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Review Article

Developmental Pharmacokinetics in Pediatric Populations

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Information on drug absorption and disposition in infants and children has increased considerably over the past 2 decades. However, the impact of specific age-related effects on pharmacokinetics, pharmacodynamics, and dose requirements remains poorly understood. Absorption can be affected by the differences in gastric pH and stomach emptying time that have been observed in the pediatric population. Low plasma protein concentrations and a higher body water composition can change drug distribution. Metabolic processes are often immature at birth, which can lead to a reduced clearance and a prolonged half-life for those drugs for which metabolism is a significant mechanism for elimination. Renal excretion is also reduced in neonates due to immature glomerular filtration, tubular secretion, and reabsorption. Limited data are available on the pharmacodynamic behavior of drugs in the pediatric population. Understanding these age effects provide a mechanistic way to identify initial doses for the pediatric population. The various factors that impact pharmacokinetics and pharmacodynamics mature towards adult values at different rates, thus requiring continual modification of drug dose regimens in neonates, infants, and children. In this paper, the age-related changes in drug absorption, distribution, metabolism, and elimination in infants and children are reviewed, and the age-related dosing regimens for this population are discussed.

INDEX TERMS: cytochrome P450, development, pediatrics, pharmacodynamics, pharmacokinetics

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INTRODUCTION

The pediatric population is composed of a number of very different subpopulations. The Food and Drug Administration (FDA) Guidance (1998) breaks down this population into the following groups: neonates (birth to 1 month), infants (1 month to 2 years), developing children (2-12 years), and adolescents (12-16 years).[1] These groups differ in terms of physical size, body composition, physiology, and biochemistry. Growth and development occur particularly rapidly during the first 2 years of life. Body weight typically doubles by 6 months of age and triples by the first year of life. Body surface area (BSA) doubles during the first year.[2] Proportions of body water, fat, and protein continuously change during infancy and childhood. Major organ systems mature in size as well as function during infancy and childhood. Additionally, the pathophysiology of some diseases and pharmacologic receptor functions change during infancy and childhood and differ from adults. For example, most cases of hypertension in children are secondary to renal disease, whereas most cases of hypertension in adults are primary or essential. This has profound effects on the design of antihypertensive drug trials with children.[3] Data available on receptor sensitivity during the neonatal period are limited. A published study found that neonates and young infants displayed an increased sensitivity to d-tubocurarine at the neuromuscular junction compared to adults.[4] All of the previously mentioned changes affect the pharmacokinetics (PK), pharmacodynamics (PD), and optimum doses of various drugs in the infant and developing child.

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Ethical concerns impeded early clinical studies in the pediatric population. Thus, clinical pharmacokinetic and pharmacodynamic studies in the pediatric population did not begin until the 1970s. The FDA Modernization Act (FDAMA; 1997) and the Pediatric Rule (1998) have been driving forces for the conduct of pediatric studies. These studies have demonstrated the existence

of many pharmacokinetic and some pharmacodynamic differences among the pediatric population.[5,6] Traditional studies demonstrated that pharmacokinetic parameters including half-life, apparent volume of distribution (Vd), and total plasma clearance vary among different age groups even when normalized by body weight.[7] These findings were supported by population analyses across broad age ranges, which found that age, in addition to body size, is an important determinant of pharmacokinetic parameters the pediatric population.[8–12] The age dependency is a function of body composition, organ functions, ontogeny of drug biotransformation pathways, disease progression, pharmacological receptor functions, and appears to be especially important during the first 2 years of life.[13] Understanding these age effects provide a mechanistic way to identify initial doses for the pediatric population.

The purpose of this review is to summarize quantitative and qualitative developmental changes in the neonate, infant, and developing child, and discuss how these affect PK, PD, and dose requirements for this population. Approaches that can use this information to determine age-specific dosing regimens are discussed.

ABSORPTION

In contrast to intravenous administration, drugs administrated extravascularly must undergo absorption in order to reach the systemic circulation. The process is characterized by 2 important parameters, the rate and the extent of drug absorption. The former affects the onset of action of the drug, and the latter essentially controls the effective dose.

In the gastrointestinal tract, several age-related anatomic and physiological changes have been found to influence drug absorption (Table 1). Gastric pH is neutral at birth but falls to pH 1-3 within 24 to 48 hours after birth. The pH then gradually returns to neutral again by day 8 and subsequently declines very slowly, reaching adult values only after 2 years of age.[14,15] This higher pH in neonates and young infants may have a protective effect on acid-labile drugs and may at least partially account for the higher bioavailability of beta-lactam antibiotics.[16] The bioavailability of orally administered weak acids, such as phenytoin, acetaminophen, and phenobarbital, may be reduced in infants and young children due to increased ionization under achlorhydric conditions.[17,18]

Gastric emptying and intestinal motility are important determinants for the rate of drug absorption in the small intestine, the major site of drug absorption. Gastric emptying time during the neonatal period is prolonged relative to that of the adult. This may partially account for delayed absorption for orally administered phenobarbital, digoxin, and sulfonamides.[19] Other factors such as reduced intestinal absorption surface area and shorter gut transit time may also be responsible for the delayed absorption observed in neonates.

