Pharmacokinetics in the newborn

Jane Alcorn\textsuperscript{a,}\textsuperscript{*}, Patrick J. McNamara\textsuperscript{b}

\textsuperscript{a}College of Pharmacy and Nutrition, University of Saskatchewan, 110 Science Place, Saskatoon, SK, S7N 5C9, Canada
\textsuperscript{b}Division of Pharmaceutical Sciences, University of Kentucky, Lexington, KY 40536, USA

Received 11 June 2002; accepted 22 January 2003

Abstract

In addition to differences in the pharmacodynamic response in the infant, the dose and the pharmacokinetic processes acting upon that dose principally determine the efficacy and/or safety of a therapeutic or inadvertent exposure. At a given dose, significant differences in therapeutic efficacy and toxicant susceptibility exist between the newborn and adult. Immature pharmacokinetic processes in the newborn predominantly explain such differences. With infant development, the physiological and biochemical processes that govern absorption, distribution, metabolism, and excretion undergo significant growth and maturational changes. Therefore, any assessment of the safety associated with an exposure must consider the impact of these maturational changes on drug pharmacokinetics and response in the developing infant. This paper reviews the current data concerning the growth and maturation of the physiological and biochemical factors governing absorption, distribution, metabolism, and excretion. The review also provides some insight into how these developmental changes alter the efficiency of pharmacokinetics in the infant. Such information may help clarify why dynamic changes in therapeutic efficacy and toxicant susceptibility occur through infancy.

Keywords: Development; Exposure; Human; Infant; Newborn; Pharmacokinetics

Contents

1. Introduction ................................................................................................................. 668
2. Absorption................................................................................................................... 669
3. Distribution................................................................................................................. 672
4. Elimination ................................................................................................................. 673

*Corresponding author. Tel.: +1-306-966-6365; fax: +1-306-966-6377.
E-mail address: jane.alcorn@usask.ca (J. Alcorn).

0169-409X/03/5 – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0169-409X(03)00030-9
1. Introduction

Adult doses, even after adjusted for differences in body weight, often lead to drastic consequences in the newborn patient. Functional immaturity of physiological processes and organ function predispose newborns to exhibit such disparate responses relative to the adult. With infant maturation, normal development may modify infant response to drug and toxicant exposures. The full impact of developmental immaturity, though, still remains unrealized as exemplified by the number of well-documented therapeutic misjudgments that continue even to this day [1–3]. We may mitigate future misjudgments through a greater understanding of how development affects the factors that govern drug and toxicant response in the newborn and young infant. Such knowledge may help ensure safe exposures to therapeutic or inadvertent compounds.

Pharmacokinetic and pharmacodynamic processes contribute to the significant differences in therapeutic efficacy and toxicant susceptibility observed between newborns, young infants and adults. With postnatal development, growth and functional maturation of the biochemical and physiological factors governing pharmacokinetics may alter the processes of absorption, distribution, metabolism and excretion. As well, these developmental changes proceed along a continuum, at different rates and patterns, resulting in tremendous interindividual variability in infant pharmacokinetics. The dynamic and highly variable character of postnatal maturation of infant pharmacokinetic and pharmacodynamic processes may have significant consequences on the way newborns and infants respond to and deal with drugs.

As its principal goal, this review discusses the affects of postnatal development on drug and toxicant pharmacokinetics in the newborn and early infancy. The article describes the age-dependent changes in the physiological and/or biochemical processes governing drug and toxicant pharmacokinetics. The article then extends these observations to discuss how developmental changes may lead to significant differences in absorption, distribution, metabolism and/or excretion between the newborn, infant and the adult. Such discussion should help explain the dynamic changes in therapeutic efficacy and toxicant susceptibility that occur through infancy.

1.1. Pharmacokinetics as a determinant of plasma concentration and response

Therapeutic and toxic responses generally correlate well with the plasma concentration of a compound. Because of this correlation, plasma concentrations may best indicate the potential safety and/or efficacy of the compound in the newborn and young infant. This presumes that the pharmacological or toxic response is direct (i.e., related to corresponding serum concentrations), expected (i.e., similar to adult response) and quantitatively similar to adults (i.e., similar pharmacodynamic parameters). A more difficult situation arises if the pharmacological or toxic response is indirect (i.e., unrelated to serum concentrations), novel (a function of the developing neonatal physiology/biochemistry) and quantitatively dissimilar to adults. Whether pharmacodynamic differences exist between pediatric population groups and adults is largely unknown. Given this presumption, two factors govern plasma concentrations, the size of the dose and the pharmacokinetic processes
of absorption, distribution, metabolism and excretion acting upon that dose. The following equations illustrate the influence of dose and pharmacokinetic processes on plasma concentrations of a compound, administered as either a multiple oral dose (Eq. (1)) or as a single oral dose (Eq. (2)).

