrespective of size, the value of Vd lies in its ability to help us determine the dose of drug to give our patients. If we know the volume of the compartment into which we are delivering drug and the concentration we want to achieve, we can calculate the desired dose (equation 1.2).

Our goal is that partygoers receive 5 cherries per cup of punch. We have established that the bowl contains 50 cups. Thus, we can calculate the number of cherries we need to add to the bowl to achieve the desired concentration of cherries:

\[
\text{concentration} = \frac{\text{dose}}{\text{Vd}} \quad \text{equation 1.0}
\]

\[
\text{dose} = \text{concentration} \times \text{Vd} \quad \text{equation 1.2}
\]

\[
\text{dose} = (5 \text{ cherries/cup}) \times (50 \text{ cup}) = 250 \text{ cherries}
\]

Clearance

Simply stated, clearance reflects a rate of change. In a pharmacokinetic context, clearance represents the fraction of the total Vd from which drug is cleared in any given unit of time. Biologically, clearance reflects the sum total of all physiologic processes that are working together to remove the drug from that compartment.

Consider our 50-cup punch bowl from the last example. Now imagine a partygoer plucking cherries from the bowl. If our partygoer removes 10 cherries per hour and the bowl contains 5 cherries per cup, then the bowl is being cleared of cherries at a rate of 2 cups per hour. Add a second partygoer with the same affinity and capacity for consuming cherries and the equivalent of 4 cups per hour are being cleared of cherries.

Apart from the innate ability of an organ (eg, kidney or liver) to remove the drug, there are other biologic factors that influence clearance rates, such as the degree of plasma protein binding, tissue extraction ratios, and cardiac output. Clearance is relevant to the practitioner because it helps to determine the frequency with which a drug must be delivered to sustain the concentrations desired in the plasma.

At the start of the party we added 250 cherries to our bowl of punch. The 2 partygoers we described are removing a combined 20 cherries per hour. To ensure that other partygoers interested in drinking the punch receive 5 cherries per cup, we can add 20 cherries back to the bowl every hour or 10 cherries every ½ hour or 40 cherries every 2 hours and so on.
Bioavailability
For drugs administered by any route other than direct intravenous instillation, factors related to both the drug and the patient influence the degree to which the drug reaches the systemic circulation. These factors can include the disintegration characteristics of the dosage form, the dissolution properties of the drug, the stability of the drug at the absorption site, and the degree to which the drug serves as a substrate for transporters and drug-metabolizing enzymes (DMEs) that may be encountered before the drug reaches the systemic circulation (eg, first-pass effect). The fraction of the administered dose that makes it into the blood as intact drug defines bioavailability. For drugs given intravenously, 100% of the administered dose reaches the systemic circulation; thus, the bioavailability is 1. For drugs given by any other route (eg, sublingual, oral, rectal, and percutaneous), the bioavailability usually is less than 1, depending on the drug and host-related factors. Understanding the concept of bioavailability is clinically relevant because it allows us to understand that comorbidities (eg, diarrheal disease, Zollinger-Ellison syndrome, and psoriasis), dietary changes, formulation manipulation (eg, crushing tablets and preparing oral liquids), and other factors can alter the dose-exposure relationship.

The concept of bioavailability is relevant also to our understanding of pharmacokinetic because the availability of the drug represents an unknown modifier that influences the estimates of Vd and clearance. Recall that our calculation of Vd relies on the concentrations we observe in the blood. When concentrations are low, we do not know whether it is because the drug has moved out of the circulation and into the tissues or because the drug never made it into the circulation in the first place. Thus, a more accurate representation of equations 1.0 and 1.1 is as follows:

\[
\text{concentration} = \frac{(\text{dose} \times \text{bioavailability})}{\text{Vd}}
\]

\[\text{equation 1.3}\]

\[
\text{Vd/bioavailability} = \frac{\text{dose}}{\text{concentration}}
\]

\[\text{equation 1.4}\]

Similarly, the term clearance is more accurately represented as clearance/bioavailability given the relationship between clearance and Vd (see the “Half-life” section).