The age-dependent changes in biliary function and activities of pancreatic enzymes can compromise the body's ability to solubilize and subsequently absorb some lipophilic drugs. For example, this is believed to reduce the absorption of prodrug esters such as erythromycin that require solubilization or intraluminal hydrolysis.[20]

Developmental changes in the activity of intestinal drug-metabolizing enzymes and transporters could potentially alter the bioavailability of drugs. At this time, these developmental changes have not been completely characterized, as few clinical studies have addressed this issue. The marked decrease in midazolam's oral clearance (CL/F) in preterm infants is believed to be the result of an immature intestinal cytochrome P450 3A4 (CYP3A4) enzyme system, which results in decreased presystemic intestinal metabolism and an increased bioavailability (F).[21] One study observed that intestinal biopsy specimens from young children (1-3 years old) had a 77% higher busulfan glutathione conjugation rate compared to older children (9-17 years old). In contrast to the effect on midazolam, this may lead to an enhanced first-pass intestinal metabolism and a reduced absorption fraction (F) in young children.[22] Gabapentin absorption is dependent on the L-amino acid transporter system in intestinal membrane. Oral clearance (CL/F) of gabapentin is 33% higher in younger children (<5 years) than in older children (5-12 years) or adults.[23] An immature L-amino transporter activity, which results in a lower bioavailability, is believed to be responsible for this effect.[24] P-glycoprotein (P-gp) is an efflux transporter that also plays a part in intestinal absorption. An analysis of P-gp expression in human intestinal tissue found relatively low levels in the neonatal group. The expression

Table 1. Developmental Factors Affecting Drug Pharmacokinetics in Neonates and Infants

Physiologic Factors	Difference Compared to Adults	PK Implications	Example Drug
Oral absorption			
Gastric pH	↑	↓ Bioavailability (weak acids)	Phenytoin, phenobarbital, ganciclovir
		↑ Bioavailability (weak bases)	Penicillin G, ampicillin, nafcillin
Gastric emptying time	↑	Delayed absorption	Phenobarbital, digoxin and sulfonamides
Intestinal CYP3A4	↓	↑ Bioavailability	Midazolam
Intestinal GST	↑	↓ Bioavailability	Busulfan
Intestinal drug transporters	↓	↓ Bioavailability	Gabapentin
Percutaneous absorption			
Hydration of epidermis	↑	↑ Bioavailability	Steroids
Intramuscular absorption			
Skeletal muscle blood flow	Variable	Unknown	n.a.
Distribution			
Body water : fat ratio	↑	↑ Volume of distribution (hydrophilic drugs)	Gentamicin, linezolid, phenobarbital, propofol
		↓ Volume of d istribution (lipophilic drugs)	Diazepam, lorazepam
Protein binding	↓	↑ Free fraction of drugs	Sulfonamides
Hepatic metabolism			
Phase I enzyme activity	↓	↓ Hepatic clearance	Theophylline, caffeine, midazolam
Phase II UGT enzyme activity	↓	↓ Hepatic clearance	Morphine
Renal excretion			
Glomerular filtration rate	↓	↓ Renal clearance	Aminoglycosides
Renal tubular absorption and secretion	↓	↓ Renal clearance	Digoxin

↑, changes increased in values; ↓, changes decreased in values; GST, glutathione S-transferase; n.a., not available; PK, pharmacokinetic; UGT, UDP glucuronosyltransferase.

increased with age to reach maximum levels in young adults (15-38 years of age). The study also found decreased levels (half the maximal adult levels) in older individuals (67-85 years).[25] However, the clinical importance of developmental changes of P-gp has not been studied.

Developmental changes also can alter the absorption of drugs by other extravascular routes. Percutaneous absorption of drugs through skin may be high in newborns and infants owing to several factors including: better hydration of the epidermis, greater perfusion of the subcutaneous layer, and the larger ratio of total BSA to body mass compared to adults. Thus, topically applied steroids in newborns and infants can result in unanticipated systemic absorption and has resulted in toxic effects in some instances.[26] The absorption of intramuscularly administered drugs may be delayed in neonates as a result of reduced blood flow to skeletal muscles, although in clinical practice absorption from this route has been found to be unpredictable.[27]

DISTRIBUTION

Independent of the route of administration, once the drug enters the blood stream, it distributes throughout the vascular system and to other areas of the body. A drug's distribution characteristics are summarized by the parameter, apparent Vd, which is the ratio of the amount of drug in the body to the corresponding plasma concentration. Clinically, a drug's Vd is important because it controls the value of a loading dose, and along with a drug's clearance, it determines a drug's half-life.[28] A large Vd (the plasma concentration is relatively small for a given amount of drug in the body) indicates extensive drug distribution to the tissues. A small Vd (the plasma concentration is relatively high for a given amount of drug in the body) suggests less extensive distribution from the plasma, and may indicate that a drug is highly bound to plasma proteins, a process that inhibits the distribution of drug from the plasma. A drug's Vd is determined by tissue binding, plasma protein binding, and the physiochemical properties of the drug, such as lipid and water solubility, which impact the body compartments that a drug can access.