\[ FD = \frac{\tau}{Cl_s} \] (multiple dose) (1)

or

\[ C_t = \frac{Fk_aD}{V_d(k_a - k_e)} \left( e^{-\frac{Cl}{V_d}} - e^{-\frac{Cl}{V_d}t} \right) \] (single dose) (2)

where \( \hat{C} \) is the average steady state plasma concentration; \( F \) is the bioavailability; \( D \) is the dose; \( \tau \) is the dosing interval; \( Cl_s \) is the systemic clearance; \( C_t \) is the plasma concentration at any time, \( t \); \( k_a \) is the absorption rate constant; \( k_e \) is the elimination rate constant and is equal to \( Cl_s/V_d \); \( V_d \) is the volume of distribution; and \( t \) is time.

According to Eqs. (1) and (2), larger doses \( (D) \) result in higher plasma concentrations of an administered compound. As well, these equations clearly illustrate the importance of absorption (indicated in the \( F \) and \( k_a \) terms), distribution (indicated in the \( V_d \) term), and metabolism and excretion (indicated in the \( Cl_s \) and \( k_e \) terms) as determinants of plasma concentrations in the newborn and young infant. Rapid changes in body size and composition, organ size and function, and maturation of the underlying physiological and biochemical processes that govern absorption, distribution, metabolism, and excretion characterize the immediate postnatal period. These developmental changes cause major age-related changes in drug absorption, distribution and elimination (metabolism and excretion), which may have a significant impact on plasma concentrations and the resultant exposure outcomes. Additionally, maturation is a dynamic process influenced by a plethora of genetic and environmental factors. The rate and pattern of maturation of each pharmacokinetic process may vary greatly among infants. This may result in marked interindividual variability in pharmacokinetics such that infants of similar age may exhibit differences in toxicant susceptibility or therapeutic efficacy.

In general, the combined effects of maturation of each pharmacokinetic process on the plasma levels of a given compound are not well understood. Premature birth (gestational age <36 weeks) and underlying pathophysiology further complicate the relationship between plasma concentrations and response and the age-related changes in pharmacokinetics. Premature infants exhibit more pronounced anatomical and functional immaturity of the organs involved in pharmacokinetic processes. The extent to which premature infants differ from the full-term infant correlates directly with the degree of prematurity [4]. This enhanced immaturity, as well as any underlying disease state(s), may impede normal postnatal development of the processes of absorption, distribution and elimination. How these and other factors may contribute to age-dependent pharmacokinetics in newborns and infants requires consideration. The proceeding discussion will summarize the available literature on the influence of postnatal maturation on drug absorption, distribution, metabolism and excretion principally in the full-term infant.

2. Absorption

Age-related differences in absorption relate to developmental changes in those factors governing passive or carrier-mediated transport across the absorptive barrier. Systemic bioavailability becomes an important consideration when compounds are absorbed from extravascular administration sites. The absorptive characteristics of the compound and the possible influence of first-pass effects may limit the systemic bioavailability of the compound. This may lead to lower plasma concentrations of the compound and reduced exposures.

2.1. Gastrointestinal absorption

Table 1 summarizes the age-dependent anatomical and physiological factors that may influence the rate and/or extent of gastrointestinal absorption. Developmental changes in one or any combination of these factors may explain the differences in absorp-
Table 1

<table>
<thead>
<tr>
<th>Physiological factor</th>
<th>Newborn (full-term)</th>
<th>Neonate (1 day–1 month)</th>
<th>Infant (1 month–2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric pH</strong></td>
<td>1–3</td>
<td>&gt;5</td>
<td>~Adult</td>
</tr>
<tr>
<td><strong>Gastric emptying time</strong></td>
<td>Reduced (variable)</td>
<td>Reduced (variable)</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Intestinal surface area</strong></td>
<td>Reduced(^a)</td>
<td>Reduced(^a)</td>
<td>~Adult</td>
</tr>
<tr>
<td><strong>Intestinal transit time</strong></td>
<td>Reduced</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Pancreatic and biliary function</strong></td>
<td>Very immature</td>
<td>Immature</td>
<td>~Adult</td>
</tr>
<tr>
<td><strong>Bacterial flora</strong></td>
<td>Very immature</td>
<td>Immature</td>
<td>Immature</td>
</tr>
<tr>
<td><strong>Enzyme/transporter activity</strong></td>
<td>Very immature</td>
<td>Immature</td>
<td>Approaching adult</td>
</tr>
<tr>
<td><strong>Pharmacokinetic outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate and extent of absorption</td>
<td>Variable</td>
<td>Variable</td>
<td>̃= Adult</td>
</tr>
<tr>
<td>Gastrointestinal first-pass effects</td>
<td>Very reduced</td>
<td>Reduced</td>
<td>Approaching adult</td>
</tr>
</tbody>
</table>

\(^a\) Adapted from Besunder et al. [7].