Half-life
The half-life (t₁/₂) of a drug is the amount of time required for the total amount of drug in the body or the blood to decrease by half (Fig 1 left). This pharmacokinetic parameter allows us to determine the fraction of drug that has been removed from the body and consequently the fraction of drug that remains. If the t₁/₂ is the time it takes concentrations in the body or blood to decrease by half, 50% of the drug will remain after 1 t₁/₂, 25% will remain after 2 t₁/₂, 12.5% after 3 t₁/₂, 6.25% after 4 t₁/₂, and 3.125 after 5 t₁/₂. Thus, approximately 97% of the drug will have left the system after 5 t₁/₂. Both Vd and clearance influence the t₁/₂ of a drug as described by equation 1.5. Alternatively, the elimination rate constant derived from the slope of the log-transformed plasma concentration versus the time curve can be used to calculate the t₁/₂ according to equation 1.6 (Fig 1 right).

\[
t₁/₂ = \frac{0.693 \times \text{Vd}}{\text{clearance}}
\]

\[\text{equation 1.5}\]

\[
t₁/₂ = \ln 2 \times \text{elimination rate constant}
\]

\[\text{equation 1.6}\]

Although t₁/₂ is perhaps the easiest pharmacokinetic parameter to understand, it is also subject to a number of assumptions, namely, that the drug conforms to a 1-compartment model and demonstrates first-order elimination.

Setting aside discussions about more complex, multiple-compartment pharmacokinetic models, we can examine the clinical importance of t₁/₂, which informs our decisions related to drug-dosing intervals to maximize efficacy and limit toxicity. The t₁/₂ can vary from hours to days and even months among different medications. Propranolol, a nonselective β-blocker commonly used to treat pediatric supraventricular tachycardia (SVT), has a t₁/₂ that ranges from 4 to 6 hours in children. By contrast, amiodarone, a class 3 antiarrhythmic agent used to treat refractory SVT, has a t₁/₂ of nearly 60 days after long-term administration. As expected, amiodarone requires less frequent dosing compared with the β-blockers.

Although drugs with relatively long t₁/₂ offer the advantage of simplified dosing schemes, they are accompanied by increased complexities associated with toxicity management should adverse effects arise. By extension, patients who experience a protracted t₁/₂ owing to comorbidities that decrease clearance or expand the Vd can develop toxicity if the dose or dosing interval is not adjusted to account for these changes. For example, a postoperative cardiac patient who has poor renal perfusion and who requires antibiotics for concerns of sepsis may require a less frequent dosing interval for vancomycin, an antibiotic that is cleared renally.

In patients with transient reductions in renal clearance, such as the postoperative patient described, not only do newly added drugs need to be dosed appropriately, but existing medications in the patient’s regimen should be...
reevaluated for the need to adjust doses or dosing intervals to avoid toxicity. This consideration is particularly relevant for drugs with a narrow therapeutic index (ie, where the amount of drug that causes therapeutic efficacy is only slightly lower than the amount that causes toxicity). If desirable plasma concentrations have been defined for these drugs, therapeutic drug monitoring is highly recommended. When measuring drug levels, proper timing is essential for accurate therapeutic monitoring. For instance, if a digoxin drug level is obtained before the drug has completely distributed into tissues, the measured value will appear falsely elevated and may lead to improper adjustments of the dose.

The parameter t½ also allows us to determine how long it will take to achieve steady state. When drugs are administered at constant intervals, they accumulate in the body until the amount administered in a given period is equal to the amount eliminated in the same period. When this plateau occurs, the drug in the body has achieved steady state (the rate in equals the rate out). Drug accumulates in a similar fashion to that described for decay, so that concentrations are greater than 97% of where they will be at steady state after 5 t½ irrespective of the frequency with which the drug is dosed (Fig 2).

Adherence to regular dosing intervals is essential to achieve and maintain a steady state. Whenever the dose or dosing interval changes, another 4 to 5 t½ must pass to achieve a new steady state. Thus, poor drug adherence, which occurs frequently with adolescent patients, will cause large fluctuations in drug concentrations due to a failure to achieve or maintain steady state. As an example, strict adherence to immunosuppressive medication use is of utmost importance after organ transplantation to avoid allograft rejection. Although the 1-year renal allograft survival rate has improved markedly in the last decade, long-term renal allograft survival remains lowest in the adolescent population mainly due to medication nonadherence. (1)

Absorption
Absorption is the process of drug movement from the site of administration or application into the systemic circulation. In addition to the factors detailed in the “Bioavailability” section, ontogenic (developmental) processes also influence the extent to which drugs find their way into the systemic circulation. Many of the differences in absorption that we observe between children and adults can be attributed to changes in anatomy and physiology that occur as part of the normal process of growth and development.

