

Chapter 2

Developmental Pharmacokinetics: Drug Disposition Relative to Age

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Introduction

The fundamental goal of drug therapy is to provide optimal efficacy for disease management without adverse event, with the most important factor in achieving this goal being drug dose. A medication's optimal dose is dependent on a number of chemical and patient-specific factors including desired target therapeutic effect(s) combined with a patient's age, body habitus, genetics, disease state(s), major organ function (e.g., kidney, liver, heart), and concurrent therapies. Once the drug is administered these variables modulate overall drug exposure and for the treatment of systemic disease, a sufficient amount of drug must be available to distribute and bind to its receptor for a sufficient period of time to elicit a therapeutic effect. This balance of systemic drug exposure, receptor binding, and therapeutic effect is dependent on the integration of a drug's pharmacokinetic (PK: drug disposition), pharmacodynamic (PD: mechanism of action), and pharmacogenomic (PG) characteristics. Pharmacokinetics describes a drug's overall disposition profile which is markedly influenced by patient age [1, 2]. Pharmacokinetics encompasses the processes of drug absorption, distribution, metabolism, and elimination—the integration of these processes relative to patient age is the focus of this chapter.

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Drug Absorption

In the absence of topical administration for local effect, a drug must be absorbed into systemic circulation to distribute to its site of action to elicit the desired therapeutic effect. The PK parameter describing drug absorption is termed bioavailability and routinely abbreviated as “F.” Although drug F is often considered the amount of drug absorbed into systemic circulation, this PK parameter estimate also encompasses the rate of drug absorption. Thus, drug F is the composite of rate as well as overall extent of drug absorption. This distinction may seem minor but in fact is very important and clinically relevant. For example, if a drug’s effect is dependent on the peak drug concentration (e.g., certain antibiotics: aminoglycosides) a drug with slow absorption characteristics may not achieve necessary peak concentrations for efficacy. Similarly for a drug that requires prolonged systemic exposure, a timed-release/sustained-release preparation might be the best formulation for optimal therapeutic effect.

Drug F is most often reported as a percent, i.e., the percent of the total amount of the drug dose administered that enters systemic circulation as the active drug. The absolute F for a drug is the ratio of the drug’s systemic exposure, as determined by a drug’s area under the serum (blood) concentration–time curve (AUC), after extravascular administration (e.g., topical, oral, intramuscular [IM]) relative to the AUC achieved after intravenous (IV) administration, i.e., AUC_{ex} divided by the AUC_{iv} . Most importantly the drug concentration used in these assessments is the amount of *active drug* that reaches systemic circulation. This important distinction accounts for those limited number of drugs that are administered as a pro-drug, i.e., an inactive (minimally active) form of the drug requiring some form of in vivo alteration to liberate the active drug [3, 4]. The manufacturing of a drug as a pro-drug is a process pharmaceutical scientists use to chemically modify drugs that cannot be easily formulated. For some drug chemicals such alteration is required for the drug to be absorbed or to manufacture a better flavored liquid formulation. A pro-drug formulation may also be necessary to assure that a drug distributes to anatomic sites that if chemically unaltered could not distribute to its target site. Examples of drugs administered as pro-drugs include codeine (converted to active morphine), the anti-influenza drug oseltamivir (Tamiflu®), and prednisolone (converted to active prednisone). In addition to pro-drug administration, certain drugs undergo substantial “first-pass” metabolism, where a large amount of the drug dose may be absorbed into systemic circulation but after its “first-pass” through the liver, only a fraction of the dose remains as the active drug with the remainder as metabolites (note: the metabolite(s) may be therapeutically active or inactive and/or be responsible for adverse effects). The bioavailability evaluation could be for the parent drug, the active metabolite(s), or both. It is important to determine and know what drug moiety is included in the bioavailability data you are presented with.

It is important to recognize that topically or orally administered drugs may also be metabolized within the cells they traverse limiting the amount that reaches systemic circulation. Furthermore, intestinal cells and many anatomic sites, including

the blood–brain barrier, placenta, and others, contain drug transporters that can enhance or oppose drug absorption [1, 2, 5–9]. The importance of drug transporters is addressed in greater detail below.

Lastly, a drug's physicochemical characteristics influence the rate and extent of drug absorption. These physicochemical characteristics include molecular weight/size, degree of ionization under physiologic and pathophysiologic conditions, and degree of lipid solubility. The most favorable physicochemical characteristic for optimal drug F (and distribution—see below) is a small, highly lipid soluble molecule of low molecular weight that is un-ionized under physiologic and/or pathophysiologic conditions.

The importance of the factors outlined above cannot be overemphasized and patient age exerts many influences on the process of drug F. Blood flow characteristics at the site of absorption, e.g., the muscle for IM injections, intestine for oral meds, as well as the type, amount, and pH of intestinal contents combined with the extent and variability of gastric emptying and intestinal motility, will all influence a drug's F. In addition, maturity and functional capacity of drug metabolizing enzymes (e.g., cytochrome P450 isoenzymes—see below) and influx/efflux transporters located within cells will also impact on the amount a drug is absorbed. Thus, the ontogeny of gastric and intestinal circulation combined with cellular and organ function can and will dramatically affect a drug's F.

