

# Developmental Pharmacokinetics

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**Abstract** The advances in developmental pharmacokinetics during the past decade reside with an enhanced understanding of the influence of growth and development on drug absorption, distribution, metabolism, and excretion (ADME). However, significant information gaps remain with respect to our ability to characterize the impact of ontogeny on the activity of important drug metabolizing enzymes, transporters, and other targets. The ultimate goal of rational drug therapy in neonates, infants, children, and adolescents resides with the ability to individualize it based on known developmental differences in drug disposition and action. The clinical challenge in achieving this is accounting for the variability in all of the contravening factors that influence pharmacokinetics and pharmacodynamics (e.g., genetic variants of ADME genes, different disease phenotypes, disease progression, and concomitant treatment). Application of novel technologies in the fields of pharmacometrics (e.g., in silico simulation of exposure–response relationships; disease progression modeling), pharmacogenomics and biomarker development (e.g., creation of pharmacodynamic surrogate endpoints suitable for pediatric use) are increasingly making integrated approaches for developmentally appropriate dose regimen selection possible.

**Keywords** Developmental pharmacology • Pediatric pharmacology • Neonatal pharmacology • Neonates • Pharmacokinetics • Pharmacogenomics • Pharmacodynamics • Drug metabolizing enzymes

## 1 Introduction

Human growth and development consists of a continuum of biologic events that includes somatic growth, neurobehavioral maturation, and eventual reproduction. The impact of these developmental changes in drug disposition is largely related to changes in body composition (e.g., body water content, plasma protein concentrations) and function of organs important in metabolism (e.g., the liver) and excretion (e.g., the kidney). During the first decade of life, these changes are dynamic and can be nonlinear and discordant making standardized dosing inadequate for effective drug dosing across the span of childhood. Consequently, “standard dosing” of many drugs during rapid phases of growth/development where both drug disposition and response may be altered is generally inadequate for the purpose of optimizing drug therapy. This goal can only be achieved through fundamental and integrative understanding of how ontogeny influences pharmacokinetics and pharmacodynamics.

Developmental pharmacokinetics must take into account normal growth and developmental pathways (Bartelink et al. 2006; Johnson et al. 2006). A better understanding of the various physiologic variables regulating and determining the fate of drugs in the body and their pharmacologic effects has dramatically improved both the safety and the efficacy of drug therapy for neonates, infants, children, and

adolescents (Kearns et al. 2003a; Van Den Anker and Rakhmanina 2006). The impact of development on the pharmacokinetics of a given drug is dependent, to a great degree, upon age-related changes in the body composition and the acquisition of function of organs and organ systems that are important in determining drug metabolism as well as drug transport and excretion (Edginton et al. 2006; Anderson and Holford 2008). Although it is often convenient to classify pediatric patients on the basis of postnatal age for the study and provision of drug therapy (e.g., newborn infants aged 1 month or less, infants between 1 and 24 months of age, children between 2 and 12 years of age, and adolescents between 12 and 16–18 years of age), it is important to recognize that changes in physiology that characterize development may not correspond to these age-defined breakpoints and are also not linearly related to age. In fact, the most dramatic changes in drug disposition occur during the first 12–18 months of life, when the acquisition of organ function is most dynamic (Kearns et al. 2003a; Van Den Anker and Rakhmanina 2006). Additionally, independent from developmental aspects, it is important to mention that the pharmacokinetics of a given drug may be altered in pediatric patients also due to intrinsic (e.g., genotype, inherited diseases) and/or extrinsic (e.g., acquired diseases, diet, co-medication) factors that may occur during the first months and years of life (Blake et al. 2006; Van Den Anker et al. 1994; Allegaert et al. 2008; Leeder 2003; Krekels et al. 2007; Leeder et al. 2010). In principle, however, these factors are also important for nonpediatric populations such as adult geriatric patients. To study pediatric pharmacokinetics it is very useful to examine the impact of development on those physiologic variables that govern drug absorption, distribution, metabolism, and excretion (Bartelink et al. 2006; Johnson et al. 2006; Edginton et al. 2006) which is summarized by the commonly used term ADME.

## 2 Drug Absorption

For therapeutic agents administered by extravascular routes, the process of absorption is reflected by the ability of a drug to overcome chemical, physical, mechanical, and biological barriers. Developmental differences in the physiologic composition and function of these barriers can alter the rate and/or extent of drug absorption (Kearns et al. 2003a; Van Den Anker and Rakhmanina 2006). While factors influencing drug absorption are multifactorial in nature, developmental changes in the absorptive surfaces (e.g., gastrointestinal tract, skin) can be determinants of bioavailability (Kearns et al. 2003a; Van Den Anker and Rakhmanina 2006). The peroral route is the principal means for drug administration to infants, children, and adolescents but the skin represents an often overlooked, but important organ for systemic drug absorption as well. Therefore, the drug absorption part of this chapter will focus on drug absorption from the gastrointestinal tract and through the skin.

## 2.1 *The Gastrointestinal Tract*

The most important factors that influence drug absorption from the gastrointestinal tract are related to the physiology of the stomach, intestine, and biliary tract. The pH of the stomach is practically neutral at birth, decreases to around 3 within 48 h after birth, returns to neutral over the next 24 h, and remains that way for the next 10 days (Bartelink et al. 2006). Thereafter, it slowly declines again until it reaches adult values at about 2 years of age. These initial changes do not occur in premature infants, who seem to have little or no free acid during the first 14 days of life (Bartelink et al. 2006). The time of gastric emptying is delayed in the period immediately after birth for both full term and preterm neonates. It approaches adult values within the first 6–8 months of life (Strolin Benedetti and Baltes 2003). Intestinal transit time is prolonged in neonates because of reduced motility and peristalsis, but appears to be reduced in older infants as a result of increased intestinal motility (Strolin Benedetti and Baltes 2003; Kearns 2000). Other factors that may play a role in intestinal drug absorption are immaturity of the intestinal mucosa leading to increased permeability, immature biliary function, high levels of intestinal  $\beta$ -glucuronidase activity, reduced first-pass metabolism, maturation of carrier mechanisms, and variable microbial colonization (Kearns 2000). These developmental differences in the physiologic composition and function of these organs can alter the rate and/or extent of drug absorption. Changes in intraluminal pH can directly impact both drug stability and degree of ionization, thus influencing the relative amount of drug available for absorption. Acid labile drugs such as penicillin G and erythromycin are therefore more efficiently absorbed, whereas the same changes in gastric pH (developmentally or caused by the use of proton pump inhibitors) will result in clinically important decreases in the absorption of weak organic acids such as phenobarbital and phenytoin, necessitating adjustment of the amount of antiepileptic drug administered to the individual patient (Strolin Benedetti and Baltes 2003). Additionally, the ability to solubilize and subsequently absorb lipophilic drugs can be influenced by age-dependent changes in biliary function. Immature conjugation and/or transport of bile salts into the intestinal lumen results in low intraduodenal levels despite blood levels that exceed those seen in adults. Gastric emptying time is prolonged throughout infancy and childhood consequent to reduced motility, which may retard drug passage into the intestine where the majority of absorption takes place (Kearns 2000). As a consequence, the rate of absorption of drugs with limited water solubility such as phenytoin and carbamazepine can be significantly altered resulting from these changes in gastrointestinal motility. Unfortunately, few studies have systematically evaluated the effect of developmental changes in gastric emptying and intestinal motility on drug absorption in infants and children. Anderson et al. showed that the oral acetaminophen (paracetamol) absorption rate was significantly lower in the first days of life before stabilizing 1 week after birth (Anderson et al. 2002). Another study showed that the time to reach the maximum concentration ( $t_{\max}$ ) of

cisapride was significantly longer in preterm infants compared with term neonates (Kearns et al. 2003b). Generally, the rate at which most drugs are absorbed is generally slower and thus, the time to achieve maximum plasma concentrations is prolonged in neonates and young infants relative to older infants and children. Despite their incomplete characterization, developmental differences in the activity of intestinal drug metabolizing enzymes and efflux transporters have the potential to markedly alter drug bioavailability.