Oral
Drugs administered by the oral route encounter a number of processes that are different in children. Among the first of these differences is an elevated gastric pH in neonates and young infants. This finding is attributed to reduced hydrochloric acid secretion and the relative frequency with which these children feed. (2) Although there are a few drugs (eg, weakly acidic drugs) for which this increase in gastric pH appears to decrease the extent of absorption, a more pronounced impact is observed for drugs that undergo chemical degradation at low pH. For example, serum concentrations of the acid-labile β-lactam antibiotic penicillin are 5 to 6 times higher in the neonate than in older children when given orally because the drug is relatively protected from degradation during its time spent in the stomach. (3)

Differences in the rate of gastric emptying also can influence drug absorption in children. The rate of drug absorption generally is slower in the neonate and young infant in whom the rate of gastric emptying is prolonged. Consequently, the time to reach maximal plasma concentrations for many medications is delayed in the newborn
and young infant. In otherwise healthy children, gastric emptying rates approach adult values at approximately 6 to 8 months of age; however, this developmental milestone will differ in children with underlying pathophysiologic conditions that alter emptying times (eg, prematurity, congenital heart disease, and gastroesophageal reflux disease). (4) Coincident with delayed emptying in the young infant is a reduction in intestinal motility compared with older children. Although the decrease in frequency and amplitude of intestinal contractions theoretically permits longer retention times at the primary absorptive surfaces of the small intestine, the impact of intestinal migration rates on the extent of drug absorption into the systemic circulation will depend largely on the characteristics of the oral formulation that is administered.

For drugs whose absorption is facilitated by bile acids, maturation of biliary function can influence drug absorption profiles. Infants younger than 6 months demonstrate lower bile salt concentrations in the intestinal lumen compared with adults, a finding that likely results from immature bile acid transport out of the liver. Pharmacokinetic studies of susceptible drugs (eg, chloramphenicol palmitate and pleconaril) have demonstrated capacity-limited absorption so that increasing the drug dose above some threshold produces little to no increase in circulating drug concentrations. It is difficult to predict which drugs may be affected by this process without confirmatory pharmacokinetic studies; however, a high degree of suspicion should be maintained for drugs whose absorption profiles in adults are enhanced with the concurrent administration of a fatty meal.

When considering developmental changes that occur along the intestinal tract, differential expression of the proteins responsible for metabolizing and transporting drugs also should be considered. We know that the intestinal lining is home to a number of DMEs, yet our knowledge of their ontogeny is restricted to a scant few. Intestinal expression of cytochrome P450 (CYP) 3A and CYP1A1 appears to increase with increasing age. The clinical consequence of this situation in neonates and children is to reduce presystemic clearance of substrates for these DMEs, leading to higher circulating concentrations of the active compound in plasma (eg, alprazolam, amlodipine, and dexamethasone). Conversely, if the medication is administered as a prodrug, which is activated by these enzymes, we state drug levels are achieved after 5 t₀, irrespective of whether the patient has received 6 doses (upper) or 1 dose (lower). Thus, the time to achieve steady state is dependent on the t₀ of the drug and independent of the dosing frequency.
would expect reduced concentrations of the active compound in the blood (eg, simvastatin and lovastatin).

In contrast to the CYPs described, activity of the phase 2 DME glutathione \(\text{S}\)-transferase (GST) appears to be higher in children younger than 5 years compared with older children and adolescents. Thus, converse expectations would hold here; younger children may experience lower blood concentrations and, as a result, require higher doses of drugs whose primary route of clearance is by intestinal glutathione conjugation (eg, busulfan). The ontogenetic profiles of other phase 1 and 2 DMEs that are quantitatively as, if not more, important than those described have yet to be defined.

Intestinal transporters also play a role in facilitating or restricting the absorption of many orally administered drugs. Unfortunately, most of the knowledge acquired to date is derived from animal models and concerns the uptake of nutrients and ions. For some of these nutrient transporters, activity reaches that of adult values at the time of birth, whereas others mature later in infancy. In humans, only limited data on the ontogeny of drug transporters have been accumulated to date. Studies examining the expression of P-glycoprotein observe that this transporter is present within the intestine as early as 1 month of age and is expressed continuously through adulthood. Other clinical pharmacokinetic studies provide indirect evidence of age-dependent expression for the intestinal organic anion-transporting polypeptides (OATPs) and cation-transporting polypeptides; however, the magnitude of these differences remains to be elucidated fully.