Drug Absorption: Physiologic Influences

For decades it has been believed that shortly after birth infants experience a relative period of achlorhydria. The original description of gastric pH by Miller in 1941 reported a gastric pH at birth of ~7, rapidly falling to pH 3 within the first few hours but slowly rising to >pH 4 [10, 11]. More recent data suggests that at birth gastric pH does rapidly decline to pH 2–3 but in fact fluctuates throughout the day and is not universally more alkaline, i.e., defined as gastric pH > 4 [11]. A better assessment of the ontogenic influences on gastric pH has been proposed to focus on the proportion of time the gastric pH peaks above 4 in a 24 h period. In preterm infants, this proportion of time has been reported to range from 46 to 70 % whereas for children up to 2 years of age the value approaches 51 % and in older children 34 % [11]. The higher proportion in younger children may partially be explained by the buffering effects of milk formula; older children are less frequently fed and receive more solid foods. In addition to gastric pH, age and diet will influence the rate of gastric emptying. Noting that most drugs are absorbed in the upper part of the small intestine the rate of an orally administered drug to transit from the stomach into the duodenum will influence drug F. Consumption of human milk and lower caloric substrates/formulas can increase (prolong) gastric emptying whereas feeds of higher caloric density or long-chain fatty acids may shorten gastric emptying [10, 12]. Lastly, the developmental pattern of bile acid synthesis and secretion can influence the absorption of lipophilic drugs which are poorly soluble in the aqueous digestive fluids [11].

Clinical relevance: With few exceptions, the maturational changes observed over the first year of life in gastrointestinal functions (as described above) have a limited effect on routine drug therapy in the care of premature, newborn, and young infants. Routine dose recommendations accommodate for these developmental processes. Nevertheless, these maturational processes are reflected in the much higher variability observed in drug F during this age period. Specific examples would include acid-labile compounds where F would be expected to be increased (e.g., penicillin G) and decreased F for weak acids (e.g., phenobarbital, ganciclovir) in premature and full-term infants as compared to adults. Also as discussed above, the type and quantity of enteral feedings and the magnitude of gastric emptying and intestinal motility can and will influence the rate and extent of oral drug F. With respect to drug F after intramuscular (IM) administration, drug absorption can be highly variable, particularly in the ill neonate and young infants, where cardiovascular function and, thus, blood flow dynamics can be compromised. For these reasons, the IV route for drug administration for ill premature and newborn infants is preferred. Nevertheless, if one is unable to establish IV access in an ill neonate/infant requiring prompt drug therapy, the IM route for drug administration, for a drug that can be administered IM, should be used initially until IV access becomes available.

Overall, these expected changes in drug F simply underscore the importance of close patient monitoring for dose–effect outcomes in each patient, that are best determined under steady-state conditions (see below). Furthermore and very important in pediatric practice is the drug formulation. The formulation can have great influence on the rate of absorption which is expected to be faster after administration of a liquid dosing formulation (liquid > suspension) compared with a solid formulation (capsule \geq tablet > sustained-/delayed-release tablet). For a drug to be absorbed from any site it must be in solution before it is available to cross membranes and enter systemic circulation.

Drug Distribution

Once drug is absorbed into systemic circulation, a dynamic equilibrium is achieved between drug bound to plasma proteins and the nonprotein-bound fraction, commonly referred to as the “free” drug. It is the free drug that is capable to distribute outside the vascular compartment, it is the free drug that crosses cells/membranes, and it is only the free drug that will bind to its receptor(s) and elicit a pharmacologic and/or toxicologic response(s). The extent to which a drug distributes throughout the body is dependent upon a number of drug- and patient-specific variables including the drug’s physicochemical characteristics as noted above (i.e., molecular weight, degree of ionization at physiologic/pathophysiologic pH, and degree of lipid solubility), affinity for cellular transporters (see below), and degree of protein binding. As noted for drug F above, a small molecule un-ionized at physiologic/pathophysiologic pH that is highly lipid soluble is associated with wide body

Table 2.1 The developmental aspects of fluid compartment sizes

Patient age	Total body water ^a	Extracellular fluid ^a	Intracellular fluid ^a
<3-Month fetus	92	65	25
Term gestation	75	35–44	33
4–6 months	60	23	37
12 months		26–30	
Puberty	~60	20	40
Adult	50–60	20	40

Adapted from [2]

^aValues expressed as percentage of total body weight

distribution or in PK terms, a drug with a large volume of distribution (V_d). The importance of the PK parameter V_d is that a drug's V_d is used to determine the size of an individual dose. A drug's V_d is influenced by a patient's size and age. As a drug must be in solution for absorption and distribution, the ontogeny of physiologic fluid compartments will influence a drug's V_d value. The developmental pattern of body fluid compartments is shown in Table 2.1 [13] and as a result, a drug's V_d is influenced greatly by the age of the pediatric patient. The importance of these developmental changes cannot be overemphasized as the volume of these fluid spaces will directly impact the absolute drug concentration and, thus, could directly influence the magnitude and time course of drug effect.