### 3 The Skin

The morphologic and functional development of the skin as well as the factors that influence penetration of drugs into and through the skin has been reviewed (Radde and McKercher 1985). Basically, the percutaneous absorption of a compound is directly related to the degree of skin hydration and relative absorptive surface area and inversely related to the thickness of the stratum corneum (Radde and McKercher 1985). The integument of the full-term neonate possesses an intact barrier function and is similar to that of an older child or adolescent. However, the ratio of surface area to body weight of the full-term neonate is much higher than that of an adult. Thus, the infant will be exposed to a relatively greater amount of drug topically than will older infants, children, or adolescents. In contrast, data of human skin from preterm infants indicates an inverse correlation between permeability and gestational age (Nachman and Esterly 1980). Permeability rates were 100- to 1,000-fold greater before 30 weeks gestation as compared with full-term neonates, with a three to fourfold greater permeation rate seen beyond 32 weeks (Ginsberg et al. 2004). In vivo studies suggest that this increased dermal permeability in preterm infants is a short-lived phenomenon with the permeability barrier of even the most premature neonates similar to that of full-term neonates by 2 weeks of postnatal life (Ginsberg et al. 2004). There are numerous reports in the literature underscoring the importance of skin absorption in neonates primarily showing toxicity after exposure to drugs or chemicals. These include pentachlorophenol-containing laundry detergents and hydrocortisone (Armstrong et al. 1969; Feinblatt et al. 1966). Therefore, extreme caution needs to be exercised in using topical therapy in neonates and young infants. In contrast, the possibility of turning enhanced skin absorption of drugs to the infant's advantage is an interesting idea and was explored exemplarily several years ago by using the percutaneous route to administer theophylline in preterm infants (Evans et al. 1985). A standard dose of theophylline gel was applied and serial theophylline levels were measured demonstrating that therapeutic theophylline levels were achieved in 11 of 13 infants and that the percutaneous route is a feasible method of administering theophylline in preterm infants.

## 4 Drug Distribution

Drug distribution is influenced by a variety of drug-specific physiochemical factors, including the role of drug transporters, blood/tissue protein binding, blood and tissue pH, and perfusion (Bartelink et al. 2006; Kearns et al. 2003a; Van Den Anker and Rakhmanina 2006). However, age-related changes in drug distribution are primarily related to developmental changes in body composition, the concentration of available binding proteins, and the capacity of plasma proteins to bind drugs. Age-dependent changes in body composition alter the physiologic “spaces” into which a drug may distribute (Friis-Hansen 1983). In very young infants, the total body water is high (80–90% of the bodyweight) while fat content is low (10–15% of the bodyweight). The amount of total body water decreases to 55–60% by adulthood. The extracellular water content is about 45% of the bodyweight in neonates, compared with 20% in adulthood (Friis-Hansen 1983). Larger extracellular and total body water spaces in neonates and young infants, coupled with adipose stores that have a higher water/lipid ratio than in adults, produce lower plasma concentrations for drugs that distribute into these respective compartments when administered in a weight-based fashion. Several hydrophilic drugs such as gentamicin and linezolid have a significantly larger volume of distribution in neonates than in infants or adults (Kearns et al. 2003c; De Hoog et al. 2005). The larger volume of distribution in neonates correlates with a larger extracellular water content. The pharmacokinetics of tramadol, a hydrophilic compound with a large volume of distribution in adults, could be described with a two-compartment model (Allegaert et al. 2005). The volume of distribution of the central compartment (a compartment more or less correlated to the extracellular water content) was increased in neonates compared to older children. The volume of distribution of the peripheral compartment (in which the drug is bound to tissue) was not affected by age (Allegaert et al. 2005). For lipophilic drugs that associate primarily with tissue, the influence of age on altering the apparent volume of distribution is not as readily apparent. The extent of drug binding to proteins in the plasma may influence the volume of distribution of drugs (Bartelink et al. 2006). Only free, unbound, drug can be distributed from the vascular space into other body fluids and, ultimately, to tissues where drug–receptor interaction occurs. Albumin, total protein, and total globulins such as  $\alpha$ 1 acid-glycoprotein are the most important circulating proteins responsible for this drug binding in plasma. The absolute concentration of these proteins is influenced by age, nutrition, and disease. Changes in the composition and amount of these circulating plasma proteins can also influence the distribution of highly bound drugs (Bartelink et al. 2006; Edginton et al. 2006). A reduction in both the quantity and binding affinity of circulating plasma proteins in the neonate and young infant often produces an increase in the free fraction of drug, thereby influencing the availability of the active moiety and potentially, its subsequent hepatic and/or renal clearance. Other factors associated with development and/or disease such as variability in regional blood flow, organ perfusion, permeability of cell membranes, changes in acid–base balance, and cardiac output can also

influence drug binding and/or distribution. Finally, drug transporters such as the ABC efflux pump P-glycoprotein (MDR1/ABCB1), which show not only an ontogenic profile in the small intestine but also in the lung, can influence drug distribution because these transporters can markedly influence the extent to which drugs cross membranes in the body and whether drugs can penetrate or are secreted from the target sites (e.g., cerebrospinal fluid).

## 5 Drug Metabolism

Drug metabolism reflects the biotransformation of an endogenous or exogenous molecule by one or more enzymes to moieties, which are more hydrophilic and thus can be more easily excreted (Bartelink et al. 2006; Kearns et al. 2003a; Van Den Anker and Rakhmanina 2006). While metabolism of a drug generally reduces its ability to produce a pharmacologic action, it also can result in a metabolite that has significant potency, and thereby, contributes to the overall pharmacological effect of the drug. In the case of a prodrug such as codeine, biotransformation is required to produce the pharmacologically active metabolite morphine. Although drug metabolism takes place in several tissues (e.g., intestine, skin, lungs, liver), hepatic metabolism has been investigated most intensively and this metabolism has been divided conventionally into two phases (Bartelink et al. 2006; Kearns et al. 2003a; Van Den Anker and Rakhmanina 2006). Phase I hepatic metabolism usually results in modifying the therapeutic agent or xenobiotic (e.g., through oxidation) in order to make the molecule more polar. Phase II hepatic metabolism usually results in addition of a small molecule (e.g., glucuronide) to the therapeutic agent in order to make it more polar. While there are many enzymes that are capable of catalyzing the biotransformation of drugs, the quantitatively most important are represented by the cytochromes P450 (CYP450) (Nelson et al. 1996). The specific CYP450 isoforms responsible for the majority of human drug metabolism are represented by CYP3A4/5, CYP1A2, CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP2E1 (Brown et al. 2008).

Development has a profound effect on the expression of CYP450. Distinct patterns of isoform-specific developmental CYP expression have been observed postnatally. As reflected by recent reviews, distinct patterns of isoform-specific developmental changes in drug biotransformation are apparent for many Phase I and Phase II drug metabolizing enzymes (Hines and McCarver 2002; McCarver and Hines 2002; De Wildt et al. 1999; Alcorn and McNamara 2002). Very recently, Hines (Hines 2008) has categorized the development of enzymes involved in human metabolism into three main categories: (1) those expressed during the whole or part of the fetal period, but silenced or expressed at low levels within 1–2 years after birth; (2) those expressed at relatively constant levels throughout fetal development, but increased to some extent postnatally; and (3) those whose onset of expression can occur in the third trimester, but substantial increase is noted in the first 1–2 years after birth. Based on literature data, CYP3A7,

Flavin-containing monooxygenase 1 (FMO1), sulfotransferase 1A3/4 (SULT1A3/4), SULT1E1, and maybe alcohol dehydrogenase 1A (ADH1A) belong to the first group. To the second group belong CYP2A6, 3A5, 2C9, 2C19, 2D6, 2E1, and SULT1A1. The third group includes ADH1C, ADH1B, CYP1A1, 1A2, 2A 6, 2A7, 2B6, 2B7, 2C8, 2C9, 2F1, 3A4, FMO3, SULT2A1, glucuronosyltransferases (UGT), and *N*-acetyltransferase 2 (Hines 2008; Balistreri et al. 1984; Card et al. 1989).

In addition to these *in vitro* data, there has been an explosion in the amount of information generated about metabolism of therapeutic agents in children during the last two decades. *In vivo* data have been generated largely through two means (Blake et al. 2005, 2007). One is through dedicated ontogeny studies in which a probe drug (e.g., dextromethorphan or acetaminophen/paracetamol) is given to children of various age groups or to the same children over a period of time (Blake et al. 2005, 2007). The other manner in which these *in vivo* data have been developed is serendipitously over the course of industry-sponsored or investigator-initiated pediatric clinical trials, which utilize the traditional age groups, and both anticipated as well as unexpected results reveal new data about the drug metabolizing enzymes involved. The most important examples of studies that have resulted in clinically important insight into the ontogeny of drug metabolism are summarized in the following paragraph.