The dramatic maturation changes in the relative amount of body water and fat have been well characterized by Friis-Hansen.[29] Total body water, expressed as percentage of body weight, decreases with age, from approximately 80% in newborns to 60% by 1 year of age. Conversely, body fat increases with age, from 1% to 2% in a preterm neonate to 10% to 15% in a term neonate and 20 to 25% in a 1-year-old. The impact of these differences on the Vd depends on the physiochemical characteristics of the drug. Highly water-soluble compounds, such as gentamicin, have larger volumes of distribution in neonates compared to adults. For example gentamicin's Vd is around 0.5 L/kg in neonates, compared to 0.25 to 0.3 L/kg in adults. As a result, a larger milligram per kilogram loading dose may be needed to achieve desired therapeutic concentrations in neonates.[30] Lipophilic drugs, such as diazepam, tend to have smaller volumes of distribution in infants than in older children and adults.[18]

Plasma protein binding of drugs tends to be reduced in neonates and infants.[31] A decreased plasma protein binding is due not only to the reduction of the total amount of plasma proteins, but also to the diminished binding affinity and the high concentrations of endogenous competing substrates. In theory reduced protein binding may result in an increased distribution of drugs from the plasma to the rest of the body, which may be associated with an increased Vd. For example, a decrease in the plasma protein binding of phenobarbital and an increased Vd was observed in neonates.[18] Changes in protein binding can also complicate the interpretation of measured drug plasma concentrations in neonates and young infants. Although the unbound concentration is the pharmacologically active critical component, typically the total plasma concentration of a drug is measured. As a result interpretation of the total plasma concentration can be difficult for drugs such as phenytoin, which are both highly bound and have a narrow therapeutic range.[32] Finally, it is worthwhile to mention that highly bound acid drugs such as sulfonamides can compete for bilirubin-binding sites on albumin and displace bilirubin when plasma albumin level is low. This leads to increased blood levels of unconjugated bilirubin and increased risk of kernicterus in the fetus or neonate.[33] Ceftriaxone is another example, although it has not been formally implicated in the pathogenesis in kernicterus. Both *in vitro* and *in vivo* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin at the therapeutic levels, leading to a possible risk of bilirubin encephalopathy in neonates.[34,35]

HEPATIC METABOLISM

Drug metabolism can be divided into Phase I and Phase II metabolism. Phase I metabolism involves small structural alterations to the drug molecule. The primary purpose is to decrease lipophilicity and enhance renal excretion of the molecule. Phase I metabolism also often results in the introduction or unmasking of a functional group. Phase II metabolism involves the conjugation of a functional group on the molecule (parent drug or Phase I metabolites) with hydrophilic endogenous substrates (e.g. glucuronidation, sulfation, acetylation). Although the kidney, intestine, lung, and skin are also capable of biotransformation, the liver is quantitatively the most important organ for drug metabolism.[36] Studies over the last decade on the age-dependent development of the drug metabolizing enzymes have found that each different enzyme system has its own