Extrinsic factors unique to children (eg, diet) also can influence the absorption of orally administered medications. For instance, infants and children consume apple juice at a rate of 16 and 5 times the national average, respectively. This specific fruit juice is known to reduce the bioavailability of drugs that serves as a substrate for OATP (eg, fexofenadine and \(\beta\)-blockers). (5) As such, drug-diet interactions involving apple juice would be expected to occur with greater frequency in children. A similar drug-diet interaction can be observed with substrates for peptide transporter 1 (PEPT1). This protein facilitates the absorption of drugs such as angiotensin-converting enzyme inhibitors, amino-\(\beta\)-lactams, and oseltamivir; however, its normal physiologic role is to absorb milk-derived peptides. In the newborn and young infant who is feeding every 2 to 4 hours, the continual presence of dietary milk-based peptides in the intestinal lumen will compete for absorption of coadministered drugs that share the PEPT1 pathway.

Even the seemingly innocuous act of altering the commercially available formulation to suit the needs of children can influence the degree to which drugs are absorbed. As expected, digoxin absorption from an elixir formulation is more efficient than observed with the tablet. Surprisingly, crushing rifapentine tablets actually impair bioavailability compared with administration of the intact dosage form. These examples of the influence of diet and formulation highlight the importance of thinking beyond age and disease when treating the pediatric patient.

**Rectal**

In a similar fashion to oral drug delivery, the absorption profile of rectally administered drugs can vary between children and adults. Rectal administration can be useful when oral or intravenous routes are contraindicated. Rectally administered drugs undergo absorption into the inferior mesenteric arteries and the hemorrhoidal veins, bypassing the portal circulation (eg, first pass). The extent of rectal absorption is dependent, in large part, on the release characteristics of the formulation and motility patterns in the lower intestinal tract. When solutions are used, rectal absorption can be very efficient (eg, diazepam for status epilepticus). However, many solid and semisolid rectal formulations will be expelled from the lower intestine in young infants before the entirety of their drug contents can be liberated because these children experience a greater number of high-amplitude, pulsatile contractions in the lower intestine.

**Percutaneous and Intramuscular**

The bioavailability of percutaneously and intramuscularly administered drugs can vary markedly among drugs (bioavailability, 0.2-1). Among the physiologic factors that determine the rate and extent of absorption by both of these routes is the blood supply at the site of application. Both skin and skeletal muscles demonstrate an increased capillary density in neonates and young children compared with older children and adults. In addition, children demonstrate enhanced skin hydration and a larger surface-to-volume ratio than do adults. Collectively, these differences contribute to enhanced absorption of many topically applied drugs in the growing child.

**Distribution**

After a drug successfully traverses the absorption barriers and enters the systemic circulation, it is free to distribute in plasma or tissues as dictated by the physiologic constitution of the host (eg, fraction of weight constituted by water, extent of circulating protein biosynthesis, and expression of tissue transporters) and the physicochemical
properties of the drug (eg, protein binding affinity, octanol-water partition coefficient, and acid dissociation constant). For drugs whose distribution is affected by physiologic factors for which we can discern age-dependent changes, the corresponding impact of growth and development on Vd is relatively predictable.

Changes in body water stores during childhood serve as the prototypic example of the impact of development on Vd. It is known that total body water as a percentage of total body weight is highest in preterm and full-term neonates (nearly 75%-80%) and decreases to the adult values (∼60%) by 1 year of age. This change is accompanied by a corresponding reduction in extracellular fluid as children age from nearly 45% to 50% in the neonatal period to adult levels of 20% to 30% by 1 year of age. The higher percentage of total body water contributes to a larger Vd for hydrophilic drugs (eg, aminoglycosides and β-lactam antibiotics) and the need for larger weight-based doses to achieve the same systemic concentrations achieved in adults. This difference is compounded in severely ill neonates who require extracorporeal membrane oxygenation (ECMO) where hemodilution, drug sequestration in the ECMO circuit, end-organ dysfunction, and systemic inflammation all contribute to expanded distribution volumes.

In contrast to body water stores, newborns and young infants demonstrate diminished body fat stores compared with adults. Although one might theoretically conclude that highly lipophilic drugs will exhibit smaller distribution volumes in these children, this effect often is not the case. Many of these drugs associate with lipids and other cellular components in such a way that pronounced differences in Vd with age are not readily apparent.