Midazolam plasma clearance, which primarily reflects hepatic CYP3A4/5 activity after intravenous administration (De Wildt et al. 2001; Kinirons et al. 1999), increases approximately fivefold (1.2–9 ml/min/kg) over the first 3 months of life (Payne et al. 1989). Carbamazepine plasma clearance, also largely dependent upon CYP3A4 (Kerr et al. 1994), is greater in children relative to adults (Pynnönen et al. 1977; Riva et al. 1985; Rane et al. 1975), thereby necessitating higher weight-adjusted (i.e., mg/kg) doses of the drug to produce therapeutic plasma concentrations. CYP2C9 and to a lesser extent, CYP2C19, are primarily responsible for phenytoin biotransformation (Bajpai et al. 1996). Phenytoin apparent half life is prolonged (~75 h) in preterm infants but decreases to ~20 h in term infants less than 1 week postnatal age and to ~8 h after 2 weeks of age (Loughnan et al. 1977). Saturable phenytoin metabolism does not appear until approximately 10 days of postnatal age, demonstrating the developmental acquisition of CYP2C9 activity.

Caffeine and theophylline are the most common CYP1A2 substrates used in pediatrics. Caffeine elimination *in vivo* mirrors that observed *in vitro* with full 3-demethylation activity (mediated by CYP1A2) observed by approximately 4 months of age (Aranda et al. 1979). Formation of CYP1A2-dependent theophylline metabolites reaches adult levels by approximately 4–5 months of postnatal age (Kraus et al. 1993), and in older infants and young children, theophylline plasma clearance generally exceeds adult values (Milavetz et al. 1986). Furthermore, caffeine 3-demethylation in adolescent females appears to decline to adult levels at Tanner stage II relative to males where it occurs at stages IV/V, thus demonstrating an apparent sex difference in the ontogeny of CYP1A2.

The following sections of this chapter will focus on neonates and young infants because no other group defines such a period of rapid growth and development. It is



well established that infants who are barely into their second trimester of gestational life born as small as a few hundred grams (400–500 g) can survive. On the other extreme, by the end of the first month of postnatal life, large for gestational age infants may weigh upwards of several kilograms. Indeed, the 95th weight percentile is approximately 5 kg. No other age groups can be defined in differences measured logarithmically. As one might expect, there are similar tremendous developmental changes in hepatic drug metabolizing enzymes during this time frame. Understanding these implications is important for individualized clinical development programs.

## 6 Phase I Enzymes

### 6.1 CYP3A

The CYP3A subfamily represents the majority of CYP total content in the liver (Brown et al. 2008). Indeed, it has been shown that over one-half of all drugs prescribed are metabolized by CYP3A (Zanger et al. 2008). The CYP3A subfamily consists of CYP3A4, 3A5, 3A7, and 3A43. CYP3A43 is not known to play a significant role in hepatic metabolism. It has been established that CYP3A4 is the predominant CYP3A enzyme in adults, whereas CYP3A7 is the predominant CYP3A enzyme in the fetus and infants. Moreover, there is a great deal of overlap of specificity of ability for CYP3A4 and CYP3A7 to metabolize therapeutic agents. In 2003, Stevens et al. published the results of examining the largest collection of fetal and pediatric liver samples to date. The study included 212 samples. Stevens and colleagues demonstrated that CYP3A7 is highest between 94 and 168 postconceptional days on a pmol/mg basis of total hepatic protein (Stevens et al. 2003). The level at birth is less than half that of the high prenatal value. However, it remains higher than that of even adult CYP3A4 levels. Furthermore, these hepatic samples demonstrated that there is minimal CYP3A4 activity prenatally that continues to increase after birth. Nevertheless, CYP3A7 content remains higher than CYP3A4 content until at least 6 months of age.

To date, two probe drugs have been researched extensively, which have demonstrated the lower activity of CYP3A4 at birth and in neonates. In 2001, De Wildt et al. published the results of midazolam metabolism given to 24 preterm infants. Only 19 of 24 preterm infants produced detectable levels of 1-OH-midazolam. Furthermore, these results firmly established that premature infants had lower CYP3A4 activity than full-term infants, than did children and adults historically. Oral cisapride has also been demonstrated to be a suitable substrate for CYP3A4 activity (Kearns et al. 2003b). Cisapride has demonstrated a similarly low activity for CYP3A4 in the neonatal period, as did midazolam (Kearns et al. 2003b; De Wildt et al. 2001).

In conclusion, CYP3A7 activity is very high before birth and continues to have high activity after birth and is even present into adulthood. CYP3A4 possesses very low activity at birth and very slowly increases in the neonatal period. Thus, when designing studies with substrates for CYP3A4 in young infants and children, great care needs to be taken to adjust for this low activity in order to achieve the goal of the FDA guidance that in children exposure and  $C_{\max}$  are not higher than that in adults.

## 6.2 CYP1A2

One of the first CYP enzymes to be studied utilizing a probe drug in the first year of life is CYP1A2. Two methylxanthines (caffeine and theophylline) have been utilized extensively to evaluate CYP1A2 in vivo in young children (Evans et al. 1989; Erenberg et al. 2000; Lambert et al. 1986; Tateishi et al. 1999). Theophylline and caffeine are two commonly utilized medications in neonates for the treatment of apnea. These medications are frequently continued from the neonatal period during the first year of life. At birth, caffeine-3-demethylation, a measure of CYP1A2 activity, is very low. Consequently, Erenberg et al. published that the efficacious dose of caffeine is 10 mg/kg every day (Erenberg et al. 2000). The half-life of caffeine is 72–96 h in infants compared to approximately 5 h in older children and adults. Similarly, 8-hydroxylation of theophylline is reduced at birth. Nevertheless, longitudinal data indicate a rapid maturation process for CYP1A2, as it appears to reach adult levels within the first year of life, often within the first 6 months of life. Finally, it is important to note that caffeine activity is highly inducible by drugs, diet, and exogenous toxins such as cigarette smoke. In the adult literature, variability in CYP1A2 activity up to 100-fold has been reported. Moreover, Blake et al. reported that caffeine elimination half-life in neonates who are breast-fed is longer than that of formula-fed infants (Blake et al. 2006); information which suggests that the composition of infant diet (i.e., an environmental factor) can influence the pattern of ontogenic expression of a drug metabolizing enzyme.

In conclusion, it is evident that CYP1A2 activity is highly reduced in young infants. Additionally, activity of the enzyme is highly inducible. Finally, maturation of CYP1A2 activity is rapid in the first year of life. Therefore, when designing clinical studies, which include neonates, great care must be taken to assure that this variability in drug response is properly assessed, especially within the first 6–12 months of life.

## 6.3 CYP2D6

CYP2D6 is one of the most polymorphically expressed enzymes in humans (Zanger et al. 2004; Gaedigk et al. 2008). Some estimates indicate that fewer than 90% of

individuals are homozygous for the wild-type allele. In 1991, Treluyer et al. published the results of liver samples from fetuses aged 17–40 weeks postconception. These results demonstrated that the concentration of hepatic CYP2D6 protein was very low or undetectable in these fetuses. This lack of CYP2D6 activity at birth led to the hypothesis that birth-related events may trigger maturation of the enzyme. In 2007, Blake et al. published in vivo results that provided further understanding of CYP2D6 activity in the first year of life. These results came from dosing infants with dextromethorphan at 0.5, 1, 2, 4, 6, and 12 months of age and measuring the metabolites in urine. These dextromethorphan results demonstrate indeed that there is low activity at birth, but that there is rapid acquisition of CYP2D6 activity in the first year of life. Already within the first 2 weeks of life there is measurable acquisition of CYP2D6 activity. Despite the discussion in the literature about the fact that the increase in renal function might conceal the enzyme development resulting in an apparent plateau of the metabolic ratio after 2 weeks (Johnson et al. 2008), very recent data show that an infant with a postmenstrual age of 52 weeks has already mature hepatic CYP2D6 activity (Allegaert et al. 2011).

Taken together, these results demonstrate the need for careful pharmacokinetic studies in infants and toddlers who are provided a pharmacologic agent, which is primarily metabolized by CYP2D6 (e.g., codeine, beta-blockers, propafenone). Not only does one need to be cognizant of potential infants who are predestined by their genome to be poor metabolizers, but potential studies need to realize the implications of low levels of CYP2D6 at birth and also the rapid maturation process that occurs within the first year of life (Stevens et al. 2008).

## 6.4 CYP2C9/CYP2C19

Lee et al. (2002) and Koukouritaki et al. (2004) have published the most extensive reviews to date on CYP2C activity in humans. They demonstrate that the two main representatives of the CYP2C subfamily of enzymes (CYP2C9 and CYP2C19) conveniently follow the CYP2C rule of 20%. Approximately 20% of hepatic CYP content of adult livers is CYP2C and these CYP2C enzymes metabolize 20% of pharmaceuticals developed to date.