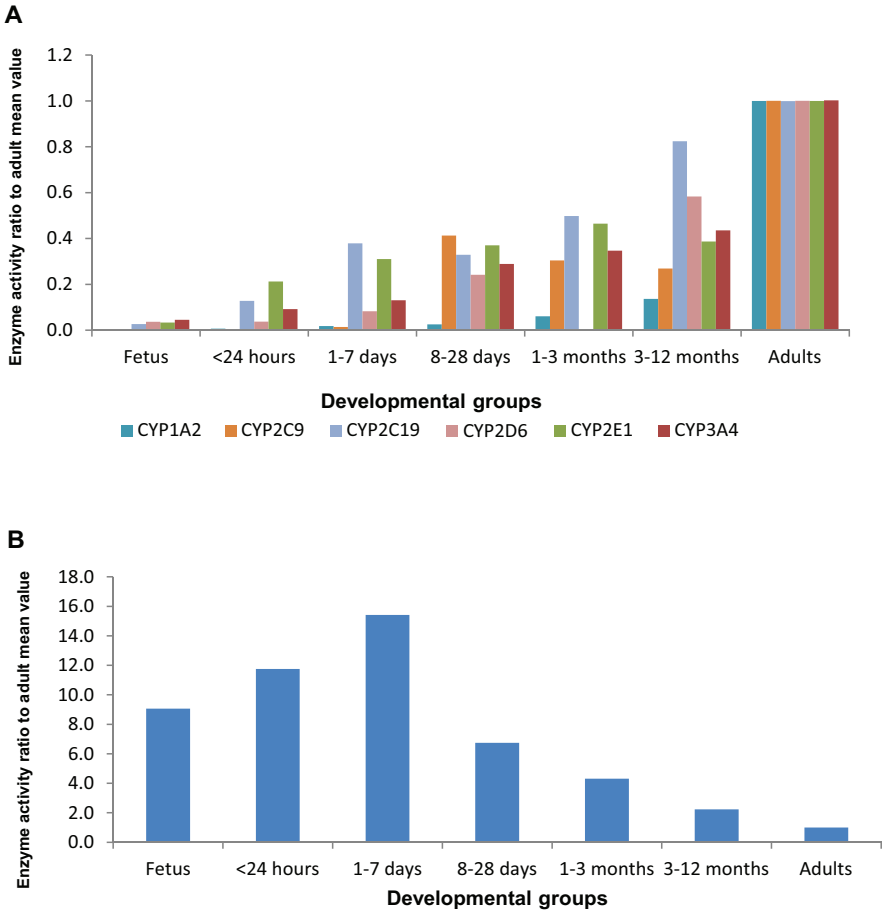

Figure 1. Developmental profiles of major hepatic cytochrome P450s (A) and CYP3A7 (B). The postnatal evolution of P450 isoforms was explored in a liver bank comprising samples from fetus, neonates, infants, and adults. Isoform enzyme activity was characterized by the following measurements: methoxyresorufin demethylation (MEROD) for CYP1A2, tolbutamide hydroxylation and immunoprotein for CYP2C9, diazepam N-demethylation and immunoprotein for 2C19, dextromethorphan O-demethylation and immunoprotein for CYP2D6, chlorzoxazone hydroxylation for CYP2E1, testosterone 6beta-hydroxylation for CYP3A4, DHEA 16alpha-hydroxylation for CYP3A7. N.D., not detectable. (Data are adapted from Ref. [40–47]).

unique pattern of development.

The majority of Phase I drug reactions are mediated by the cytochrome P450 (CYP) enzymes, a super family of multiple hemeproteins. The specific families or enzymes that are of greatest importance in the metabolism of drugs are CYP3A4/7, 2C9, 2C19, 2D6, 1A2, 2E1, and 2B6. [37] Other than CYPs, the flavin-containing monooxygenase (FMO) enzymes are also important for the oxidative metabolism of a wide variety of therapeutic drug, including nicotine, clozapine, sulindac sulfide, and ranitidine.[38,39] In comparison to the CYP family, less is known about the role played by this family of enzymes, but it appears to be less crucial to the efficacy and/or toxicity of drugs than the CYP family.[38] Figure 1 lists the ontogenesis for primary CYP enzymes.[40–47] Briefly, CYP3A7 is the primary isoenzyme expressed during the prenatal period. It declines rapidly after birth and is barely measurable in adults. The expression of CYP2E1 and CYP2D6 begin to rise at the time of birth. The expression of CYP3A4, 2C9, and 2C19 occurs during the first weeks of life. The expression of CYP1A2, the last enzyme to develop, is present by 1 to 3 months of life. The activity of these enzymes increases over time but not in a linear manner with age. By 1 to 2 years of age, all the isoenzyme activities are similar to those of adults.[48]

Clinically, the elimination of a drug is quantified using the parameter clearance, which is a measure of the body's ability to remove drug from the plasma. The developmental changes observed in the enzymatic systems have been supported by the age-related changes in the clearance in several drugs, as well as changes in the metabolic ratios of probe substrates to their metabolites *in vivo*. For example, the rise of the expression of CYP2D6 was associated with the rise in dextromethorphan *O*-demethylation, which was assessed using the urinary ratio of dextromethorphan to dextorphan.[49,50] Similarly, the delayed ontogenesis of CYP1A2 protein was consistent with the *in vivo* data where CYP1A2 mediated N3 and N7

Table 2. *In Vitro* Ontogeny of Human Hepatic Phase II Enzymes (Adapted From Ref. [55,56])

Isoenzyme	Fetus	Neonate (0-1 month)	1 month to 1 year	Adult	Ontogeny Facts
UDP glucuronosyltransferase (UGT)					
UGT1A1	–	+	+	+	Adult levels attained by 3-6 mo
UGT1A6	–	+	+	+	Maturation complete until puberty
UGT2B7	+	+	+	+	Adult levels attained by 2-3 mo
Sulfotransferases (SULT)					
SULT1A3	++	+	+	–	Substantial decrease in perinatal period
Glutathione S-transferase (GST)					
GSTA1/2	+	++	++	++	Increase dramatically to adult levels shortly after birth
GSTM	+	++	++	++	Increase dramatically to adult levels shortly after birth
GSTP	++	+	+	–	Substantial decrease in perinatal period
Epoxide hydrolase (EPH)					
EPHX1	+	+	+	+	No correlation between EPHX1/EPHX2 activity and gestational or postnatal age
EPHX2	+	+	+	+	
N-acetyltransferase (NAT)					
NAT2	+	+	+	+	Enzyme polymorphisms affect isoniazid metabolism more importantly than ontogeny

–, activity or protein not detectable; +, activity or protein detectable; ++, high level of activity or protein expression.

demethylation products of caffeine represented 6% to 8% of the total biotransformation in neonates and increased to about 28% in infants aged 2 to 10 months.[51] In addition, the developmental sequence of the CYP isoenzymes can also be demonstrated by noting changes in the relative amount of metabolites produced from the different pathways. For example, CYP2D6-mediated *O*-demethylation of diazepam has been reported to develop sooner than the CYP3A4-mediated *N*-demethylation by, which is in line with the *in vitro* observations on the ontogeny of CYP2D6 and CYP3A4 CYP3A4.[52]

The ontogeny of hepatic FMO exhibits a similar developmental pattern as the CYP3A family. The isoenzyme FMO1 has a similar developmental pattern to CYP3A7. Its expression is at the highest at 8 to 15 weeks of gestation. It subsequently declines during the fetal development and completely absent within 72 postnatal hours. FMO3 is more analogous to CYP3A4. It has negligible expression in the neonatal period and becomes detectable only by 1 to 2 years of age. The delayed onset of FMO3 expression results a null FMO phenotype in the neonate.[53] Since FMO3 is selective in the N-oxygenation of trimethylamine, this observation may explain the transient trimethylaminuria reported in a 2-month-old infant.[54]