Qualitative and quantitative changes in protein binding represent another developmental pattern that has an enormous role in determining the Vd. For moderately and highly protein-bound drugs, changes in Vd can be observed when the absolute amount of protein (eg, albumin, globulin, α1-acid glycoprotein, and lipoprotein) is reduced, when the affinity of the protein for the drug is diminished, and when other substrates capable of displacing the drug from its binding site on the protein are present. Of note, all 3 of these biological scenarios are at work in children.

Albumin is a large, negatively charged plasma protein (∼67 kDa) that binds to many positively charged, acidic drugs. In neonates, serum albumin levels are reduced compared with adults, resulting in fewer overall binding sites. (6) Moreover, fetal albumin is still present in the circulation of newborns, and this isoform of albumin demonstrates reduced binding affinity for many drugs that are bound to albumin. The circulating levels of α1-acid glycoprotein and other lipoproteins that bind negatively charged, basic drugs also are found to be lower in the fetus and neonate. Finally, newborns have higher circulating concentrations of bilirubin and free fatty acids, which can serve to displace drugs from their protein-binding sites. The cumulative effect of these changes is a reduction in protein binding and an increase in the unbound (ie, free fraction) of many drugs during early infancy (eg, propranolol, verapamil, ampicillin, phenytoin, and phenobarbital). (7) It is important to know that the risk of displacement is bidirectional and highly protein-bound drugs can displace bilirubin, which, in a jaundiced neonate, can increase the risk of kernicterus.

Given that the overall pharmacodynamic effect of a medication depends on the amount of free (ie, unbound) drug that reaches the target receptor, the clinical implication of the developmental changes in protein binding is greatest for highly protein-bound drugs or those with a narrow therapeutic index. For many such drugs (eg, thiopental and sufentanil) reduced dosage requirements are necessary in young children to achieve effects comparable to those observed in adults. The highly protein-bound anticonvulsant phenytoin provides a great illustration of this principle. In the healthy adult, approximately 99% of circulating phenytoin is protein bound (1% free). If the extent of protein binding decreases to 98% (2% free), the free fraction has effectively doubled. If the extent of protein binding decreases to 95% (5% free) a 5-fold increase in free drug will be experienced. Consequently, very small changes in protein binding can markedly alter the risk of toxicity. By contrast, a reduction in ampicillin binding from 22% (78% free) in adults to 10% (90% free) in neonates results in only a modest (15%) increase in free fraction and a negligible alteration in risk profile.

Although ontogenic data are lacking, we would be remiss not to introduce the potential impact of cellular transporters on drug distribution. Transporter proteins are scattered throughout the body and contribute to the uptake and efflux of normal biological substrates from tissues. These substrates are used to different extents, within different tissues, and at different times during development; thus, the transporters that facilitate their uptake ostensibly demonstrate differential expression or activity profiles during human maturation. Unfortunately, the use of drugs that rely on these transporters in children is outpacing the acquisition of knowledge about their ontogeny. A temporal clinical example is the use of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (ie, statins). Given the ongoing
childhood obesity epidemic and the increased incidence of dyslipidemia associated with obesity, the number of children and adolescents who require statin therapy is increasing. Several of these statins are transported into the site of action (ie, the hepatocyte) by an OATP. A previous study in children with familial hyperlipidemia suggests that the functional expression of OATP differs between children and adults with the same genetic variation. The impact of these differences on the efficacy and toxicity of statins in children remains to be determined.

**Metabolism**

Although several organs (eg, kidney, gastrointestinal tract, lungs, and skin) contain DMEs, the liver serves as the predominant organ for drug metabolism. The disposition of hepatically cleared drugs can occur by a number of mechanisms. Phase 1 metabolism is composed of oxidation, reduction, hydrolysis, and methylation reactions that serve to increase the polarity of a drug, whereas phase 2 metabolism is responsible for converting drugs into a more water soluble form for excretion. Drugs that require biotransformation for removal from the body can undergo either or both types of metabolism, and the developmental expression profile for the enzymes that support phase 1 and phase 2 metabolism can have a marked impact on the pharmacokinetics of a drug and the corresponding efficacy and safety profile in children.