Understanding the body distribution characteristics for a drug is important when prescribing a drug and calculating the dose to be administered. For example, if target drug receptors are located within the central nervous system (CNS) the drug must distribute into the CNS for therapeutic effect. Although the absolute value of a drug's V_d does not correlate with any real physiologic volume (i.e., hence the formal name for V_d is *apparent* volume of distribution), knowledge of this PK parameter provides insight into the total amount of drug present in the body relative to its concentration in blood and, thus, tissue distribution. Clinically it can be speculated with a moderate degree of certainty that a drug with a very large V_d (e.g., 10 L/kg) can be assumed to distribute widely throughout the body (possibly even into the CNS, e.g., anesthetics), whereas a drug with a very low V_d value (e.g., 0.1 L/kg) might be expected to have limited body distribution. However, regardless of a drug's V_d numeric value, what really matters is the drug effect. Independent of a drug's V_d , what matters clinically is that a sufficient amount of drug distributes to and binds to the necessary receptor site to stimulate the desired pharmacologic effect(s).

Identification of the age-appropriate V_d for a drug can be obtained from most computer information/pediatric drug dosing references. The reported V_d value is unique to each individual drug and will change relative to age and possibly even by disease, particularly for those diseases that result in large volume shifts. A comparison of V_d values between neonates and adults for a few select drugs is shown in Table 2.2.

Table 2.2 Comparison of volume of distribution and elimination half-life for selected drugs in neonates compared to adults

Example drug (brand name)	Neonate		Adult	
	V_d	$t_{1/2}$	V_d	$t_{1/2}$
Amikacin (Amikin [®])	0.6	8.4	0.3	2.3
Amoxicillin (Amoxil [®])	0.7	3	0.2	1.7
Bumetanide (Bumex [®])	0.22	6.5	0.13	1.5
Caffeine citrate (Cafcit [®])	0.85	84	0.6	5
Caspofungin (Cancidas [®])	0.43	8.3	0.25	13
Cefepime (Maxipime [®])	0.43	5.0	0.26	2.1
Gentamicin (Garamycin [®])	0.7	7.2	0.31	2.5
Levetiracetan (Keppra [®])	0.89	9	0.6	6
Morphine	2.3	7.0	3.0	2
Pantoprazole (Protonix [®])	—	3.1	—	1–1.5
Phenobarbital	0.71	108	0.54	60–80
Tobramycin (Nebcin [®])	0.7	8.3	0.33	2.2
Vancomycin (Vancocin [®])	0.57	6–10	0.39	6

The drug brand name noted is one example as many of the drugs listed may have multiple brand names

Data presented represent best estimate averages for comparative purposes and were obtained from published parameter estimates in premature and newborn infants usually during the first week of life

V_d , apparent volume of distribution presented in L/kg (kg body weight); $t_{1/2}$, elimination half-life in hours (h)

Drug Distribution: Protein Binding

In addition to body fluid compartments, the amount (%) of drug binding to protein will influence the amount of drug distributed within the body. Drug bound to proteins (or other fractions) is not pharmacologically active or available for metabolism or excretion—it is only the free (unbound) fraction of the absorbed drug that is pharmacologically (also toxicologically) active, capable of diffusing outside the circulatory compartment/across cell membranes distributing to the site(s) of action, and available for body elimination, e.g., liver metabolism and/or renal excretion. Important differences exist between the degree of drug–protein binding in premature and newborn infants compared to adults and examples are outlined in Table 2.3. The concentration of plasma proteins is reduced in the immediate post-delivery period as well as there are select, endogenous circulating compounds found in a neonates circulation that may/will compete for plasma/albumin binding. The most important of these compounds is bilirubin for which controversy persists surrounding possible displacement of bilirubin from its albumin binding sites by drugs and possibly precipitating kernicterus. Although such an albumin–drug–bilirubin displacement interaction is possible, the magnitude of such an interaction depends on a number of variables but most notably, the absolute concentration of drug(s) and

Table 2.3 Percent (%) protein binding of select representative drugs in newborn infants compared to that in adults

Drug	Percent bound	
	Newborn	Adult
Ampicillin	10	18
Diazepam (Valium®)	84	99
Digoxin (Lanoxin®)	20	32
Ibuprofen (Caldolor®)	95	99
Micofungin (Mycamine®)	96.7	99.6
Morphine	35	45
Nafcillin (Unipen®)	69	89
Phenytoin (Dilantin®)	80	90
Phenobarbital	32	47
Theophylline	36	56

The drug brand name noted is one example as many of the drugs listed may have multiple brand names
Data presented represent best estimate averages for comparative purposes and were obtained from published parameter estimates in premature and newborn infants usually during the first week of life

bilirubin relative to the circulating albumin concentration, number of available albumin binding sites, and the presence of other albumin binding compounds that will compete for the same albumin binding sites. Fortunately, this combination of required events rarely occurs in clinical medicine. In fact more recent animal data suggests that the immaturity of the efflux pump, P-glycoprotein, in the blood–brain barrier may be the most important determinant of bilirubin-brain concentrations rather than a simple drug–protein displacement interaction [8]. Further complicating this controversy is the fact that our knowledge of the extent to which a drug is usually bound to albumin, e.g., 50 and 90 %, provides little to no dependable clinically relevant information as to the extent a drug might displace bilirubin from its albumin binding sites. For example, two drugs frequently used in the care of premature and newborn infants furosemide (Lasix®) and midazolam (Versed®) are both highly bound to plasma albumin [14] and unassociated with any drug–bilirubin–albumin displacement reaction.