\(^b\) From Ref. [8].

Age-dependent factors affecting gastrointestinal absorption and the resultant pharmacokinetic outcome relative to adult levels

Gastrointestinal pH affects the absorption of weakly acidic and basic organic compounds. At birth, newborns have an alkaline gastric pH (pH 6–8) [9,10]. Gastric acid production increases over the next 24–48 h to achieve adult pH levels (pH 1–3) [11–13]. Following this initial burst of hydrochloric acid secretion, gastric acid production declines and gastric acidity remains relatively low in the first months of life [11,14]. Postnatal increases in gastric acid production generally correlate with postnatal age [15] and, on a per kg basis, adult levels are approached by 2 years of age [16].

The pharmacokinetic consequences of high gastric pH in the newborn and young infant may involve enhanced bioavailability of weakly basic compounds, but reduced bioavailabilities of weakly acidic compounds. This may explain the increased bioavailability of ampicillin and penicillin G (basic drugs) [17–19] and decreased bioavailability of phenobarbital (acidic drug) [19,20] observed in young infants.

Certain compounds require pancreatic exocrine and biliary function for adequate absorption. Newborns have immature pancreatic and biliary function at birth [21]. The levels of most pancreatic enzymes are significantly reduced [22], and bile formation, bile acid pool size (50% adult values), bile acid synthesis and metabolism, and bile acid intestinal absorption are all reduced in the newborn [23–25]. Pancreatic and biliary function rapidly develop in the postnatal period [22,26]. A deficiency of bile salts and pancreatic enzymes may result in a reduction in the bioavailability of those drugs that require solubilization or intraluminal hydrolysis (i.e., prodrug esters) for adequate absorption.

2.1.1. Gastrointestinal secretions

Gastrointestinal pH affects the absorption of weakly acidic and basic organic compounds. At birth, newborns have an alkaline gastric pH (pH 6–8) [9,10]. Gastric acid production increases over the next 24–48 h to achieve adult pH levels (pH 1–3) [11–13]. Following this initial burst of hydrochloric acid secretion, gastric acid production declines and gastric acidity remains relatively low in the first months of life [11,14]. Postnatal increases in gastric acid production generally correlate with postnatal age [15] and, on a per kg basis, adult levels are approached by 2 years of age [16].

2.1.2. Gastrointestinal motility

Gastrointestinal motility may affect the rate and/or extent of drug absorption. In general, newborns exhibit delayed gastric emptying rates and prolonged intestinal transit times relative to the adult [27,28]. The full-term newborn infant demonstrates qualitatively similar gastrointestinal motility patterns with the adult, but premature infants exhibit disorganized motility patterns.
and inefficient motility patterns [29,30]. In general, feeding triggers the postnatal development of gastrointestinal motility [5]. Reduced gastrointestinal motility may have variable and unpredictable effects on drug bioavailability in newborns and young infants. In general terms, delayed gastric emptying may reduce the rate of drug absorption since the small intestinal mucosa acts as the principal absorptive site for most drugs. Alternatively, slower intestinal transit times may improve drug bioavailability due to longer retention times in the small intestine. The exact effect of developmental maturation of gastrointestinal motility on drug bioavailability depends upon the physico-chemical properties of the drug and its interaction with the anatomical and physiological factors of the gastrointestinal tract.

2.1.3. Gastrointestinal metabolism and transport

Bacterial flora, principally concentrated in the ileum and colon [31], may influence the extent of drug absorption due to its influence on gastrointestinal motility and ability to metabolize compounds [32]. At birth, infant gastrointestinal flora is very immature and little information is available on the effect of postnatal maturation of bacterial flora on bioavailability [32,33]. In general, the bacterial flora of the infant gastrointestinal tract approaches adult populations by 4 years of age [34].