Although not to the same extent as CYP2D6, the two main CYP2C representatives are polymorphically expressed. To date, over 30 alleles of CYP2C9 and CYP2C19 have been identified and more than 25 alleles of CYP2C19 have been reported in the literature (Lee et al. 2002; Koukouritaki et al. 2004). Just as with CYP2D6, some of these polymorphisms may result in poor metabolizer status, which may confound studies in infants and young children.

The ontogeny of CYP2C9 is much better established than CYP2C19. Indeed, hepatic liver samples have shown that CYP2C9 activity is functionally very low just prior to birth. However, much like CYP2D6, this activity increases quickly in the first year of life. The classic example of the effects of this very low level of CYP2C9 activity at birth can be seen with phenytoin (Suzuki et al. 1994). Indeed,

the recommended daily dose for newborns is 5 mg/kg/day, but by 6 months to 3 years of age this increases to 8–10 mg/kg/day consequent to increased CYP2C9 activity.

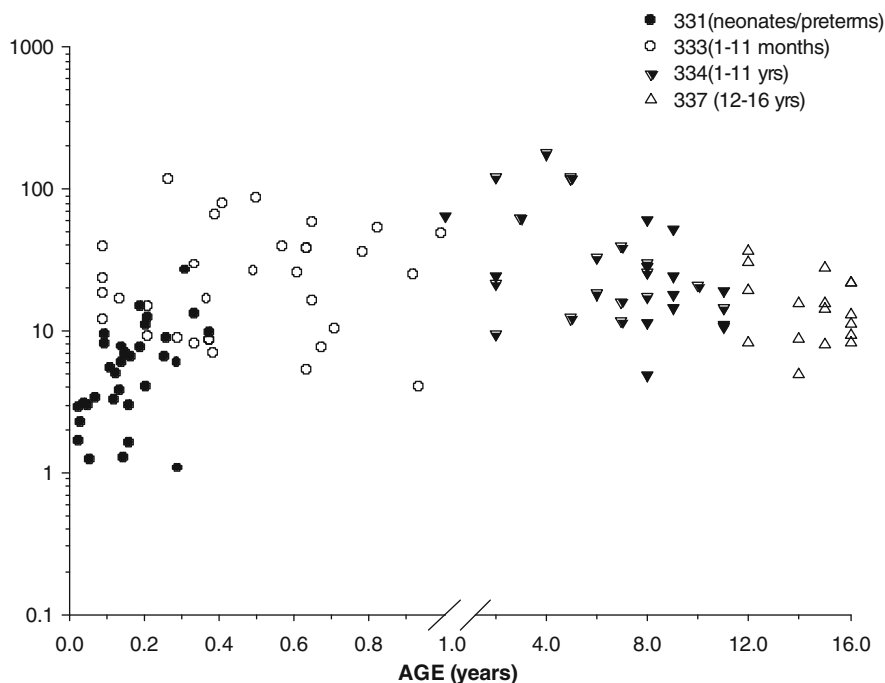
Two major pharmaceutical classes of drugs (i.e., benzodiazepines and proton pump inhibitors) have major representative therapeutic agents that are metabolized by CYP2C19 (Kearns et al. 2003d). Indeed, characteristic representatives from these classes are used in the literature to indirectly ascertain the ontogeny of CYP2C19 activity. Hydroxylation of diazepam is attributed to CYP2C19 activity and is a classic example of the effects of the maturation process of CYP2C19 (Jung et al. 1997). In neonates, the half-life of diazepam is reported to be 50–90 h. Within the first year of life, that half-life of 40–50 h is much closer to the adult value, which is reported as 20–50 h (Klotz 2007).

More recently, the effects of the ontogeny on proton pump inhibitor metabolism have been reviewed. To date, all proton pump inhibitors other than rabeprazole are metabolized by CYP2C19. Of the drugs in this class, the biotransformation of pantoprazole is predominantly dependent upon CYP2C19 activity (Kearns and Winter 2003). When the weight-normalized apparent oral clearance of pantoprazole is examined in pediatric patients from 1 month to 16 years of age (Fig. 1), a developmental profile for the acquisition of CYP2C19 activity is apparent. As expected, exposures of the CYP2C19 metabolism-dependent proton pump inhibitors are universally increased in the youngest infants when genetic polymorphisms of CYP2C19 are fully accounted (Kearns and Winter 2003; Jung et al. 1997).

Taken together, these results demonstrate an important trend when designing pharmaceutical studies that depend on hepatic metabolism through the two major CYP2C enzyme pathways. It is extremely important to be cognizant of the limited activity of these enzymes in early childhood. Moreover, much like with CYP2D6, it is important to recognize the impact of genetic polymorphisms when studying individuals who take substrates of these enzymes (Brandolese et al. 2001). Finally, the first 3 months of life represents a dramatic maturation time for the activity of many drug metabolizing enzymes. When considered in the context of a similar dramatic, nonlinear increase in body size (i.e., both weight and length), individualization of drug dose based on pharmacokinetic data is often a real challenge, especially for agents where attainment of critical target plasma concentrations (or systemic exposures) is necessary. Therefore, one can assume that there will be great variability of exposure in studies with infants in this age group, especially when “standard doses” of a drug are given without adjustment during the first few months of life.

## 6.5 CYP2E1

CYP2E1 is being increasingly recognized for its importance in the oxidative metabolism of a wide variety of pharmaceuticals (e.g., acetaminophen, halothane,



**Fig. 1** Aggregate apparent oral clearance (CL/F) data for pantoprazole obtained from four pediatric clinical pharmacokinetic studies of the drug (study numbers 331, 333, 334, and 337) performed as part of pediatric labeling studies conducted under a written request from the U.S. Food and Drug Administration. All studies involved administration of a single oral dose of pantoprazole given as the proprietary drug formulation. To illustrate the association of development with pantoprazole pharmacokinetics, the value of CL/F has been normalized to a “standard” adult weight of 70 kg

and ethanol) (Jimenez-Lopez and Cederbaum 2005). However, only in the last 5 years has the developmental pattern of this important enzyme been well understood (Johnsrud et al. 2003). Nevertheless, human hepatic CYP2E1 developmental expression is difficult to appreciate due to the multiple levels of regulation in its activity. For example, CYP2E1 is known to be elevated in individuals who have high levels of ethanol consumption, in individuals who are obese, and finally in individuals who have type 2 diabetes (Caro and Cederbaum 2004). Finally, an increasing number of genetic polymorphisms, which lead to lower CYP2E1 protein concentration, have been demonstrated in the literature (Hanioka et al. 2003).

To date, Johnsrud et al. have published the largest study of the activity of fetal and pediatric liver samples to determine the ontogeny of CYP2E1 (Johnsrud et al. 2003). Measurable CYP2E1 activity was demonstrated in 18 of 49 second trimester livers and 12 of 15 third trimester samples. Moreover, measurements of mean concentrations of CYP2E1 protein as part of total milligrams of microsomal protein found that second trimester infants averaged 0.35 pmol/mg, third trimester

infants 6.7 pmol/mg, newborns 8.8 pmol/mg and older infants aged 30–90 days 23.8 pmol/mg, and finally children aged 90 days to 18 years 41.4 pmol/mg. Thus, this implies a rapid maturation starting in late fetal life and continuing through early infancy in CYP2E1 activity. It would appear that these data demonstrate that careful attention would be required in studies of new CYP2E1 substrates in infants under the age of 90 days.

## 7 Drug Excretion

The kidney is the primary organ responsible for the excretion of drugs and their metabolites. Maturation of renal function is a dynamic process that begins early during fetal organogenesis and is complete by early childhood (Rhodin et al. 2009; Chen et al. 2006). The developmental increase in glomerular filtration rate (GFR) involves active nephrogenesis, a process that begins at 9 weeks and is complete by 36 weeks of gestation, followed by postnatal changes in renal and intrarenal blood flow. Following birth, the GFR is approximately 2–4 ml/min/kg in term neonates and as low as 0.6–0.8 ml/min/kg in preterm neonates (Van den Anker et al. 1995a). GFR increases rapidly during the first 2 weeks of life followed by a steady rise until adult values are reached by 8–12 months. This increase in GFR in the first weeks of life is mainly because of an increase in renal blood flow. Similarly, tubular secretory pathways are immature at birth and gain adult capacity during the first year of life.