In contrast to the CYP enzymes, isoform-specific quantitative data for the development of Phase II enzymes are very limited. The timelines for the detection of Phase II enzymes in the fetus, neonate, and infant are shown in Table 2.[55,56] The development of the uridine 5-diphosphoglucuronic acid glucuronyl transferases (UGTs) is of greatest interest since this family of enzymes is responsible for the metabolism of almost 15% of drugs eliminated by metabolism.[57] Several drugs commonly used in the pediatric population are substrates for the UGTs. These substrates include acetaminophen (UGT1A6 and, to a lesser extent, 1A9), morphine (UGT2B7), and zidovudine (UGT1A6). Among the UGT isoforms, UGT 1A1 and 2B7 develop quickly, and UGT1A6 and 1A9 develop more slowly.[58] The expression of UGT1A1, the major enzyme responsible for bili-

rubin glucuronidation, is triggered at birth and the activity reaches adult levels by 3 to 6 months postnatal age (PNA). UGT2B7 is present in fetus, and increases at birth. Adult levels are attained by 2 to 6 months of age. UGT1A6 is undetectable in the fetus. Its expression increases slightly in neonates, but does not reach adult levels until 10 years of age.

These data are consistent with the pharmacokinetic data of UGT substrates assessed *in vivo*. For example, the metabolic clearance of morphine, which is primarily metabolized by UGT2B7 to morphine 6-glucuronide and morphine-3-glucoroide, is low in neonates and reaches adult levels between 2 and 6 months.[59] Morphine-6-glucuronide, which contributes to the analgesic effect of morphine, is primarily eliminated renally. Thus, it is possible that the clearance of this metabolite will be reduced in neonates due to immature renal function. Although lower morphine doses may be effective in neonates, it is difficult to translate the lower clearance of morphine into specific dosing recommendations. As an additional complication, it is possible that the opioid receptors may not be fully developed in this population. [59] Similarly, acetaminophen glucuronidation is lower in newborns and young children compared to adolescents and adults.[60] The "gray-baby" syndrome, which is associated with the administration of chloramphenicol (substrate of UGT2B7) in neonates and consists of emesis, abdominal distension, abnormal respiration, cyanosis, cardiovascular collapse, and death, is believed to be the result of the reduced glucuronidation and clearance of chloramphenicol in this population, which leads to very high plasma concentrations of the drug.[61]

Sulfation, another Phase II conjugation, appears to be well developed at birth. The variation in the development and function of the two Phase II reactions is reflected by acetaminophen metabolism. In early infancy, acetaminophen is primarily converted into the sulfate conjugates, but with increasing age, glucuronidation becomes the predominant form of metabolism.[13] Studies on the development of acetylation have found reduced activity in the first month of life. Interestingly, the effect of age appears to be less dominant than that of polymorphism of N-acetyltransferase.[56] Esterase activity is also reduced in newborn and this may partly account for the prolonged effects of local anesthetics.[62]

In conclusion, both Phase I and II metabolic processes are immature at birth. These deficiencies may result in the increased risk for drug toxicity in infants and young children. The ontogeny of drug-metabolizing enzymes will clearly have to translate into age-related dosage adjustment for some therapeutic agents in pediatric patients. A typical example is the clinical use of theophylline in neonates and infants with apnea or chronic lung disease. Since the hepatic metabolism of theophylline is decreased in neonates due to the protracted expression of CYP1A2, a greater portion of theophylline is excreted in the urine compared to older children and adults.[63] The theophylline clearance is about two- to three fold less in neonates than in adults due to the compensate renal elimination pathway.[64] A small portion of theophylline is also methylated to form caffeine, an active metabolite. Since neonates have decreased demethylation, theophylline-derived caffeine cannot be easily metabolized and therefore accumulates. As a result, the maintenance dose of theophylline is substantially reduced in neonates .[65] Other drugs that undergo extensive metabolism, including diazepam, phenytoin, and chloramphenicol, are often observed to have prolonged half-lives in neonates and young infants. As a result, a decreased daily maintenance dose or an increased dosing interval may be needed in order to avoid drug accumulation.

The transporter-mediated uptake of drugs into the hepatocytes and efflux into the bile is often referred to as the Phase III hepatic pathway. Important uptake transporters include the organic anion transporting polypeptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs). Clinically important efflux transporters at canalicular membrane include P-gp, breast cancer resistant protein (BCRP), bile salt export protein (BSEP), and multidrug resistance protein 1 (MRP1). At this time, there are few data in humans on the ontogeny expression of liver transporters.[66] There are some data on the developmental pattern of P-gp in humans. P-gp mRNA and protein were detected in human liver as early as 11 to 14 weeks of gestation.[67] A single study suggested that hepatic P-gp expression increases during the first few months of life and reaches adult levels by 2 years of age.[68] The clinical significance of developmental changes in transporter functions has not been systematically studied in humans.