The proximal small intestine acts as the principal absorptive site and site for significant first-pass effects for many orally administered compounds. In the adult, the small intestinal mucosa functionally expresses a limited number of phase I and phase II enzymes and their expression has led to significant inter- and intra-individual variability in oral bioavailability [35]. Cytochrome P450 (CYP) 3A4 is the predominant CYP enzyme expressed in enterocytes [36,37], and CYP2C has the second highest expression levels [37]. Very low activity levels for CYP1A1 [38] and CYP2D6 [35,39] were detected in intestinal microsomes. The maturation of CYP enzymes in the intestinal mucosa remains largely uninvestigated. One study reported significantly lower CYP3A4 activity levels in intestinal microsomes from infants aged 0–3 months and a developmental increase in activity with age [40]. As well, CYP3A7, the fetal hepatic form of CYP3A, appears to lack expression in extrahepatic tissues [41].

The developmental maturation of gastrointestinal Phase II conjugation enzymes [42–47] remains unknown. However, β-glucuronidase activity of the infant small intestine has been reported to exceed adult activities by as much as 7-fold [48]. This enhanced β-glucuronidase activity may enable re-absorption of glucuronide drug conjugates. For drugs that undergo enterohepatic recirculation (i.e., chloramphenicol, indomethacin) β-glucuronidase activity enhances their bioavailability.

The adult intestinal tract functionally expresses various members of the ATP-binding cassette and solute carrier transporter families [49,50]. These transporters may have an important impact on drug absorption and bioavailability in the small intestine [51], but their exact role remains largely unknown. The literature provides evidence of postnatal maturation of transport protein activities in other organ systems [52–58] suggesting gastrointestinal transporter function may also undergo postnatal maturation.

2.2. Gastrointestinal first-pass effects

The gastrointestinal tract may play an important role in the first pass metabolism of an orally administered compound [51]. Consequently, developmental maturation of gastrointestinal metabolic and transport function may have significant consequences in gastrointestinal first-pass effects and oral bioavailability. In adults, some drugs undergo extensive metabolism in the gastrointestinal tract with a concomitant marked reduction in their oral bioavailability [59–61]. Immature gastrointestinal metabolic reactions may result in improved oral bioavailability as gastrointestinal first-pass metabolism has less influence on the extent of absorption of such drugs. Conversely, some drugs are dependent upon carrier-mediated uptake systems in the intestinal mucosa for their efficient absorption [62]. Immature development of transport function may lead to significantly reduced oral bioavailability.

Some transporter proteins expressed in the intestinal mucosa promote the active extrusion of drug from the enterocyte back into the lumen of the gastrointestinal tract after its absorption (i.e., MDR1) [63,64]. These transporter proteins compete with absorption processes and may decrease the rate of absorption and, potentially, the oral bioavailability.
The interplay between CYP3A4 and the active efflux transporter, MDR1, illustrates this concept [63,64]. Again, immature development of these active efflux processes may result in enhanced oral bioavailability. The exact effect of postnatal maturation on oral bioavailability will depend upon the interaction of the principal factors influencing bioavailability (physico-chemical properties of the compound, physiology and anatomy of the gastrointestinal tract, metabolic enzymes, transport processes) [51] and the degree of their postnatal maturation.

3. Distribution

Postnatal changes in body composition, extent of binding to plasma proteins and tissue components, and hemodynamic factors (cardiac output, tissue perfusion and membrane permeability) may alter distribution characteristics in the developing infant. The apparent volume of distribution \( V_d \) provides a useful marker to assess age-related changes in drug distribution.

3.1. Body composition and tissue perfusion

Body composition may significantly affect drug \( V_d \). Changes in body composition correlate with both gestational and postnatal age. Table 2 illustrates total body water, total protein and total fat content in the newborn, during infancy and in the adult stages. Total body water decreases significantly in the early postnatal period [65], while total body fat increases progressively in the first months of life [66].

Age-related changes in total body water are primarily attributed to decreases in the relative percentage of extracellular water [65,67]. Extensive tissue binding or partitioning into fat contribute to large \( V_d \) values. Polar compounds generally exhibit \( V_d \) equivalent to total body water or blood volumes. Hence, age-related changes in fat, muscle and total body water composition may produce significant quantitative changes in \( V_d \) and plasma concentrations. In newborns, the high relative proportion of total body water and low proportion of fat results in a general increase in \( V_d \) for water-soluble compounds and a lower \( V_d \) for fat-soluble drugs relative to adults.

Key pharmacokinetic parameters (i.e., clearance and volume of distribution) are often ‘normalized’ according to total body weight or body surface area. Therefore, it is critical to understand the developmental changes in these body indices with postnatal age, which is depicted in Fig. 1. While both total body weight and surface area rise steadily during the first year of life, a considerable change in their ratio occurs during the initial 3 months of life.