There is a clear controversy regarding the use of serum creatinine to predict renal function in children (Filler and Lepage 2003). Serum creatinine depends on many factors and residual maternally derived creatinine interferes with the assay in the first days of life in neonates (Capparelli et al. 2001). In addition, factors that have a negative influence on the use of plasma creatinine to predict renal function are renal tubule integrity issues and GFR values of less than 20 mL/min/1.73 m<sup>2</sup>. In these individuals, GFR is probably overestimated. If creatinine is measured with the Jaffé reaction ketoacids, serum bilirubin and cephalosporins interfere with the reaction and therefore the use of an enzymatic method should be advised because of less interference as compared to the Jaffé method (Van den Anker et al. 1995c). A more direct approach to estimate the GFR is to use a marker that is freely permeable across the glomerular capillary and neither secreted nor reabsorbed by the tubulus. Markers that have been mentioned to measure the GFR are inulin, polyfructosan S, cystatin C, <sup>51</sup>Cr-EDTA, <sup>125</sup>I-iothalamate, or mannitol (Filler and Lepage 2003; Hayton 2002). A marker to estimate the active tubular secretion in children is *p*-aminohippuric acid (Hayton 2002).

However, a comparison between serum creatinine with inulin clearance in preterm infants showed a good and clinical useful correlation and supported serum creatinine as an appropriate measure of GFR in preterm infants already on day 3 of life (Van Den Anker et al. 1995c).

Collectively, the aforementioned changes in GFR dramatically alter the plasma clearance of compounds with extensive renal elimination and thus provide a major determinant for age-appropriate dose regimen selection. Pharmacokinetic studies of drugs primarily excreted by glomerular filtration such as ceftazidime and famotidine have demonstrated significant correlations between plasma drug clearance and normal, expected maturational changes in renal function (Van den Anker et al. 1995a; James et al. 1998). For example, tobramycin is eliminated predominantly by glomerular filtration, necessitating dosing intervals of 36–48 h in preterm and 24 h in term newborns (De Hoog et al. 2002). Failure to account for the ontogeny of renal function and adjust aminoglycoside dosing regimens accordingly can result in exposure to potentially toxic serum concentrations. Also, concomitant medications (e.g., betamethasone, indomethacin) may alter the normal pattern of renal maturation in the neonate (Van Den Anker et al. 1994). Thus, for drugs with extensive renal elimination, both maturational and treatment associated changes in kidney function must be considered and used to individualize treatment regimens in an age-appropriate fashion.

## **8 Other Factors Influencing the Absorption, Distribution, Metabolism, and Excretion of Drugs in Neonates and Young Infants**

In addition to growth and development, there are several other major variables that will influence the pharmacokinetic parameters of drugs such as inborn or acquired diseases, environmental influences such as body cooling, and pharmacogenomics. It is outside the scope of this chapter to provide extensive information on these important variables but a few will be highlighted here.

Hypoxic–ischemic events are encountered regularly in sick neonates and these events might result in a decrease in the rate and amount of drug absorption as well as impaired renal function. There are data to show that after perinatal asphyxia the GFR in neonates is 50% less as compared to neonates born without asphyxia, resulting in a decreased clearance of renally cleared drugs (Van den Anker et al. 1995b). The persistence and/or closure of a patent ductus arteriosus has a major impact on both the volume of distribution and elimination of frequently used drugs in the newborn (Van den Anker et al. 1995d). This has been shown for drugs such as ceftazidime where the existence of a patent ductus and or the exposure to indomethacin to close this ductus was associated with a decreased GFR and a larger volume of distribution of ceftazidime, a solely renally cleared drug. In another study investigating ibuprofen, there was a significant increase in the clearance of ibuprofen after closure of the ductus (Van Overmeire et al. 2001). Finally, total body cooling is a new treatment modality that is being used to improve the neurological outcome of neonates who suffered from perinatal asphyxia. In a

study investigating the pharmacokinetics of morphine in neonates with and without body cooling, a clinically impressive decrease in morphine clearance was seen in neonates on body cooling (Roka et al. 2008).

## 9 Pharmacogenomics: Impact for Pediatric Populations

The contribution of genetic factors to explain heterogeneity of drug response in infants and children is another important issue with the ultimate goal for better treatment of children based on the individual genetic makeup. One of the major tasks is to optimally adapt the choice and amount of a drug to the individual need of a patient and, for instance, to prevent overdosing with the risk of adverse drug reactions. Genetic variability influences almost all ADME processes including drug absorption (e.g., via the intestinal drug transporter P-glycoprotein/ABCB1), drug metabolism (e.g., cytochrome P450 enzymes 2C9, 2C19, 2D6), and drug elimination, thereby resulting in alteration of pharmacokinetics and subsequently of pharmacodynamic processes.

There is an increasing body of evidence that genetic variants in drug metabolizing enzymes (e.g., CYP450 enzymes; <http://www.cypalleles.ki.se/>;) as well as in drug transporters (e.g., ABCB1/P-gp, SLCO1B1/OATP1B) (Schwab et al. 2003; Nies et al. 2008; Niemi et al. 2011) are functional relevant (e.g., loss of function variants or gain of function polymorphisms) with in part dramatic changes in mRNA and/or protein expression and function (Zanger et al. 2008). Genetic variants in drug targets such as receptor molecules or intracellular structures of signal transduction and gene regulation directly and/or indirectly may also influence drug response and tolerability in the neonate and young infant. Based on several novel and promising genomic technologies such as high-throughput genotyping (e.g., MALDI-ToF mass spectrometry), genome-wide association studies, and next generation sequencing, pharmacogenomic knowledge will improve our understanding of pharmacotherapy in children but will also stimulate the drug development process for innovative agents in the future (Russo et al. 2010).

To illustrate the impact of pediatric pharmacogenomics the link between development and genetics related to CYP2D6, one of the most studied enzymes, will be described. Genetic variation in CYP2D6 has been the subject of several comprehensive reviews in recent years (Zanger et al. 2004; Stevens et al. 2008). Poor (PM), intermediate (IM), extensive (EM), and ultrarapid (UM) metabolizer phenotypes are observed when a population is challenged with a probe substrate. Inheritance of two recessive loss-of-function alleles results in the “poor-metabolizer phenotype,” which is found in about 5–10% of Caucasians and about 1–2% of Asian subjects (see earlier). At the other end of the spectrum, the presence of CYP2D6 gene duplication/multiplication events, which occurs at a frequency of 1–2% in Caucasians, most often is associated with enhanced clearance of CYP2D6 substrates although cases of increased toxicity due to increased formation of pharmacologically active metabolites have also been reported. Recently, this was even



illustrated by a case of a breastfeeding woman with a UM phenotype, treated with codeine for pain after delivery, who formed so much morphine out of codeine that she intoxicated her newborn infant (Koren et al. 2006).

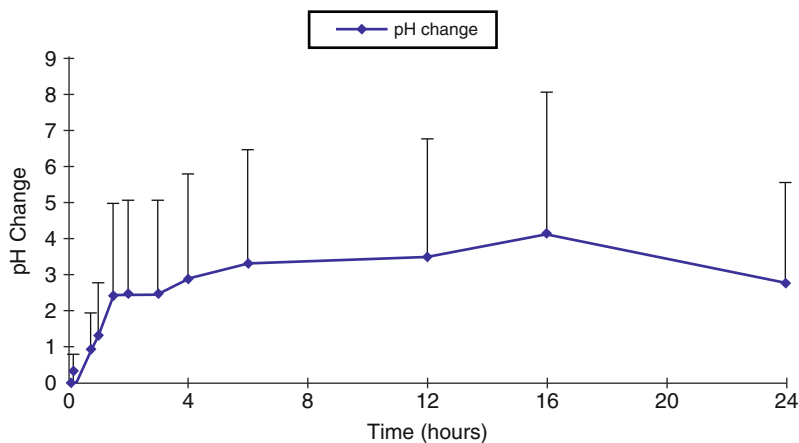
The ultimate utility of genomic information in the context of pharmacokinetics is when the genotype is shown to be predictive of the phenotype; specifically, when it can reliably predict the functional activity of a given enzyme and/or drug transporter. This is exemplified by use of the CYP2D6 activity score, which is derived based upon the functional impact (on CYP2D6 activity) of a given combination of *CYP2D6* alleles. A potential caveat with use of the CYP2D6 activity score resides with the fact that it has been validated in adults in whom the phenotypic CYP2D6 activity is fully developed (Zanger et al. 2001). In other words, the contribution of the genetic variation (e.g., CYP2D6 polymorphisms) to the phenotypic variability in drug disposition in adults has been explored. Very recently, Gaedigk et al. reported the use of this activity score also in infants (Gaedigk et al. 2008), but we still have to fit this genetic variation into the age-dependent maturation during infancy. At present we know that age and genetic determinants of CYP2D6 expression constitute significant determinants of inter-individual variability in CYP2D6-dependent metabolism during ontogeny. Very recently, it was documented that the *in vivo* phenotypic CYP2D6 activity was concordant with the genotype from 42 weeks postmenstrual age onwards (Allegaert et al. 2008; Blake et al. 2007). This indicates that for clinicians treating neonates, young infants, children, and adolescents the genetic variation in CYP2D6 is the major player to consider if prescribing CYP2D6 substrates.