In addition to size and ontogeny of enzyme and transporters, other factors such as genetic polymorphism, prenatal or postnatal exposure to modifiers of the activity of the drug metabolizing enzymes and transporter systems might also have an independent impact on the phenotypic metabolic activity observed.[69] Tramadol (M) hydrochloride is catalyzed to *O*-demethyl tramadol (M1) in liver primarily by CYP2D6. The urinary ratio of tramadol to *O*-demethyl tramadol (log M/M1) is widely used as a marker of CYP2D6 activity in adults. Allegaert et al[70] recently found a significant decrease in urine log and plasma log M/M1 with increasing CYP2D6 genotype activity score. The activity score is a quantitative classification of CYP2D6 genotypes with values indicating the relative activity of each *CYP2D6* allele to the fully functional reference *CYP2D6*1* allele. The results indicated CYP2D6 polymorphisms had a significant impact on *O*-demethylation of tramadol in neonates and young infants, and contributed to the interindividual variability.

RENAL ELIMINATION

Excretion of drugs by the kidneys is dependent on 3 processes: glomerular filtration, tubular excretion, and tubular reabsorption. To summarize, in the first step of excretion the free drug in the plasma (the protein bound component is too large) is filtered across the glomerular membrane into the renal tubule. The tubule transporter systems in the renal tubular membrane may augment drug excretion by promoting the passage of drugs from the plasma into the tubule. In the distal part of the renal tubule, lipophilic drugs may be reabsorbed by passive diffusion from the tubule back into the blood. The renal clearance (CL_r) of drugs is the sum of 3 processes (Equation 1). Each of these processes exhibit independent rate and pattern of development.

$$CL_r = CL_{\text{glomerular filtration}} + CL_{\text{tubular secretion}} - \text{tubular reabsorption} \quad \text{(Equation 1)}$$

The glomerular filtration rate (GFR) is often used to assess renal function, and Figure 2 shows the how it changes over time in the pediatric population.[71,72] In the full-term newborn, GFR is around 10 to 20 mL/min/m^2 at birth. This increases rapidly to 20 to 30 mL/min/m^2 during the first weeks of life and typically reaches adult values (70 mL/min/m^2) by 3 to 5 months. Furthermore, the increase in GFR is highly dependent on PNA, the chronological age since birth. Hayton et al[65] described the maturation of GFR with PNA using a nonlinear function. A more practical equation (Equation 2) for estimating age-specific renal glomerular filtration rate (CL_{GFR}) was proposed by Schwartz and coworkers.[73]

$$CL_{GFR} = CL_{r,\,Cr} = K*Ht/SCr \quad \text{(Equation 2)}$$

Where, $CL_{r,\,Cr}$ is creatinine clearance (mL/min/1.73 m^2); Ht is height (cm) and SCr is serum creatinine concentration (mg/dL); K is a constant of proportionality, which is different for children in different age bands. K is 0.33, 0.45, 0.55, 0.55, and 0.7 for preterm infants, full term infants (0-12 months), children (1-12 years), female adolescents (13-21 years), and male adolescents (13-21 years), respectively.

For drugs that are mainly excreted by glomerular filtration (e.g. aminoglycosides), initial dose adjustments can be made by either increasing the dosing interval or decreasing the dose.

In contrast to glomerular filtration, tubular secretary and reabsorptive capacity appear to mature at much slower rates. Tubular secretion, assessed by the renal clearance of p-aminohippurate (a substrate of renal OAT), is reduced at birth to approximately 20% to 30% of adult capacity but matures by 15 months of age.[72] The development of other renal uptake transporters such as OCT and OATP is unknown.

Tubular reabsorption is the last renal function to mature and does not reach adult levels until 2 years of age. This delay in the development of tubular functions may have variable effect on some drugs' clearance for which tubular secretion or reabsorption is important in adults. For example, digoxin, which undergoes some active secretion, has a reported average renal clearance of 1.92, 3.94, and 5.20 L/hr/1.73 m^2 in full term infants less than 1 week of age, 3-month-old infants, and children of 1.5 years of old, respectively.[74] At this time, there is little information in the literature about the ontogeny of renal drug transport systems and their impact on renal elimination in infants and children. Generally, for drugs principally eliminated by kidney, immature renal clearance processes result in the inefficient elimination of drugs and prolongation of their half-lives.[75]