Developmental changes in \( V_d \) may also relate to postnatal enhancements in cardiac output, organ blood flows and tissue perfusion, changes in membrane permeabilities [70–72] and maturation of carrier-mediated transport systems [55–58,73–75], and changes in tissue binding affinities or capacities since newborns and young infants have significantly

<table>
<thead>
<tr>
<th>Age</th>
<th>Body mass (kg)</th>
<th>Water</th>
<th>Protein</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn: full-term</td>
<td>3.5</td>
<td>74</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>4 months</td>
<td>7.0</td>
<td>61.5</td>
<td>11.5</td>
<td>27</td>
</tr>
<tr>
<td>12 months</td>
<td>10.5</td>
<td>60.5</td>
<td>15</td>
<td>24.5</td>
</tr>
<tr>
<td>Adult</td>
<td>70</td>
<td>55–60</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\( ^a \) Adapted from Geigy Scientific Tables [66].

\( ^b \) Obesity decreases the percentage of total body water.
greater liver, kidney and brain masses relative to total body mass [66,67,76].

3.2. Plasma protein binding

Postnatal development of plasma protein binding may affect both the distribution and elimination of compounds in the newborn and young infant. In general, newborns and young infants exhibit larger unbound fractions of a compound relative to the adult. This may result in enhanced distribution into tissues and a larger \( V_d \). Age-related differences in plasma protein binding affinity, plasma protein concentrations and availability of competing endogenous compounds largely explain the differences in the extent of binding.

Compounds bind principally to albumin and \( \alpha_1 \)-acid glycoprotein. Albumin is the major plasma protein [77], and concentrations of \( \alpha_1 \)-acid glycoprotein, an acute phase reactant protein [78], fluctuate significantly in response to various diseases, trauma or chemical insult [79,80]. In general, the newborn may exhibit lower binding affinities of compounds (i.e., penicillin, phenobarbital, phenytoin and theophylline) [81] to albumin and \( \alpha_1 \)-acid glycoprotein [82–84]. High unbound fractions may lead to significantly larger \( V_d \) values, and enhanced renal clearance by glomerular filtration and hepatic clearance of low extraction ratio compounds in the newborn.

Developmental changes in plasma protein concentrations have the most significant affect on the extent of plasma protein binding in the young infant. Total plasma protein levels are lower in the newborn relative to the adult [85]. Lower plasma protein levels reduce the plasma protein binding capacity in the newborn. Fig. 2 illustrates the postnatal increase in albumin and \( \alpha_1 \)-acid glycoprotein concentrations relative to adult levels. A strong correlation exists between the postnatal increase in plasma albumin concentrations and the fraction bound [86]. This suggests adult binding characteristics (i.e., unbound fraction) for a given compound and the ratio of infant and adult albumin concentrations may provide an estimate of infant unbound fractions for that compound [86]. On the other hand, a weak correlation exists between the postnatal increase in \( \alpha_1 \)-acid glycoprotein plasma concentrations and the fraction bound in the infant relative to the adult [86].

Several endogenous substances (i.e., bilirubin, fatty acids) may compete for plasma protein binding sites [82,87–89]. This competition may further reduce the bound fraction of a compound in the newborn, or cause displacement of the endogenous molecule from its protein binding sites. For instance hyperbilirubinemia reduces the binding of the acidic drugs ampicillin, penicillin, phenobarbital and phenytoin [81,90]. Conversely, displacement of bilirubin by drugs (i.e., sulfonamides) may enhance the risk for bilirubin encephalopathy [7]. Hepatic and renal disease, hypoproteinemia due to malnutrition, cystic fibrosis, burns, malignant neoplasms, surgery, trauma and acidosis may further decrease plasma protein drug binding due to decreased protein synthesis or competition for binding.

4. Elimination

Systemic clearance provides a measure of the efficiency of elimination and is often the most important pharmacokinetic determinant of plasma concentrations and resultant response (see Eq. (1)). In general, hepatic and/or renal elimination pathways effect the removal of most compounds from the body. These pathways are generally underdeveloped and inefficient in the newborn. The various pathways
of elimination mature at different rates and patterns of development and maturation to adult levels (adjusted for body weight differences) is generally achieved after the first year of postnatal life. Recent in vitro and in vivo probe substrate data have provided important information on the maturation characteristics of hepatic and renal elimination mechanisms (reviewed in Alcorn and McNamara, 2002 [91]). This data provides the basis for the proceeding discussion. Additionally, for more in depth discussion of the maturation of systemic clearance mechanisms the reader is referred to excellent reviews by Hakkola et al. [92], Ring et al. [93], Gow et al. [94], McCarver and Hines [95], Hines and McCarver [96], de Wildt et al. [97], and Hayton [98].