In summary, both genetic and environmental factors contribute to inter-individual variability in the PK of medications metabolized by CYP2D6 (Leeder 2003; Krekels et al. 2007). In this context, a recent paper using a whole body physiology-based pharmacokinetic (PBPK) modeling approach to investigate the contribution of CYP2D6 genetics on codeine administration in breastfeeding mothers and their babies supports the evidence that pediatric pharmacogenomics comprises more than a single gene, and developmental aspects of physiological processes need to be considered (Willmann et al. 2009).

If CYP2D6 genotyping is becoming a standard laboratory test and the CYP2D6 activity score has been validated in infants, children, and adolescents, this will surely improve our capacity to predict the doses of CYP2D6 substrates required to treat the neonates, young infants, children, and adolescents in a more safe and effective way.

## 10 The Interface of Pharmacokinetics and Pharmacodynamics

Although, it is generally accepted that developmental differences in drug action exist, there is little scientific evidence of real age related pharmacodynamic variation among children of different age groups and adults. Age-related pharmacokinetic variation in drug clearance has the potential to alter the systemic



**Fig. 2** Time dependent change in intragastric pH in a population of neonates administered a single intravenous dose of famotidine. Figure adapted from James et al. (1998)

exposure of drug from given dose with the consequence of producing less or more drug being available at the receptor(s) consequent to whether drug clearance is decreased or increased relative to values in adults. The resultant alteration in the dose–concentration profile may result in an attenuated (ineffective) or exaggerated (toxicity) pharmacodynamic response in an infant or child, a situation which is especially relevant for drugs with a narrow therapeutic index (e.g., aminoglycoside antibiotics, digoxin, antiarrhythmic agents). Thus, in some circumstances, apparent developmental differences in drug response/effect may be simply explained on pharmacokinetic basis. This is illustrated by the  $H_2$  antagonist famotidine where consequent to a marked reduction in plasma clearance (i.e., renal elimination), a single intravenous dose produced a sustained increase in the intragastric pH in neonates for a 24-h postdose period (Fig. 2) (James et al. 1998).

## 11 Pediatric Dose Selection Based upon Pharmacokinetic Principles

Most current age-specific dosing requirements are based on the known influence of ontogeny on drug disposition. Current gaps in our knowledge (e.g., incomplete developmental profiles for hepatic and extrahepatic drug metabolizing enzymes, lack of knowledge with regard to expression of drug transporters that may influence drug clearance and/or bioavailability) prevent the use of simple formulas and/or allometric scaling for effective pediatric dose prediction; a fact especially true in very young infants where the relationship between body size and the maturation of

pathways predominantly responsible for drug clearance are not linear (Holford 2010). Such approaches (e.g., allometric scaling) may have some potential clinical utility in children older than 3 years of age and adolescents whose organ function and body composition approximates that of young adults.

Age-specific dosing regimens for selected commonly used drugs where developmental differences in the dose–concentration profile have been well characterized serve to illustrate this point. For drugs whose plasma concentrations are routinely measured clinically (e.g., aminoglycosides, digoxin, caffeine, phenytoin, phenobarbital, carbamazepine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil), or for whom pharmacokinetic characteristics were defined in pediatric patients during the drug development process, individualization of treatment based on patient-derived and in selected instances, population-estimated pharmacokinetic parameters is easily achieved. However, in the absence of such pharmacokinetic data and/or established pediatric dosing guidelines, alternate methods for dose selection must be used.

As discussed previously, the majority of age-adjusted pediatric drug dosing regimens utilize either body weight or surface area as surrogates to reflect the developmental determinants of drug disposition. Dose selection based on body weight or body surface areas will generally produce similar plasma concentration profiles except for those drugs whose apparent volume of distribution ( $V_d$ ) corresponds to the extracellular fluid pool (i.e.,  $V_d < 0.3$  L/kg), where a body surface area based approach is preferable. In contrast, for drugs whose apparent  $V_d$  exceeds the extracellular fluid space (i.e.,  $>0.3$  L/kg), a body weight based approach for dose selection is preferable and as a result is the most frequently used approach for dosing in pediatrics.

When the pediatric dose for a given drug is not known these principles can be used to best approximate a proper dose for the initiation of treatment. Ritschel and Kearns (2009) have described an approach to determine dose in infants that is illustrated by the following equations:

$$\text{Infant dose (if } V_d < 0.3 \text{ L/kg)} = (\text{infant BSA in m}^2 / 1.73 \text{ m}^2) \times \text{adult dose},$$

$$\text{Infant dose (if } V_d \geq 0.3 \text{ L/kg)} = (\text{infant BW in kg} / 70 \text{ kg}) \times \text{adult dose}.$$

This approach is only useful for selection of dose size, and does not offer information regarding dosing interval since the equations contain no specific variable that describes potential age-associated differences in drug clearance. It is also important to note that this approach assumes that the body height and weight of a given child are appropriate (i.e., normal) for age and there are no abnormalities in body composition (e.g., edema, ascites) that can be produced by disease.

In neonates and young infants, the dosing interval for drugs with significant (i.e.,  $>50\%$ ) renal elimination by glomerular filtration can be approximated by estimation of the apparent elimination half-life ( $t_{1/2}$ ) of the drug at a given point in development by using the following equations:

$$k_{el \text{ infant}} = k_{el \text{ adult}} \{ [((GFR_{\text{infant}}/GFR_{\text{adult}}) - 1) \times F_{el}] + 1 \},$$

$$T_{1/2 \text{ infant}} = 0.693/k_{el \text{ infant}},$$

where  $k_{el}$  represents the average terminal apparent terminal elimination rate constant, GFR is an estimate of the glomerular filtration rate (which can be obtained from either a creatinine clearance determination or age-related normal values), and  $F_{el}$  is the fraction of drug excreted unchanged in the urine.

Alternatively, projection of pediatric dose requirement can be performed using *in silico* techniques (e.g., whole body physiologically based pharmacokinetic/pharmacodynamic models, population-based simulation, PK-Sim Packages, Simcyp Pediatric ADME Simulator) (Johnson and Rostami-Hodjegan 2011). The success of these approaches (i.e., prediction accuracy) is based upon the availability and reliability of parameter estimates (either pharmacokinetic, pharmacodynamic, or pharmacogenomic) and their prior knowledge in the specific subpopulation being used for dose projection (Espie et al. 2009). These caveats are especially important during early infancy where dynamic changes in drug disposition and action are likely consequent to ontogeny and developmental maturity in drug clearance pathways has not yet been attained.

## 12 Conclusions

The pediatric patient population consisting of neonates, infants, children, and adolescents shows unique differences in pharmacokinetic parameters as compared to adults and therefore requires specific dosage recommendations. While the paucity of pharmacokinetic and physiological data makes it difficult to precisely determine drug doses in pediatric patients, knowledge of the effects of growth, maturation, environmental influences, and pharmacogenetic background on absorption, distribution, metabolism, and elimination of frequently used medicines will allow more appropriate dosing recommendations for this patient population. Clearly, much more research is needed to fully understand the impact of development on the disposition of a drug. As described in this chapter, studies with substrates as markers for hepatic metabolic activity or renal function and *in vitro* data are very useful for a better understanding of this impact. Finally, there is an urgent need to better understand the metabolic activity, carrier mechanisms, and drug transporters related to the gastrointestinal tract.