PHARMACODYNAMICS

Unlike the rapidly accumulating knowledge

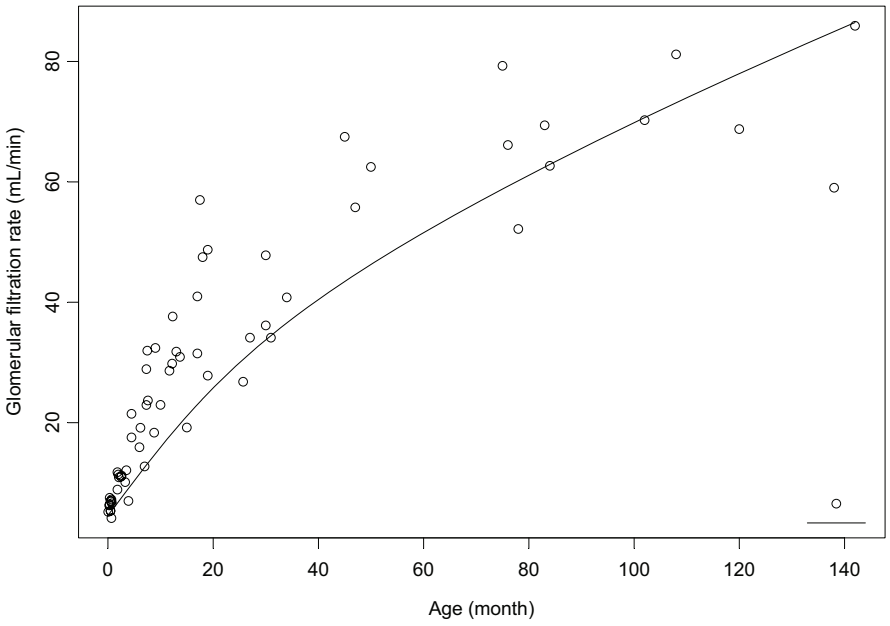

Figure 2. Developmental changes of renal glomerular filtration rate (GFR) measured by mannitol clearance. (Data adapted from Ref. [71,72]).

of the pharmacokinetic changes associated with development, little is known about receptor development, and how maturation affects the drug-receptor interaction and response. Most often, the apparent developmental differences in drug efficacy or the incidence of adverse effects have been linked with pharmacokinetic differences. For example, the higher acid inhibition effect of lansoprazole in infants appears to be associated with reduced drug elimination.[76,77] The increased hepatoxicity of valproic acid in young children was related to increased formation of hepatoxic metabolites.[32] The existence of true age-dependent differences in receptor sensitivity appears to be supported by data on a few drugs. For example, Takahashi et al[78] reported that the mean plasma concentrations of unbound S-warfarin in the prepubertal (age 1-11 years), pubertal (age 12-17 years), and adult patients were comparable, but the prepubertal patients showed significantly greater international normalized ratio than the adult patients. The data suggested that prepubertal patients are more sensitive to the effects of warfarin than adult patients.

Marshall and Kearns[79] reported the *in vitro* developmental PD for cyclosporine. Two independent and specific pharmacodynamic markers of cyclosporine-mediated immunosuppression, peripheral blood monocyte (PBM) proliferation and interleukin-2 expression, were studied. The mean IC_{50} of cyclosporine on the inhibition of PBM proliferation was twofold lower among infant subjects than older subjects. The mean IC_{90} of cyclosporine that corresponded to 90% inhibition of interleukin-2 expression in PBM cultures was sevenfold lower in infants than in older age groups. The study provided relevant information on developmental changes in receptor binding characteristics *in vitro*, but this may not be reflective of the response *in vivo*, owing to the complexity of the *in vivo* immune system. Reliable *in vivo* surrogate markers for cyclosporine must be developed and combined with individual PK in order to fully understand drug response in the pediatric population and to identify optimum therapeutic plasma concentrations in this group.

APPROACH TO AGE-RELATED DOSING REGIMENS

Simple dosage formulas (normalized by body weight or BSA) and allometric scaling may be clinically applicable in children older than 2 years of age.[80] In neonates and young infants, where age-related developmental changes in drug disposition are underway, age-specific dosing regimens are needed based on observed age-related changes in bioavailability, Vd, and overall clearance. Those examples have been demonstrated in a widely used pediatric dosage handbook. However, the rationales behind those age-related dosing regimens have not been well elaborated. This section will comment on the clinical study design, data collection, and analysis approaches, which are used to support those conclusions.

In clinical practice, when pharmacokinetic

data in children are available standard pharmacokinetic equations can be used to estimate doses based on drug clearance and target exposure. The traditional approach to generating pharmacokinetic data is based on a relatively small number of subjects from whom multiple samples are taken. Individual pharmacokinetic parameters are determined and then pooled. However, it is usually not practicable to recruit sufficient numbers of patients to assess the true interindividual variability. The results generated from these descriptive PK or PK/PD studies usually have little impact on dosing guidelines for a specific therapeutic agent and generally have not been found to provide sufficient guidance for clinicians.[81] For this reason, the population pharmacokinetic data analysis from a large number of individuals in well-designed population PK or PK/PD studies is recommended.[82]

The population approach is ideal for studying the pediatric population since a large heterogeneous population can be studied by taking only a few samples per patient at flexible sampling times.[83] Pharmacokinetic parameters and associated variability are calculated for all patients simultaneously. Furthermore, covariate analysis can be performed to identify demographic factors that explain the variability, such as body weight and age. The population pharmacokinetic approach is commonly used to obtain age-associated pharmacokinetic parameters. The selected population model usually includes the relationship between patient characteristics such as body weight and age and one or more of the pharmacokinetic parameters. For example, body weight may be added as an important determinant of the parameter clearance (CL), which is used to assess elimination. Weight is often included using allometric scaling according to the formula (Equation 3):

$$CLi = CL_{TV} \times \left(\frac{BW_i}{medianBW}\right)^{EXP} \quad \text{(Equation 3)}$$

where CL_i represents the clearance in the patient, CL_{TV} the typical value for clearance in the specific population, BW_i the individual body weight, median BW is the median body weight of the population, and EXP the exponent. The exponent can be either fixed or estimated during the analysis.[12] For example, in the study of zidovudine PK in HIV-infected infants and children, the above model was used for clearance and Vd with the EXP fixed at 0.75 for clearance and 1 for Vd.[9] The effect of other patient characteristics such as age and liver enzymes data was also evaluated.