4.1. Hepatic clearance

Hepatic blood flow, plasma protein binding and intrinsic clearance (defined as the maximal enzymatic or transport capacity of the liver) constitute the physiological determinants of hepatic clearance [99,100]. Each of these determinants undergoes significant postnatal changes, and their maturation results in an enhanced capacity for hepatic elimination of compounds with advancing postnatal age.

4.1.1. Intrinsic clearance

Intrinsic clearance processes principally govern the capacity of newborns to eliminate drug by the liver. Although hepatocellular transport and biliary excretion processes contribute to intrinsic clearance and are deficient at birth [74,101,102], hepatic biotransformation processes have the greatest impact on hepatic drug elimination in the developing infant. Phase I and Phase II reactions principally mediate the metabolism of compounds in the developing infant. Often a compound undergoes sequential metabolism with Phase I metabolic reactions preceding Phase II metabolism [103].

Of the phase I reactions, cytochrome P450 (CYP) enzymes have the most important role in the elimination of most compounds. The postnatal maturation of other Phase I enzymes, such as the alcohol and aldehyde dehydrogenases, esterases and the flavin-containing monoxygenases, are reviewed in Hines and McCarver, 2002 [96]. Important phase II reactions include glucuronidation, sulfation, glutathione conjugation, and acetylation. Since most compounds are eliminated by more than one metabolic pathway, postnatal changes in the efficiency of Phase I and Phase II reactions, differences in their rate and pattern of development, and changes in the hepatocellular distribution and expression of Phase I and Phase II enzymes [104] may have a significant impact on the qualitative and quantitative characteristics of hepatic elimination in the newborn and developing infant. To predict the exact nature of these consequences requires an understanding of the postnatal maturation of the individual hepatic metabolic pathways that mediate drug and toxicant removal from the body.

4.1.1.1. Cytochrome P450 enzyme-mediated metabolism

The CYP enzymes represent a superfamily of heme-containing enzymes [105], CYP1A2, CYP2A6, CYP2B6, CYP2C’s, CYP2D6, CYP2E1, and CYP3A4/7 comprise the principal CYP enzymes important in drug and toxicant metabolism [106–108]. The rate and pattern of postnatal CYP enzyme development may have a significant impact on therapeutic efficacy and toxicant susceptibility in the newborn and developing infant. Interindividual differences in their developmental patterns, genetic polymorphisms, and their induction/inhibition potential further complicate the role of CYP enzyme maturation on pharmacokinetics in the newborn and young infant.

The postnatal maturation of CYP enzymes is evidenced in numerous literature reports of shortening half-lives and enhanced hepatic elimination of drugs in developing infants [109,110]. These studies suggest hepatic metabolic pathways undergo rapid postnatal development. Recently, in vitro studies have examined the maturation of individual CYP enzymes in age-dependent fetal and infant hepatic microsomes [111–115]. These studies corroborate the findings of the in vivo studies and have further elucidated the maturation characteristics of individual CYP enzymes. As well, these studies have shown the CYP enzymes mature at characteristic rates and patterns of development and may be grouped according to their general developmental pattern of activity [116]. Fig. 3 highlights the general pattern of CYP enzyme development as a fraction of adult levels.
biotransformation and, in general, CYP enzyme-mediated metabolism improves with postnatal age and generally approaches adult levels only after the first year of life [117,120]. Table 3 summarizes the maturation of individual CYP enzyme activity levels based upon in vitro determinations of CYP enzyme activity in fetal, infant and adult age group hepatic microsomes [111–115].

4.1.1.1. Maturation of individual CYP enzymes Fetal hepatic microsomes exhibit negligible CYP1A2 enzyme activity [107,121,122]. CYP1A2 enzyme activity remains very low after birth and significant in vitro activity is detected only by 1–3 months of age [112]. By the first year of life CYP1A2 enzyme activity levels are only 50% adult values and mature to adult activity levels sometime after a year of age [112,120]. This pattern of development explains the long half-life and low systemic clearance values of theophylline in the newborn [123]. Immature CYP1A2 enzyme development prevents the biotransformation of theophylline resulting in prolonged half-lives in the newborn and infant. Significant increases in theophylline systemic clearance values are observed only after 1–3 months of age [123,124]. This pattern of theophylline clearance with advancing postnatal age reflects the postnatal development of in vitro CYP1A2 enzyme activity in the infant.

Fetal livers fail to express CYP2A6 and CYP2B6 enzyme activity [107,122]. Otherwise, the postnatal development of CYP2A6 and CYP2B6 remains largely unknown. Both CYP enzymes likely achieve adult capacities only after the first year of life [120].