Clinical relevance: Knowledge of the age-appropriate V_d in liters per kg body weight (V_d L/kg) for a given drug allows the clinician a simple yet accurate method to calculate the peak drug concentration achieved with the *first dose* of drug. The peak concentration obtained after the first dose can be calculated using the following relationship: peak drug concentration=drug dose (μ g or mg) divided by drug V_d (l/kg) multiplied by the patient’s body weight in kg. For example, if you order a 5 mg dose of a drug to be administered to an 800 g infant and the drugs V_d is 0.4 L/kg, the estimated peak concentration right after the full dose is administered would be peak=(5,000 μ g dose) divided by (320—infant body weight (0.8 kg) multiplied by the drug V_d in milliliters—400 mL); thus it would be ~15.6 μ g/mL. Conversely, if you want to determine the dose of a drug to achieve a specific target blood concentration the equation can be rearranged to: dose (μ g or mg)=(desired blood level

in $\mu\text{g/mL}$) multiplied by (the drug V_d in mL/kg) (patient body weight (kg)). The most common errors observed in these simple mathematical calculations are those related to converting units properly, i.e., mg to μg and kg to g . Note: the reason this simple calculation is only valid after the first dose is these equations assume no drug is present in the body at the time of the first dose. After multiple doses the amount of drug must be inserted into the calculation (subtracted from the peak concentration) to accurately determine a drug's V_d .

With respect to drug binding to plasma proteins the extent of binding for a specific drug is most often of limited to no clinical significance. The defined clinically used dosing strategy accounts for the amount of drug bound and the amount of free drug. However for certain drugs, the “target” serum drug concentration differs from that defined for infants as compared to older infants, children, or adults. This important clinical discrepancy is merely due to the reduced drug–albumin binding for various drugs in the neonate vs. older infants, children, and adults (see Table 2.3). The importance of this factor is that defined, target “therapeutic serum/plasma drug concentrations” determined in adults may be totally appropriate for older infants and children but may be different in the neonate underscoring the importance of drug concentration definitions for different post-conceptual ages (PCA). Table 2.3 provides some estimates in the percent of protein binding for select drugs used in the NICU.

Drug Metabolism

Most drugs are not excreted from the body unchanged, but rather undergo biochemical modification usually by specialized enzymatic systems in a process known as xenobiotic metabolism or biotransformation. These enzymes are found in most human tissues (e.g., lung, kidney) with the highest concentrations in the liver and small and large intestines. While the liver is considered the major source of drug metabolizing activity, the enzymes located within the epithelial cells of the small intestine initiate the biotransformation of most orally administered medications. As noted in absorption above, once drugs are intestinally absorbed they enter the portal circulation for the aforementioned “first-pass” through the liver. Any hepatically metabolized drug that “escapes” this initial pass through the liver eventually undergoes sufficient metabolism on subsequent passes through the portal circulation. One can avoid or minimize the impact of intestinal and/or hepatic first-pass drug metabolism by using the sublingual (e.g., nitroglycerine), nasal, and in some cases rectal routes for drug administration. Some drugs are not easily metabolized and, hence, remain in the body for longer periods of time whereas other drugs may not undergo any metabolism and will be eliminated from the body unchanged.

Historically, the enzyme systems responsible for drug biotransformation have been grouped into either Phase I or Phase II reactions. Phase I reactions are those involving oxidation, reduction, or hydrolysis reactions that will add or expose functional groups on the drug molecule, thus increasing the compound's polarity,

Table 2.4 Metabolic enzymes involved in human drug metabolism

Phase I metabolism	Phase II metabolism
Cytochrome P450 oxidases (CYPs)	UDP-glucuronosyltransferases (UGTs)
Flavin-containing monooxidases (FMOs)	Sulfotransferases (SULTs)
Monoamine oxidases	Glutathione-S-transferases (GSTs)
Alcohol/aldehyde dehydrogenase	<i>N</i> -acetyltransferases (NATs)
Peroxidases	Methyltransferases (MTs)

reducing its likelihood for absorption or reabsorption, and fostering its body elimination. A drug may undergo Phase I metabolism resulting in inactive metabolite(s) that may either be excreted or act as a substrate for Phase II metabolism. In some cases, a drug's Phase I metabolism may result in converting a pharmacologically inactive compound (a pro-drug) into a pharmacologically active one—pro-drug conversions were addressed specifically in absorption above.