Phase 1 metabolism is performed primarily by a group of oxidases referred to as CYPs. In the last 20 years there has been significant advancement in our knowledge of DMEs and their expression profiles from fetal life into adulthood. (8) CYP3A4, one of the most qualitatively and quantitatively important DMEs in humans, is responsible for the metabolism of a number of drugs (Table). Although expressed at very low levels in the human hepatocyte at birth, activity increases to 30% to 60% of adult levels within the first week of life and achieves adult levels near 1 year of age. (9) Similarly, CYP2C19, CYP2E1, and CYP1A2 appear to increase gradually to adult levels at 6 months, 1 year, and 10 years of age, respectively.

In contrast, CYP2D6 and CYP2C9 appear to be fully functional shortly after birth, and ontogeny appears to be less relevant than inheritance when it comes to explaining interindividual variability in their activity. Although in vitro and in vivo activity does not always correlate, in general, drugs that are substrates for CYP3A4 CYP2C19, CYP2E1, and CYP1A2 may require a lower dose or expanded dosing intervals in children.

The effect of diet on DME activity in infants can overlay the effects of development. Several studies have shown that the maturation of enzymes responsible, in part, for the metabolism of caffeine and dextromethorphan (eg, CYP1A2 and CYP3A4) is accelerated in formula-fed infants compared with those who are breastfed. (10) It is believed that components in formula act in a similar fashion to drugs that are known inducers of these same CYPs (eg, phenobarbital, phenytoin, carbamazepine, and rifampin). Thus, the prescribing clinician should expect that drug exposure and response profiles may differ between formula- and breastfed children. Furthermore, the clinician should remain cognizant of the additive drug-interaction potential, in breastfed infants, of drugs and herbal remedies with the potential to induce or inhibit DMEs (eg, St. John’s Wort, ginkgo biloba, and milk thistle) when ingested by the mother and transmitted to the infant via human milk.

### Table. Cytochrome P450 (CYP) Enzymes and Examples of Common Pediatric Drug Substrates

<table>
<thead>
<tr>
<th>CYP Enzymes</th>
<th>Drug Substrate(s)</th>
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<tbody>
<tr>
<td>CYP1A2</td>
<td>Melatonin, Propranolol, Verapamil, Zolpidem, Amitriptyline, Carvedilol, Phenytoin, Warfarin</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>CYP2C19, Diazepam, Imipramine, Citalopram, Dexamfetamine, Oxycodone, Propranolol</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Carvedilol, Codeine, Dextromethorphan, Oxycodone, Propranolol</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Halothane, Isoflurane, Sevoflurane, Theophylline</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Alprazolam, Amitriptyline, Clarithromycin, Cyclosporine, Erythromycin, Lovastatin, Simvastatin</td>
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</table>
Phase 2 metabolism enhances water solubility by conjugation of the drug with GST, glucuronide (uridine 5'-diphospho-glucuronosyltransferase [UGT]), sulfate (sulfotransferase [SULT]), and N-acetyl (acetyltransferase) functional groups. Most of these phase 2 DMEs are constituted by multiple isoforms, each of which demonstrates a unique developmental expression profile. GST1 demonstrates activity levels that increase progressively to adult levels in the first 18 months of life. In contrast, GSTA1 and A2 increase 1.5- to 2-fold at birth (vs fetal levels) without significant change into adulthood. Of the phase 2 DMEs with slightly more clinical relevance, UGT1A1 (a major enzyme responsible for bilirubin glucuronidation) increases immediately after birth and attains adult levels by 3 to 6 months of age. (11) UGT2B7 activity also increases through the first year of life. The SULTs, involved primarily with the conjugation of endogenous steroids (eg, estrone and ethyl estradiol) demonstrate discordant ontogenic profiles. The expression of SULT1A1 does not undergo significant changes during development, whereas SULT1E1 shows a progressive decline in activity from the fetus into adulthood, and SULT2A1 displays an increase of activity from birth into adulthood.

Despite the variety of developmental profiles observed for the phase 1 and phase 2 DMEs, infants expressing low levels of any given DME are not always disadvantaged when it comes to eliminating drugs. The redundancy built into human detoxification system permits mature pathways to compensate for pathways that have yet to develop so that the net rate of clearance for some drugs does not change with age. For other drugs, the contributions of minor pathways, although important, are less efficient, the result being a delay in clearance rates until the primary pathway matures.