Fetal and newborn (<1 week of age) livers demonstrate very limited CYP2C enzyme activity.

Table 3

<table>
<thead>
<tr>
<th>CYP enzyme</th>
<th>Fraction of adult activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fetus</td>
</tr>
<tr>
<td>1A2</td>
<td>0.05</td>
</tr>
<tr>
<td>2C</td>
<td>–</td>
</tr>
<tr>
<td>2D6</td>
<td>0.04</td>
</tr>
<tr>
<td>2E1</td>
<td>–</td>
</tr>
<tr>
<td>3A4</td>
<td>0.03</td>
</tr>
<tr>
<td>3A7</td>
<td>5</td>
</tr>
</tbody>
</table>

Adapted from Refs. [111–115].
Within the first month of postnatal life, CYP2C enzyme activity surges to 50% adult levels. After this surge of activity, CYP2C enzyme activity levels decline slightly for the first year of life and adult levels are reached sometime after 1 year of age. As a substrate of the CYP2C enzyme subfamily, diazepam metabolite urinary levels are consistent with the in vitro pattern of CYP2C enzyme development. Newborns exhibit very low urinary diazepam metabolite levels. However, diazepam urinary metabolite levels increase significantly in infants greater than 1-week-old. Thereafter, metabolite levels remain relatively stable in children up to 5 years of age.

Fetal livers may express very low levels of CYP2D6 enzyme activity. A dramatic increase in CYP2D6 activity occurs in the immediate postpartum period. By the first month of life, CYP2D6 enzyme activity levels reach ~30% adult levels, and CYP2D6 maturation may be completed by 1 year of age. In vivo assessment of the hepatic clearance of CYP2D6 substrates is lacking in the newborn and young infant.

Fetal hepatic microsomes may express low levels of CYP2E1 enzyme activity. Parturition triggers a dramatic increase in CYP2E1 enzyme activity within the first 24 h of life. CYP2E1 enzyme activity levels achieve 50% adult levels by 1–3 months of age and development is essentially complete after 1 year of age.

CYP3A subfamily is the most abundantly expressed CYP enzyme in the liver. CYP3A4 enzyme is the principal enzyme of the adult liver, while fetal livers predominantly express CYP3A7 enzyme. Although CYP3A4 and CYP3A7 enzymes exhibit 95% similarity in their nucleotide sequences, important differences in substrate specificities exist between these two CYP3A enzymes. Few studies have examined the substrate profile of CYP3A7 enzyme. The ability of fetal livers to metabolize a wide variety of substrates suggests CYP3A7 enzyme also may metabolize a wide range of substrates and demonstrate some substrate overlap with CYP3A4 enzyme.

Total CYP3A enzyme protein levels remain relatively constant throughout development. Fetal livers demonstrate high levels of CYP3A7 enzyme activity and express limited CYP3A4 enzyme activity (~10% adult levels). CYP3A7 enzyme activity levels peak 1 week after parturition, then declines significantly during the first year of life. Adult livers may express only 10% fetal levels. During the postnatal period, activity levels of CYP3A4 enzyme increase concomitantly with the decreases in CYP3A7 enzyme activity. CYP3A4 enzyme activity reaches 30–40% adult levels by 1 month of age and adult levels by 1 year. The pharmacokinetic consequences of this postnatal developmental switch from CYP3A7 to CYP3A4 remain largely unknown since the substrate profile of CYP3A7 enzyme has received limited investigation. However, some studies suggest newborns and adults will exhibit significant differences in their capacity to eliminate known CYP3A4 enzyme substrates. For example, premature and full-term newborns eliminate the CYP3A4 enzyme substrate, midazolam, with poor efficiency. A 5-fold increase in the elimination efficiency of midazolam occurs by 3 months of age. These data suggest midazolam is not an efficient CYP3A7 enzyme substrate.

### 4.1.1.2. Phase II metabolism

Phase II or conjugation reactions contribute significantly to the elimination of a wide variety of exogenous and endogenous compounds. Glucuronidation, sulfation, acetylation, glutathione conjugation, comprise the most important Phase II pathways in drug and toxicant metabolism. In general, changes in the expression patterns of the different Phase II enzymes or changes in their catalytic efficiency may occur with development. Such changes may have important consequences on the elimination of compounds in the newborn and young infant. In general, inefficient conjugation capacity of the newborn will result in a significant reduction in the ability of the newborn to eliminate both exogenous and endogenous compounds. Table 4 and Fig. 3 summarize the known maturation patterns of important Phase II enzymes. For a more in depth discussion of the development of Phase II metabolic pathways, the reader is referred to the review by McCarver and Hines.