Phase II metabolism consists of conjugation reactions, including glucuronidation, sulfation, acetylation, and methylation among others. Like Phase I reactions, the end product of a Phase II reaction is the genesis of a compound that is usually pharmacologically inactive but more water soluble (hydrophilic) promoting efficient body elimination. Occasionally Phase I and/or Phase II metabolism can result in the formation of a toxic metabolite, which can elicit an adverse reaction. An important example of such a reaction involves acetaminophen (e.g., Tylenol®), a drug that is metabolized via the cytochrome P450 enzyme system (CYP2E1) to the toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), in overdose or in situations of excess acetaminophen consumption. A list of the enzymes responsible for carrying out Phase I and Phase II metabolism can be found in Table 2.4.

Phase I Metabolism

The cytochrome P450 enzyme superfamily (or CYPs) are the primary enzymes involved in Phase I metabolism. While this family of enzymes do play an important role in the biotransformation of numerous endogenous chemicals in the body, they also account for the transformation of up to 75 % of exogenously administered compounds. The human genome project identified 57 genes divided into 18 families of CYPs. However, only a handful of CYPs (1A2, 2C9, 2C19, 2D6, 2E1, and 3A4) are responsible for the vast majority of drug metabolism (~90 %), with CYP3A4 being the most prominent in drug metabolism [15–18]. Most CYPs have very broad substrate specificity and can metabolize multiple compounds. This broad substrate specificity also means that many drugs can be substrates for and metabolized by multiple CYPs. The selectivity of the CYPs for certain compounds is determined by the inherent characteristics of the drug (i.e., lipophilic vs. hydrophilic compounds) and cannot be predicted by drug class. This is perhaps best illustrated by the antidepressant medications fluoxetine (e.g., Prozac®), paroxetine (e.g., Paxil®), and

sertraline (e.g., Zoloft®), all members of the class of selective serotonin-reuptake inhibitors (SSRIs)—fluoxetine and paroxetine are extensively metabolized by CYP2D6 whereas sertraline's metabolism does not appear to be affected by any specific or predominate CYP.

Phase II Metabolism

A large number of physiologic enzymes are involved in Phase II metabolism including, but not limited to, the UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), glutathione-S-transferases (GSTs), *N*-acetyltransferases (NATs), and methyltransferases (MTs). Among the most important of the Phase II enzymes are the UGTs and, like the CYPs, the UGTs possess broad substrate specificity. Unlike, the CYPs only two families of UGT enzymes exist (UGT1 and UGT2), with the vast majority of drug metabolism involving the UGT1 family.

Drug Metabolism: Physiologic Influences

The rate and extent of drug metabolism can vastly influence both the safety and efficacy of a drug. Should a compound be metabolized to an inactive entity too quickly, its therapeutic effectiveness may be greatly diminished. Conversely, drugs that are metabolized very slowly can accumulate in the body, potentially resulting in an adverse drug reaction. The factors controlling the extent and rate of metabolism are both complex and varied. Some of the known factors include age, disease, gender, environmental, drug dose, drug–drug interactions, diet, and genetics, among others. Some of these variables are discussed in more detail below.

Age

Important differences in the maturational pathways for both Phase I and Phase II drug metabolizing enzymes exist. These developmental changes can have significant impact on the efficacy and safety profile of drugs administered to infants and children. These changes are best exemplified by the administration of chloramphenicol to newborns, a lifesaving antibiotic once used but replaced by safer agents today. Glucuronyltransferase activity, which is greatly diminished at birth, is necessary for converting chloramphenicol to the inactive glucuronide metabolite (more water soluble) for renal excretion. The immaturity of the glucuronyltransferase enzyme leads to very diminished chloramphenicol metabolism with accumulation of unaltered chloramphenicol and subsequent cardiovascular collapse or “Grey Baby Syndrome.” While not all drugs administered to infants and children will have such deleterious effects, it is nevertheless important to consider the age-related

changes in drug metabolizing enzymes. Huge variability in morphine metabolism is partially explained by variability in the UGT pathways. The importance of the maturation and activity variability relative to patient age is becoming increasingly important at the bedside for many Phase I- and Phase II-metabolized drugs.

The greatest amount of research into the ontogeny of drug metabolism has focused on the aforementioned cytochrome P450 superfamily of enzymes known as the CYPs [18]. As previously mentioned, CYP3A4 is the most common drug metabolizing enzyme in humans. However, this enzyme is expressed at very low levels at birth. Instead, CYP3A7, a CYP usually undetectable in adults, is the predominant CYP in fetal liver [17]. After birth CYP3A4 activity increases upwards of 60 % of adult levels within the first week of life and achieves full adult levels by a child's first birthday. Conversely, CYP3A7 peaks shortly after birth and then rapidly declines. Other distinct patterns of CYP developmental expressions have also been observed. CYP2C19 and CYP2E1 activities appear shortly after birth and gradually increase until adult levels are reached at ~6 months and 1 year, respectively. Some CYPs, such as CYP2D6 and CYP2C9, do not exhibit vastly different activity across the age spectrum. As would be expected, the maturational changes of each CYP enzyme potentially represent an altered PK profile for any substrate [15–18].