Acetaminophen offers an excellent example of the latter scenario. UGT1A6 and SULT1A1 serve as the primary routes of metabolism for acetaminophen. In adults, most of the metabolite recovered is the glucuronide conjugate, whereas sulfate conjugates account most of the acetaminophen metabolites recovered in newborns. Although SULT1A1 serves as an alternate route of clearance in newborns, this pathways is less efficient than UGT, and, as a result, infants exhibit a longer overall of clearance in newborns, this pathways is less eficient, whereas SULT1E1 shows a progressive decline in activity from the fetus into adulthood, and SULT2A1 displays an increase of activity from birth into adulthood.

With advances in our understanding of the ontogeny of DMEs, we have been able to optimize drug dosing and improve efficacy for many therapeutic agents while minimizing the incidence of dose-related (ie, type A) adverse drug reactions (ADRs). However, the underlying basis for many ADRs (eg, allergic reactions and rash) that are deemed to be idiosyncratic (ie, type B) remains to be elucidated. It may be several years before the authors of subsequent pediatric pharmacokinetic reviews can provide insights into environmental and genetic factors that predispose patients to idiosyncratic ADRs.

Excretion

Two organ systems are responsible for most drug excretion: the liver (via bile) and the kidneys (via urine). Hepatic drug clearance relies primarily on active transport processes, whereas both active and passive processes work in concert in the kidneys. Active transporters that mediate efflux into the biliary canaliculus include breast cancer–related protein, multidrug resistance–associated protein 2 (MRP2), multidrug resistance protein 1 (MDR1), and bile salt export pump. In the kidney, members of the organic anion transporter and organic cation transporter families facilitate influx into the proximal tubular cells, whereas MDR and MRP family members mediate efflux into the lumen of the proximal convoluted tubules. Although mouse models suggest developmental dependence in the expression of these transporters, the correlation with human transporters is still lacking.

Consequently, the magnitude of drug interactions that would be expected at these excretion sites in children remains unclear. For instance, the histamine2-receptor antagonist cimetidine has been shown to inhibit the secretion of metformin into the urine, causing potentially dangerous increases in plasma concentrations. (12) The extent to which the transporter involved in this interaction is expressed in children and is involved in the clearance of metformin will determine the clinical impact of this drug-drug interaction.

In addition to the influence of age on the functional expression of transporters, disease can play a role as well. Intrinsic hepatic disease (eg, Alagille syndrome), injury (eg, asphyxia and cardiogenic shock in congenital heart disease), and cholestasis (as induced by total parenteral nutrition) will influence the expression profile of these proteins and have an impact on drug clearance.

Pathologic processes in the kidney also can influence clearance rates; however, the impact of age-related changes in renal physiology and drug clearance is perhaps more remarkable because the structural and functional development of the kidney is incredibly well characterized. Although nephrogenesis is complete by 36 weeks of gestation, maturation continues throughout childhood.
Kidney length more than doubles from birth through 12 years of age, with kidney weight exhibiting a comparable linear increase during this same time frame. Microscopically, glomerular diameter and proximal tubular length also increase as children age. Furthermore, the radius of small pores in the glomerulus increases more than 25%, and the ratio of large pores to small pores shifts in favor of the former during the first few months of life. In the first year of life, children also experience changes in vascular resistance and renal blood flow as fractional cardiac output to the kidney increases almost 4-fold, with a commensurate increase in glomerular filtration rate (GFR). This normal developmental pattern contributes to an increase in the renal excretion of drugs during the first few years of life to levels that eventually exceed those observed in adults.

Maturation of the kidney corresponds with postconceptional age; thus, preterm infants and neonates with impaired renal blood flow demonstrate lower rates of drug clearance than do otherwise normal newborns. The clinical consequence of these changes is the need for a lower dose and less frequent dosing interval for many drugs administered during the newborn period. For example, an infant who has significant birth asphyxia and end-organ damage (eg, acute renal failure) being treated for presumed sepsis will require a more protracted dosing interval due to a lower than normal GFR. As described, these neonates require close monitoring of drugs with a narrow therapeutic index and those with nephrotoxic potential (eg, gentamicin and vancomycin), given the nature of their renal function.