Moreover, if clinical response data are available, it may be possible to create integrated pharmacokinetic-pharmacodynamic model, which would allow better optimization of pediatric dosing. For example, a population PK-PD model developed for the postoperative sedative effect of midazolam was used to optimize the dose of midazolam in nonventilated infants aged 3 months to 2 years old.[84]

In the absence of established dosing guidelines or complete pharmacokinetic data in children, methods to approximate the initial dose for an infant are proposed as "bottom-up" approaches. To date there are several "bottom-up" approaches for pediatric dose selection. Bartelink et al[85] proposed dosing guidelines on the basis of the route of administration, the pharmacokinetic characteristics of the drug, and the age of the child. In general, the loading dose of a drug is based on the Vd, whereas the maintenance dose is determined by the clearance. With respect to Vd, Bartelink et al[85] pointed out that potential changes are drug dependent and that drugs with a large Vd in adults are best normalized to bodyweight in young children younger than 2 years. In contrast, drugs with a small Vd in adults are best normalized to BSA. With respect to clearance, Bartelink et al[85] pointed out that after the maturation process is complete clearance is mainly determined by growth and the blood supply to the kidneys and liver. They recommend that drugs primarily metabolized by the liver should be administered with extreme care until the age of 2 months and that modification of the dose should be based on response and on therapeutic drug monitoring. They recommend the use of a general guideline based on body weight as the basis of dosing from 2 to 6 months and BSA after 6 months of age except for drugs that are primarily metabolized by CYP2D6 and UGTs. For drugs that are significantly excreted by the kidney, measures of renal function such as creatinine clearance should be used for dose justification in children < 2 years of age. Once the kidneys are fully matured, BSA is recommended as the basis for drug doses.

Physiologically based pharmacokinetic (PBPK) modeling offers a promising alternative approach to assist with first-time dosing in children.[86] A number of pediatric PBPK models have been

developed to predict PK in children, one of which was presented by Edginton et al[87] who used PK-Sim to apply the model to acetaminophen, alfentanil, morphine, theophylline, and levofloxacin. In general, an existing adult PBPK model is extended to reflect age-related physiological changes in children from birth to age 18. The age-modified model is then used together with a previously developed age-specific clearance model that incorporates information on the development of renal and/or hepatic function to predict pediatric plasma concentrations.[88–90] PBPK models combine the developmental physiological processes of the child with adult PK data. Thus they require the drug-specific information (PK parameters in the adult) and system-specific information on the ontogeny of anatomical, physiological, and biochemical variables from birth to age 18. Often physiological data from multiple literature sources is required, and in many cases accurate data from humans of all ages is not as yet available. Moreover, there is no consensus on the value of the physiological parameters in the pediatric population. Usually age-related functions are applied to existing data from various sources and the missing data for some age ranges are interpolated or extrapolated from these functions. Many of these equations are often validated internally by each author or modeling group. For example, 4 different ontogeny functions on hepatic cytochrome P450 3A4 enzyme have been in published PBPK papers.[87,88,91,92] Additionally, data on tissue composition (proportion of lipids, protein, and water) are limited in the pediatric population. This information is critical for the prediction of the tissue blood partition coefficient.[93] In the absence of this information, the coefficient in children may be assumed to be equal to that in adults.

CONCLUSION

An advance in developmental pharmacology during the past decades has improved our understanding of the influence of growth and maturation on the absorption, disposition, and actions of drugs. Pediatric clinical studies, encouraged by regulatory agencies, have facilitated improvements in drug therapy for this population.[94] Based on the current knowledge, it should be obvious that the dosing regimen for adults cannot be simply or linearly extrapolated to children, particularly in neonates and infants. The application of population pharmacokinetic-pharmacodynamic methods to this population has been widely advocated and is described in the Guidance Documents of FDA and European Medicines Agency (EMA).[1,95] The use of PBPK models has been recommended to help in the first time dosing in children as well as in the design of pediatric clinical studies.[91,96] However, there is a strong need for more research on developmental pharmacology such as the ontogeny of drug metabolizing enzymes, transporters, receptor system, and disease progress. As the gaps in our knowledge are gradually filled, the development of therapeutic pediatric dosing regimen will be enhanced, and drugs will eventually be provided to children with greater precision and safety.

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Abbreviations BSA, body surface area; CYP, cytochrome P450; CL, clearance; EMA, European Medicines Agency; FDA, Food and Drug Administration; FDAMA, Food and Drug Administration Modernization Act; FMO, flavin-containing monooxygenase; GFR, glomerular filtration rate; NAT, N-acetyltransferase; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PBM, peripheral blood monocyte; PBPK, physiologically based pharmacokinetics; PD, pharmacodynamics; P-gp, P-glycoprotein; PK, pharmacokinetics; PNA, postnatal age; UGT, uridine 5-diphosphoglucuronic acid glucuronyl transferases; Vd, volume of distribution

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