Unfortunately, less information is known about the ontogenic expression of the Phase II enzymes [16]. Studies with specific drugs have shown that individual UGT isoforms have, like the CYPs, unique maturational profiles which result in differing PK profiles of drugs dependent on these enzymes for elimination from the body. An example of this would be the case of morphine, a UGT2B7 substrate. The drug and its metabolites, morphine 3-glucuronide and morphine 6-glucuronide, are detected in various proportions with increasing age and body weight.

Genetics

Both Phase I and Phase II drug metabolizing enzymes are influenced by an individual's genetic makeup. Genetic variation in the expression and/or activity of enzymes can influence an individual's response to drug with respect to either therapeutic efficacy or adverse events. Patients may inherit variable numbers of gene copies that define the activity or functional capacity, of that enzyme. To date, patients are classified as to the expected activity of the enzyme based on their genotype, i.e., two nonfunctional (or "inactive") alleles—poor metabolizers (PM), two functional or "normal" copies or one functional allele and one reduced activity level allele—extensive metabolizers (EM), two reduced activity alleles or one functional and one reduced activity allele (significantly below capacity seen in PM)—intermediate metabolizers (IM), and patients with multiple copies of functional alleles—ultrarapid metabolizers (UM). In reality and based on our family tree, the entire spectrum from zero to extremely rapid activity is possible and can result in altered patient response [17].

Unfortunately, the clinical utility of genotyping test results has yet to keep up with the technology developed to identify various genotypes. Moreover, there are

Table 2.5 Selected list of known inducers of CYP enzymes

CYP1A2	Tobacco
CYP2C9	Rifampin
CYP2C19	Carbamazepine, prednisone
CYP2D6	Dexamethasone, rifampin
CYP3A4	Phenytoin, phenobarbital, rifampin, St. John's Wort

CYP cytochrome P450

apparent discrepancies in a patient's clinical response and the predicted response based on genotype results, often termed the "genotype–phenotype discordance." This discordance is primarily reflective of the involvement of multiple genes in overall drug disposition and/or the drug's pharmacologic effect rather than one polymorphism responsible for the observed phenotype [17]. In addition, multiple compensatory mechanisms are inherent to our genome which can be expressed to enhance or stop an encoded process thereby mitigating the effects of particular genotypes. Similarly, environmental factors (e.g., age, disease severity) will influence the ultimate phenotypic expression within an individual patient.

Enzyme Inhibition and Induction

Not only can drugs and endogenous compounds act as substrates for the various drug metabolizing enzymes, but they are also capable in some cases of altering the activity of the enzymes themselves. A drug that is known to either induce or inhibit enzymes may either enhance or diminish the metabolism of other drugs but also its own metabolism. Enzyme-inducing drugs include various anticonvulsants and anti-infective agents, among others. This effect is usually only noticed after repeated use and can take days to weeks to reach maximum activity levels. Patients receiving enzyme-inducing drugs may require much higher doses of concurrent medication(s) to achieve a therapeutic effect as is the case with patients receiving chronic phenobarbital therapy requiring higher warfarin doses to achieve adequate anticoagulation. As noted, a drug may also induce its own metabolism potentially leading to reduced therapeutic effectiveness of the inducing drug as well as concurrent medications. The classic example of a drug that induces its own metabolism and the metabolism of many others is carbamazepine. In such circumstances the dose of the inducing drug may also require adjustments as well as the affected co-administered drug(s). A partial list of drugs that may enhance drug metabolism is provided in Table 2.5.

Conversely, drugs that inhibit certain enzyme activity do so either via competitive substrate inhibition or via irreversible substrate-mediated enzyme inactivation and require less time, hours to days, to achieve this effect—enzyme stimulation requires time for the body to generate more enzyme whereas inhibition can occur immediately with the proper concentration. Enzyme inhibition may result in impaired elimination of a drug and potentiate its effects. This is especially true of

Table 2.6 Selected list of known inhibitors of CYP enzymes

CYP1A2	Fluvoxamine, ciprofloxacin
CYP2C9	Fluconazole
CYP2C19	Proton pump inhibitors
CYP2D6	Bupropion, fluoxetine, paroxetine
CYP3A4	Itraconazole, ketoconazole, erythromycin, clarithromycin, grapefruit juice
<i>CYP</i> cytochrome P450	

drugs with narrow therapeutic indices as was the case with terfenadine (e.g., Seldane®, a second generation “nonsedating” antihistamine) leading to its removal from the market. Terfenadine requires metabolism by CYP3A4 to its active and safe metabolite fexofenadine (Allegra®). When terfenadine was co-administered with a CYP3A4 inhibitor (e.g., erythromycin), the cardiotoxic parent compound, terfenadine, accumulated leading to fatal cardiac arrhythmias prompting the drug to be withdrawn from the market. A partial list of drugs that may inhibit important enzymes is provided in Table 2.6.