In premature newborns, this concern extends to drugs that rely on renal pathways for clearance until the primary hepatic pathway matures. Caffeine and theophylline, used to treat apnea of prematurity, are prototypic examples of drugs that demonstrate very slow rates of elimination in this population (almost 17-fold that of adults) until the primary hepatic clearance pathways catch up. (13)

### Overview

The complexity of pediatric drug disposition is vast, but understanding the physiology of the developing child should assist the prescribing physician in conceptualizing the principles of pharmacokinetics, which are relevant to determining proper dosing. Although our knowledge has improved vastly in the last 20 years, countless knowledge gaps remain that contribute to the challenges of prescribing drugs to our pediatric patients. The continual accumulation of new knowledge will have an enormous impact on safe and effective pediatric drug use.

### Summary

- A number of factors combine to influence the concentration of drug that is reached in plasma or tissue.
- Volume of distribution, clearance, and bioavailability combine to influence the concentration of drug that is reached in plasma or tissue.
- Anatomical and physiologic factors are what determine each individual’s distribution volume, clearance, and bioavailability.
- The half-life of a drug plays an important role in determining when steady state will be reached and must be considered when deciding on an appropriate dosing interval. Drug concentrations approach a steady state after 5 half-lives.
- The half-life also determines how long measurable concentrations of drug will remain in the body after dosing is stopped. Most of the drug is removed from the body after 5 half-lives.
- Absorption of a drug is influenced by the characteristics of the formulation that is administered, the route of administration, and factors within each route, such as blood flow, pH, and the presence of drug metabolizing enzymes and transporters.
- Distribution of a drug is influenced by biochemical and host characteristics, such as body water, fat, and circulating protein stores.
- Metabolism of drugs, especially in the intestine and liver, plays a key role in determining drug concentration.
- Diet can influence pharmacokinetics, including the infant diet, where we can observe differences between breastfed and formula-fed infants.
- Hepatic and renal excretion is critical in determining drug concentrations.
- Disease will affect the way the body handles drugs and as a result the concentrations that are achieved after dosing.
- Pediatricians must be aware of the normal changes that occur throughout the body as children grow and develop to understand how drugs are handled at different ages.

### ACKNOWLEDGMENTS

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### References

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**PIR Quiz**

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online only. No paper answer form will be printed in the journal.

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1. You have recently diagnosed a patient with epilepsy and are starting the drug phenytoin. Based on your review of the package insert, the plasma half-life is approximately 24 hours (1 day). After how many days of the same dose would you expect a steady state level to be reached?
   - A. 1 day.
   - B. 2 days.
   - C. 5 days.
   - D. 12 days.
   - E. 20 days.

2. You are evaluating a child with cellulitis in your office and are debating whether to give outpatient oral clindamycin or hospitalize for intravenous clindamycin. Which of the following is true of the intravenous as opposed to the oral form of a medication?
   - A. The intravenous form has a longer half-life.
   - B. The intravenous form has a higher bioavailability.
   - C. The intravenous form has a greater volume of distribution.
   - D. The intravenous form has more rapid hepatic metabolism.
   - E. The intravenous form has more rapid renal excretion.

3. You are caring for a patient with congenital diaphragmatic hernia currently receiving extracorporeal membrane oxygenation (ECMO) in the intensive care unit. The child was recently diagnosed with a gram negative urinary tract infection, and you decide to treat with an aminoglycoside. Of the following factors, which is most likely to affect the aminoglycoside level in a child on ECMO?
   - A. Infants on ECMO have induction of P450 cytochromes.
   - B. Infants on ECMO have decreased renal clearance.
C. Infants on ECMO have reduced drug glucoronidation.
D. Infants on ECMO have increased volume of distribution.
E. Infants on ECMO have reduced total body water.

4. You are prescribing the drug erythromycin (a potent inhibitor of the cytochrome CYP3A4 enzyme) to child with a renal transplant. Of the following medications, which would you be most concerned about having a drug interaction with the erythromycin?
   A. Azathioprine.
   B. Cyclosporine.
   C. Prednisone.
   D. Propanolol.
   E. Trimethoprim/sulfamethoxazole.

5. A factor in infants that may affect the bioavailability of drugs taken orally is:
   A. Increased gastric pH compared to adults.
   B. Decreased gastric pH compared to adults.
   C. Increased intestinal motility compared to adults.
   D. Increased bile salt concentration in the intestinal lumen compared to adults.
   E. Increased cleavage of drugs by pancreatic enzymes.

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Poetic License

Pharmacokinetics, though complex
Are needed to know drug effects.
As physiology changes
We need dosing ranges
To prevent problems no one expects!

–MCM