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## References

- Alcorn J, McNamara PJ (2002) Ontogeny of hepatic and renal systemic clearance pathways in infants: part I. *Clin Pharmacokinet* 41:959–998
- Allegaert K, Anderson BJ, Verbesselt R, Debeer A, de Hoon J, Devlieger H et al (2005) Tramadol disposition in the very young: an attempt to assess in vivo cytochrome P-450 activity. *Br J Anaesth* 95:231–239
- Allegaert K, van Schaik RH, Vermeersch S, Verbesselt R, Cossey V, Vanhole C et al (2008) Postmenstrual age and CYP2D6 polymorphisms determine tramadol O-demethylation in critically ill neonates and infants. *Pediatr Res* 63:674–679
- Allegaert K, Rochette A, Veyckemans F (2011) Developmental pharmacology of tramadol during infancy: ontogeny, pharmacogenetics and elimination clearance. *Paediatr Anaesth* 21(3): 266–273
- Anderson BJ, Holford NH (2008) Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol* 48:303–332
- Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH (2002) Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology* 96:1336–1345
- Aranda JV, Collinge JM, Zinman R, Watters G (1979) Maturation of caffeine elimination in infancy. *Arch Dis Child* 54:946–949
- Armstrong RW, Eichner ER, Klein DE, Barthel WF, Bennett JV, Jonsson V et al (1969) Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxicologic studies. *J Pediatr* 75:317–325
- Bajpai M, Roskos LK, Shen DD, Levy RH (1996) Roles of cytochrome P450C9 and cytochrome P450C19 in the stereoselective metabolism of phenytoin to its major metabolite. *Drug Metab Dispos* 24:1401–1403
- Balistreri W, Zimmer L, Suchy FJ, Bove KE (1984) Bile salt sulfotransferase: alterations during maturation and non-inducibility during substrate ingestion. *J Lipid Res* 25:228–235
- Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN (2006) Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet* 45:1077–1097
- Blake MJ, Castro L, Leeder JS, Kearns GL (2005) Ontogeny of drug metabolizing enzymes in the neonate. *Semin Fetal Neonatal Med* 10:123–128
- Blake MJ, Abdel-Rahman SM, Pearce RE, Leeder JS, Kearns GL (2006) Effect of diet on the development of drug metabolism by cytochrome P-450 enzymes in healthy infants. *Pediatr Res* 60:717–723
- Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C et al (2007) Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. *Clin Pharmacol Ther* 81:510–516
- Brandolese R, Scordo MG, Spina E, Gusella M, Padriani R (2001) Severe phenytoin intoxication in a subject homozygous for CYP2C9\*3. *Clin Pharmacol Ther* 70:391–394
- Brown CM, Reisfeld B, Mayeno AN (2008) Cytochromes P450: a structure-based summary of biotransformations using representative substrates. *Drug Metab Rev* 40:169–184
- Capparelli EV, Lane JR, Romanowski GL, McFeely EJ, Murray W, Sousa P et al (2001) The influences of renal function and maturation on vancomycin elimination in newborns and infants. *J Clin Pharmacol* 41:927–934
- Card SE, Tompkins SF, Brien JF (1989) Ontogeny of the activity of alcohol dehydrogenase and aldehyde dehydrogenases in the liver and placenta of the guinea pig. *Biochem Pharmacol* 38:2535–2541
- Caro AA, Cederbaum AI (2004) Oxidative stress, toxicology, and pharmacology of CYP2E1. *Annu Rev Pharmacol Toxicol* 44:27–42
- Chen N, Aleksa K, Woodland C, Rieder M, Koren GL (2006) Ontogeny of drug elimination by the human kidney. *Pediatr Nephrol* 21:160–168

- De Hoog M, Mouton JW, Schoemaker RC, Verduin CM, van den Anker JN (2002) Extended-interval dosing of tobramycin in neonates: implications for therapeutic drug monitoring. *Clin Pharmacol Ther* 71:349–358
- De Hoog M, Mouton JW, van den Anker JN (2005) New dosing strategies for antibacterial agents in the neonate. *Semin Fetal Neonatal Med* 10:185–194
- De Wildt SN, Kearns GL, Leeder JS, van den Anker JN (1999) Glucuronidation in humans: pharmacogenetic and developmental aspects. *Clin Pharmacokinet* 36:439–452
- De Wildt SN, Kearns GL, Hop WC, Murry DJ, Abdel-Rahman SM, van den Anker JN (2001) Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol Ther* 70:525–531
- Edginton AN, Schmitt W, Voith B, Willmann S (2006) A mechanistic approach for the scaling of clearance in children. *Clin Pharmacokinet* 45:683–704
- Erenberg A, Leff RD, Haack DG, Mosdell KW, Hicks GM, Wynne BA (2000) Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. *Pharmacotherapy* 20:644–652
- Espie P, Tytgat D, Sargentini-Maier ML, Poggesi I, Watelet JB (2009) Physiologically based pharmacokinetics (PBPK). *Drug Metab Rev* 41:391–407
- Evans NJ, Rutter N, Hadgraft J, Parr G (1985) Percutaneous administration of theophylline in the preterm infant. *J Pediatr* 107:307–311
- Evans WE, Relling MV, Petros WP, Meyer WH, Mirro J Jr, Crom WR (1989) Dextromethorphan and caffeine as probes for simultaneous determination of debrisoquin-oxidation and N-acetylation phenotypes in children. *Clin Pharmacol Ther* 45:568–573
- Feinblatt BI, Aceto T, Beckhorn G, Bruck E (1966) Percutaneous absorption of hydrocortisone in children. *Am J Dis Child* 112:218–224
- Filler G, Lepage N (2003) Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? *Pediatr Nephrol* 18:981–985
- Friis-Hansen B (1983) Water distribution in the foetus and newborn infant. *Acta Paediatr Scand* 305:7–11
- Gaedigk A, Simon D, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS (2008) The CYP2D6 activity score: translating genotype information into a quantitative measure of phenotype. *Clin Pharmacol Ther* 83:234–242
- Ginsberg G, Hattis D, Miller M, Sonawane B (2004) Pediatric pharmacokinetic data: implications for environmental risk assessment for children. *Pediatrics* 113:973–983
- Hanioka N, Tanaka-Kagawa T, Miyata Y, Matsushima E, Makino Y, Ohno A et al (2003) Functional characterization of three human cytochrome P450 2E1 variants with amino acid substitutions. *Xenobiotica* 33:575–586
- Hayton WL (2002) Maturation and growth of renal function: dosing renally cleared drugs in children. *AAPS PharmSci* 2:e3
- Hines RN (2008) The ontogeny of drug metabolism enzymes and implications for adverse drug events. *Pharmacol Ther* 118:250–267
- Hines RN, McCarver DG (2002) The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J Pharmacol Exp Ther* 300:355–360
- Holford N (2010) Dosing in children. *Clin Pharmacol Ther* 87:367–370
- James LP, Marotti T, Stowe C, Farrar HC, Taylor B, Kearns GL (1998) Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol* 38:1089–1095
- Jimenez-Lopez JM, Cederbaum AI (2005) CYP2E1-dependent oxidative stress and toxicity: role in ethanol-induced liver injury. *Expert Opin Drug Metab Toxicol* 1:671–685
- Johnson TN, Rostami-Hodjegan A (2011) Resurgence in the use of physiologically based pharmacokinetic models in pediatric clinical pharmacology: parallel shift in incorporating the knowledge of biological elements and increased applicability to drug development and clinical practice. *Paediatr Anaesth* 21(3):291–301
- Johnson TN, Rostami-Hodjegan A, Tucker GT (2006) Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin Pharmacokinet* 45:931–956

- Johnson TN, Tucker GT, Rostami-Hodjegan A (2008) Development of CYP2D6 and CYP3A4 in the first year of life. *Clin Pharmacol Ther* 83:670–671
- Johnsrud EK, Koukouritaki SB, Divakaran K, Brunengraber LL, Hines RN, McCarver DG (2003) Human hepatic CYP2E1 expression during development. *J Pharmacol Exp Ther* 307:402–407
- Jung F, Richardson TH, Raucy JL, Johnson EF (1997) Diazepam metabolism by cDNA-expressed human 2C P450s: identification of P4502C18 and P4502C19 as low K(M) diazepam N-demethylases. *Drug Metab Dispos* 25:133–139
- Kearns GL (2000) Impact of developmental pharmacology on pediatric study design: overcoming the challenges. *J Allergy Clin Immunol* 106:S128–S139
- Kearns GL, Winter HS (2003) Proton pump inhibitors in pediatrics: relevant pharmacokinetics and pharmacodynamics. *J Pediatr Gastroenterol Nutr* 37(Suppl I):S52–S59
- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE (2003a) Developmental pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med* 349:1157–1167
- Kearns GL, Robinson PK, Wilson JT, Wilson-Costello D, Knight GR, Ward RM et al (2003b) Cisapride disposition in neonates and infants: in vivo reflection of cytochrome P450 3A4 ontogeny. *Clin Pharmacol Ther* 4:312–325
- Kearns GL, Jungbluth GL, Abdel-Rahman SM, Hopkins NK, Welshman IR, Grzebyk RP et al (2003c) Impact of ontogeny on linezolid disposition in neonates and infants. *Clin Pharmacol Ther* 74:413–422
- Kearns GL, Anderson T, James LP, Gaedigk A, Kraynak RA, Abdel-Rahman SM et al (2003d) Omeprazole disposition in children following single dose administration. *J Clin Pharmacol* 43:840–848
- Kerr BM, Thummel KE, Wurden CJ, Klein SM, Kroetz DL, Gonzalez FJ et al (1994) Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. *Biochem Pharmacol* 47:1969–1979
- Kinirons MT, O'Shea D, Kim RB, Groopman JD, Thummel KE, Wood AJ et al (1999) Failure of erythromycin breath test to correlate with midazolam clearance as a probe of cytochrome P4503A. *Clin Pharmacol Ther* 66:224–231
- Klotz U (2007) The role of pharmacogenetics in the metabolism of antiepileptic drugs: pharmacokinetics and therapeutic implications. *Clin Pharmacokinet* 46:271–279
- Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder JS (2006) Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 368:704
- Koukouritaki SB, Manro JR, Marsh SA, Stevens JC, Rettie AE, McCarver DG et al (2004) Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther* 308:965–974
- Kraus DM, Fischer JH, Reitz SJ, Kecskes SA, Yeh TF, McCulloch KM et al (1993) Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther* 54:351–359
- Krekels EH, van den Anker JN, Baiardi P, Cella M, Cheng KY, Gibb DM et al (2007) Pharmacogenetics and paediatric drug development: issues and consequences to labelling and dosing recommendations. *Expert Opin Pharmacother* 8:1787–1799
- Lambert GH, Schoeller DA, Kotake AN, Flores C, Hay D (1986) The effect of age, gender, and sexual maturation on the caffeine breath test. *Dev Pharmacol Ther* 9:375–388
- Lee CR, Goldstein JA, Pieper JA (2002) Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in vitro and human data. *Pharmacogenetics* 12:251–263
- Leeder JS (2003) Developmental and pediatric pharmacogenomics. *Pharmacogenomics* 4:331–341
- Leeder JS, Kearns GL, Spielberg SP, van den Anker JN (2010) Understanding the relative roles of pharmacogenetics and ontogeny in pediatric drug development and regulatory science. *J Clin Pharmacol* 50(12):1377–1387