Drug Transporters

All drugs undergo some form of passage through a cell membrane at various point(s) in the drugs’ sojourn throughout the body. This is required for absorption, distribution, metabolism, and excretion. The process by which this occurs can vary according to, among other things, the cells involved and the inherent characteristics of a drug. These processes can happen passively, via simple diffusion, or require carrier-mediated transport. Carrier-mediated transport can require energy, as in active transport, or facilitated diffusion where no energy input is required, such as glucose’s movement mediated via the GLUT4 transporter across a cell membrane. These mechanisms can be required for a drug to distribute to where it needs to go (absorption and distribution) or to remove it from the body (metabolism and excretion). Transporters play an important role in defining a drug’s pharmacokinetic profile. The most pharmacologically important transporters usually fall into one of the two superfamilies, the ATP binding cassette (ABC) and solute carrier (SLC) transporters. ABC transporters are active transporters while the SLC group involves facilitated or secondary activated transporters [5–9].

Transporters, located in all cell membranes throughout the body, control the influx and efflux of endogenous, usually nutrients and waste products, and exogenously administered compounds like drugs. Because transporters can control the cell’s exposure to a drug, they can be crucial in a drug’s efficacy as well as toxicity profiles. Multiple transporters may work together to facilitate a drug’s movement into and out of cells affecting the absorption, distribution, and elimination from the body.

Transporters in the Intestine: Absorption

Both ABC and SLC transporters are present in the apical membrane of the enterocyte that work to facilitate drug absorption or decrease a drug's bioavailability. The most extensively researched ABC transporter is P-glycoprotein (ABCB1). This protein transports drug from the enterocyte back into the intestinal lumen, thereby decreasing a drug's absorption into the body. Hence, P-glycoprotein and members of the ABC superfamily are often referred to as efflux transporters [5–9]. The efflux transporters have a diverse group of substrates and can also serve as a source of the ever important drug–drug interaction. Like the CYP drug metabolizing enzymes, P-glycoprotein activity may be affected by exogenously administered substrates and/or genetics. Therefore, drugs that inhibit the transporter's activity can result in increased absorption of a drug that would normally be removed from the enterocyte if the transporter was functioning at normal capacity. Likewise, if P-glycoprotein was induced or overactive, normally well-absorbed drugs may be “effluxed” out of the enterocyte thereby limiting drug absorption. Unfortunately, the data involving these findings in humans is incomplete and occasionally conflicting. This is also true of the SLC transporters whose role in drug absorption remains unclear. Most importantly, much more data is needed describing the ontogenic influences that influence transporter functional capacity along the age continuum and what effects, if any, are observed in clinical response.

Transporters in the Liver and Kidney: Elimination

Transporters play an important role in both the uptake of drug into the liver and removal of the drug from hepatocytes. The uptake of drug into the liver, when simple diffusion is not sufficient, is usually accomplished by the SLC transporters. This entry into the hepatocytes allows for the drug to be presented to drug metabolizing enzymes. Once the drug enters the hepatocyte, the ABC transporters can then facilitate the removal of the drug or its metabolites into the blood or bile, eventually to be removed from the body completely [6–8].

For drugs with little hepatic metabolism or biliary excretion and/or metabolites, the kidney represents the major process for drug elimination (see below). The secretion of drugs into the renal tubular lumen is usually a transport-mediated multi-step process mostly carried out in the proximal tubule. For the clinician, the most important aspect to remember about this process rather than how it occurs is that the process is saturable, modifiable, and subject to genetic mutations. Therefore, some drug's renal elimination may be reduced at high concentrations. Further, drugs can compete for a similar transporter, resulting in reduced elimination of one compound. This may not always be a disadvantage as exemplified by the historical maneuver of co-administering probenecid along with penicillin derivatives to extend the limited supplies of penicillin during World War II, soon after the discovery of

penicillin. Finally, genetic mutations can influence protein function or expression. However, the clinical influences of these findings are limited.

Clinical relevance: The metabolism for many drugs can involve multiple metabolic pathways, i.e., primary and possibly one or more secondary pathways. Knowing the developmental pattern of the drug metabolizing pathways allows one to accurately calculate repeat doses for ongoing drug therapy. If a primary pathway is compromised by enzyme inhibition or is modified by inheritance, i.e., genetics, a secondary pathway(s) may become important to the body elimination of a drug ultimately leading to no or only minimal change in the drug's overall body disposition and, thus, no observable change from that expected with the original routine drug dose. An example would include the drug amitriptyline (Elavil®), a tricyclic antidepressant used for the treatment of depression and sleep disorder in adults and ADHD in select children. Amitriptyline is metabolized by multiple CYP pathways but primarily by two polymorphically expressed cytochrome P450 isoenzymes, CYP2C19 and CYP2D6. The patient may be a CYP2D6PM but a CYP2C19EM or similar perturbations where the sum of the metabolic pathways results in the expected drug elimination and, thus, desired clinical response. This situation is often the basis for the discordance sometimes observed in patients receiving multiple medications and you expect a drug–drug interaction but it is not observed. This occurs as the metabolism of the drug or drugs has alternate pathways unaffected by the primary drug interaction. With the case of amitriptyline, if the patient is a CYP 2D6 and CYP 2C 19 PM or receives a drug or drugs that interfere with both CYPs the patient may experience increased toxicity as the drug elimination is slowed because of diminished to null activity in both metabolic pathways. Lastly, enzyme inhibition may reduce or ameliorate enzyme activity thereby making an individual with “normal” enzyme activity function as a poor metabolizer.

The converse is true for enzyme inducers. It is important to recall that enzyme induction requires time to generate additional enzyme and the timing of when one might observe the clinical effects from an enzyme induction drug interaction varies (often 5 days to 3 weeks) and that the effect will be gradual until full induction is achieved. If co-administered drug doses are increased to compensate for the observed induction one simply needs to recall that if the dose of the enzyme-inducing drug is decreased or the drug discontinued completely the doses of the other co-administered drugs can be reduced appropriately as well.

Drug Elimination

Drugs can be removed from the body by various processes of elimination, with the kidney and liver being the two most important organs involved. Drugs and their metabolites may also be eliminated from the body via sweat, saliva, bile, expired air, and other bodily fluids, though the kidney and liver represent the pathways for the majority of clinically used agents. Drugs may either be eliminated as a “whole” or otherwise unaltered as the parent compound or, as described above, may be

metabolized to various metabolites which are then eliminated from the body via one mechanism or another, typically the kidney. The PK parameter clearance (CL) best describes the rate of drug elimination from the body. This PK parameter comprises all routes of drug clearance from the body, i.e., hepatic, renal, lung, etc., and is usually described as $CL = \text{renal CL} + \text{nonrenal CL}$. Obviously a drug's CL is dependent on the functional capacity of the body to remove agents as well as any impact that the environment or disease may have on elimination routes.

Clearance is especially useful in designing a regimen for long-term drug administration as it provides the clinician insight into the subsequent or maintenance doses that should be administered in order to maintain drug concentrations within the therapeutic window and most importantly, achieve the desired therapeutic effect(s). When most drugs are eliminated from the body, they typically do so in a linear fashion. This means that the rate of elimination is the same, regardless of the dose and resultant plasma drug concentration—the CL is constant, a concept known as linear or first-order PK. However, for a few drugs, most notably ethanol, aspirin, and phenytoin (e.g., Dilantin®), the rate of clearance is not constant as the rate of elimination is proportional to the plasma concentration of the drug. These drugs are said to undergo nonlinear or “saturable” elimination. The importance of this PK characteristic is for these later drugs a small increase in dose can lead to a substantial increase in the amount of drug in the body (e.g., elevated plasma drug concentrations) and lead to toxic effects.

Another important PK parameter in relation to drug elimination from the body is the time it takes for the serum concentration of a drug to decrease by 50 %, otherwise known as the drug half-life ($t_{1/2}$). This value is very helpful at the bedside in estimating the time to reach steady-state conditions, i.e., steady state is where the rate of drug administration equals the rate of drug elimination. For drugs that follow linear or first-order PK (proportional), it takes ~ 5 drug half lives to reach this state of equilibrium, steady state. Furthermore, the $t_{1/2}$ can be helpful in determining when to restart drug dosing or initiate new drug therapy after temporary discontinuation of a medication regimen. Total elimination from the body is usually complete by $\sim 10 t_{1/2}$ s but clinically relevant elimination (i.e., $>90\%$) is usually achieved after four drug $t_{1/2}$ s. For drugs that follow nonlinear or saturation PK, the $t_{1/2}$ is often unhelpful as the $t_{1/2}$ continues to change as the drug's plasma concentration changes.

Clinical relevance: The functional capacity of renal function depends on gestational age as well as postnatal adaptations. Nephrogenesis begins as early as 9 weeks gestation and is nearly complete by ~ 36 weeks gestation. Postnatally, changes in renal and intrarenal blood flow lead to increases in glomerular filtration rate (GFR). GFR rates vary widely among different PCA. Term infants have decreasing vascular resistance with concomitant increases in cardiac output as the infant grows until adult GFR values are reached by ~ 1 year. Adult values of renal tubular secretion and reabsorption are invariably reached by ~ 6 – 9 months of age, despite being only 20–30 % of adult values at birth. For infants born preterm, there is tremendous variability in renal functional activities with relation to the infant's gestational and postnatal ages. The maturation of these activities is best correlated with the PCA

combined with any underlying disease state(s). These changes dramatically alter the CL of drugs or metabolites that undergo extensive renal elimination. A classic example would be the dosing regimens of aminoglycosides requiring every other day administration in preterm neonates but daily administration in term infants. Thus, the infant's age which correlates directly with renal functional capacity must be accounted for in designing drug dosing in premature and young infants with the same principles employed in older infants and children with varying degrees of renal dysfunction.

Conclusion

Pharmacokinetics describes the overall disposition of a drug in the body accounting for the dosage form and route of drug administration. The disposition characteristics are influenced by a number of important chemical as well as patient- and disease-specific variables. Age as it is reflective of major organ function and maturation is an important influence upon drug PK in the pediatric patient. Using knowledge of and by integrating a drug's pharmacokinetic profile with the drug's pharmacodynamic and pharmacogenomic profiles we can design more optimal drug dose regimens for patients, regimens with the greatest likelihood of prompt effectiveness with limited to no adverse effects.

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