- Loughnan PM, Greenwald A, Purton WW, Aranda JV, Watters G, Neims AH (1977) Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. *Arch Dis Child* 52:302–309
- McCarver DG, Hines RN (2002) The ontogeny of human drug metabolizing enzymes: phase II conjugation enzymes and regulatory mechanisms. *J Pharmacol Exp Ther* 300:361–366
- Milavetz G, Vaughan LM, Weinberger MM, Hendeles L (1986) Evaluation of a scheme for establishing and maintaining dosage of theophylline in ambulatory patients with chronic asthma. *J Pediatr* 109:351–354
- Nachman RL, Esterly NB (1980) Increased skin permeability in preterm infants. *J Pediatr* 96:99–103
- Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Feyereisen R, Waxman DJ et al (1996) P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. *Pharmacogenetics* 6:1–42
- Niemi M, Pasanen MK, Neuvonen PJ (2011) Organic anion transporting polypeptide1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev* 63(1):157–181
- Nies AT, Schwab M, Keppler D (2008) Interplay of conjugating enzymes with OATP uptake transporters and ABCC/MRP efflux pumps in the elimination of drugs. *Expert Opin Drug Metab Toxicol* 4:545–568
- Payne K, Mattheyse FJ, Liedenberg D, Dawes T (1989) The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 37:267–272
- Pynnönen S, Sillanpää M, Frey H, Iisalo E (1977) Carbamazepine and its 10,11-epoxide in children and adults with epilepsy. *Eur J Clin Pharmacol* 11:129–133
- Radde IC, McKercher HG (1985) Transport through membranes and development of membrane transport. In: MacLeod SM, Radde IC (eds) *Textbook of pediatric clinical pharmacology*. PSG, Littleton, MA, pp 1–16
- Rane A, Bertilsson L, Palmer L (1975) Disposition of placentally transferred carbamazepine (Tegretol) in the newborn. *Eur J Clin Pharmacol* 8:283–284
- Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M et al (2009) Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol* 24:67–76
- Ritschel WA, Kearns GL (eds) (2009) *Handbook of basic pharmacokinetics*, 7th edn. American Pharmacists Association, Washington, DC, pp 274–276
- Riva R, Contin M, Albani F, Perucca E, Procaccianti G, Baruzzi A (1985) Free concentration of carbamazepine and carbamazepine-10,11-epoxide in children and adults. Influence of age and phenobarbitone co-medication. *Clin Pharmacokinet* 10:524–531
- Roka A, Melinda KT, Vasarhelyi B, Machay T, Azzopardi D, Szabo M (2008) Elevated morphine concentrations in neonates treated with morphine and prolonged hypothermia for hypoxic ischemic encephalopathy. *Pediatrics* 121:e844–e849
- Russo R, Capasso M, Paolucci P, Iolascon A, TEDDY European Network of Excellence (2010) Pediatric pharmacogenetic and pharmacogenomic studies: the current state and future perspectives. *Eur J Clin Pharmacol* ePub 2011;67 suppl 1:17–27 Epub 2010 Nov 11
- Schwab M, Eichelbaum M, Fromm MF (2003) Genetic polymorphisms of the human MDR1 drug transporter. *Annu Rev Pharmacol Toxicol* 43:285–307
- Stevens JC, Hines RN, Gu C, Koukouritaki SB, Manro JR, Tandler PJ et al (2003) Developmental expression of the major human hepatic CYP3A enzymes. *J Pharmacol Exp Ther* 307:573–582
- Stevens JC, Marsh SA, Zaya MJ, Regina KJ, Divakaran K, Le M et al (2008) Developmental changes in human liver CYP2D6 expression. *Drug Metab Dispos* 36:1587–1593
- Strolin Benedetti M, Baltes EL (2003) Drug metabolism and disposition in children. *Fundam Clin Pharmacol* 17:281–299
- Suzuki Y, Mimaki T, Cox S, Koepke J, Hayes J, Walson PD (1994) Phenytoin age-dose-concentration relationship in children. *Ther Drug Monitor* 16(2):145–150



- Tateishi T, Asoh M, Yamaguchi A, Yoda T, Okano YJ, Koitabashi Y (1999) Developmental changes in urinary elimination of theophylline and its metabolites in pediatric patients. *Pediatr Res* 45:66–70
- Treluyer JM, Jacqz-Aigrain E, Alvarez F, Cresteil T (1991) Expression of CYP2D6 in developing human liver. *Eur J Biochem* 202:583–588
- Van den Anker JN, Rakhmanina NY (2006) Pharmacological research in pediatrics: from neonates to adolescents. *Adv Drug Deliv Rev* 58:4–14
- Van den Anker JN, Hop W, de Groot R, van der Heijden AJ, Broerse HM, Lindemans J et al (1994) Effects of prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate in the preterm infant. *Pediatr Res* 36:578–581
- Van den Anker JN, Schoemaker R, Hop W, van der Heijden BJ, Weber A, Sauer PJ et al (1995a) Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. *Clin Pharmacol Ther* 58:650–659
- Van den Anker JN, Van der Heijden AJ, Hop WCJ, Schoemaker RC, Broerse HM, Neijens HJ et al (1995b) The effect of asphyxia on the pharmacokinetics of ceftazidime in the term newborn. *Pediatr Res* 38:808–811
- Van den Anker JN, de Groot R, Broerse HM, Sauer PJ, van der Heijden BJ, Neijens HJ et al (1995c) Assessment of glomerular filtration rate in preterm infants by serum creatinine: comparison with inulin clearance. *Pediatrics* 96:1156–1158
- Van den Anker JN, Hop WCJ, Schoemaker RC, Van der Heijden AJ, Neijens HJ, De Groot R (1995d) Ceftazidime pharmacokinetics in preterm infants: effects of postnatal age and postnatal exposure to indomethacin. *Br J Clin Pharmacol* 40:439–443
- Van Overmeire B, Touw D, Schepens PJC, Kearns GL, van den Anker JN (2001) Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. *Clin Pharmacol Ther* 70:336–343
- Willmann S, Edgington AN, Coboeken K, Ahr G, Lippert J (2009) Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modelling study. *Clin Pharmacol Ther* 86:634–643
- Zanger UM, Fischer J, Raimundo S, Stuvén T, Evert BO, Schwab M, Eichelbaum M (2001) Comprehensive analysis of the genetic factors determining expression and function of hepatic CYP2D6. *Pharmacogenetics* 11:573–585
- Zanger UM, Raimundo S, Eichelbaum M (2004) Cytochrome P450 2D6: overview and update on pharmacology, genetics and biochemistry. *Naunyn-Schmiedeberg Arch Pharmacol* 369:23–37
- Zanger UM, Turpeinen M, Klein K, Schwab M (2008) Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem* 392:1093–1108

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