#### 4.1.1.2.1. Maturation of individual conjugation reactions

The uridine 5'-diphosphate-glucuron-
Table 4: Maturation patterns of phase II enzymes

<table>
<thead>
<tr>
<th>Phase II enzyme</th>
<th>Maturation pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGT</td>
<td>Fetal livers exhibit limited enzyme activity; activity ( \sim 25% ) adult levels at 3 months; maturation is isoforms specific; adult activity levels achieved by 6–30 months.</td>
</tr>
<tr>
<td>ST</td>
<td>Fetal livers exhibit significant activity; maturation is isoform specific.</td>
</tr>
<tr>
<td>GST</td>
<td>Fetal livers exhibit significant activity; maturation is isoform specific; total activity remains stable throughout infancy.</td>
</tr>
<tr>
<td>NAT</td>
<td>Fetal livers exhibit low activity; low activity at birth through the first months of life; adult levels achieved after 1 year of age.</td>
</tr>
</tbody>
</table>

UGT, Uridine 5'-diphosphate-glucuronosyltransferase; ST, Sulfotransferase; NAT, \( N \)-acetyltransferase; GST, Glutathione-S-transferase.

Sulfotransferases (ST) consist of a number of individual enzymes and have substrate specificities that demonstrate significant overlap with the UGT enzymes [148]. Although changes in activity of the individual ST enzymes with development occur, the data on their development is limited and confusing. In general, fetal, newborn and infant livers express significant ST activity, and sulfate conjugation is a relatively efficient pathway at birth [149–151]. Consequently, the newborn and young infant may eliminate ST enzyme substrates very efficiently. For instance, the ST and UGT enzyme substrate ritodrine, a \( \beta_2 \)-adrenoceptor agonist, underwent extensive sulfate conjugation in infants [149]. The study demonstrated no age-related differences in the overall systemic clearance of ritodrine, only quantitative differences in metabolite levels (glucuronide conjugates and sulphate conjugates) between infants and adults [149].

Glutathione-S-transferases (GST) represent a superfamily of dimeric enzymes responsible for the detoxification of a number of potentially toxic drug or drug metabolites [152]. Five different subunit classes (\( \mu, \alpha, \theta, \pi \) and \( \zeta \)) of GST enzymes have been classified [152,153]. As with the ST enzymes, the GST enzymes demonstrate age-related expression of individual enzymes in the liver [154–156]. For example, preterm newborn livers exhibited 60% greater activity towards chloramphenicol than fetal livers, but showed similar activity levels towards chlorodinitrobenzene [157]. However, the literature remains sparse and presents conflicting information with respect to individual enzyme development [156,157]. In general, though, GST activity is relatively well-developed in the newborn and infant, and total GST activity may remain relatively stable throughout development [158]. The clinical significance of the quantitative and qualitative differences in the developmental expression of individual GST enzymes remains unknown, but may have important implications in toxicant susceptibility.

\( N \)-acetyltransferases (NAT) consist of two enzymes, NAT1 and NAT2, and NAT2 demonstrates polymorphic activity [159–161]. Very limited data exists on the developmental expression of NAT1 and NAT2 enzyme activity. Fetal livers express activity
towards several NAT enzyme substrates, but at much lower levels than the adult \[47,162\]. Consequently, the newborn exhibits a limited capacity to acetylate substrates. The acetylation status of the infant may reflect adult levels only well past the first year of life \[163–165\].

4.1.1.3. Consequences of variability in the postnatal maturation of phase I and phase II reactions

Many compounds undergo multiple routes of metabolism. Quantitative and qualitative differences in the developmental expression profiles of metabolic pathways of the liver may modify the rate and pattern with which newborns and infants eliminate compounds throughout development. These interindividual differences may lead to altered metabolite profiles as the relative contribution of the different routes of metabolism may vary with infant age. Differences in metabolite profiles become significant when a particular metabolite has pharmacological or toxicological activity. Consequently, the rate, pattern and extent of metabolic pathway maturation are important considerations in the pharmacokinetic consequences of postnatal maturation of hepatic clearance pathways. Interindividual differences in the rates and patterns of individual elimination pathway maturation may largely explain the tremendous interindividial variation observed in the capacity of newborns and infants to eliminate drugs. Superimposed upon the interindividial variability in metabolic enzyme maturation is the influence of metabolic enzyme induction and/or inhibition. In utero and/or postnatal exposure to certain exogenous or endogenous compounds may cause rapid enzyme induction or inhibition in the fetus, newborn and infant \[166\]. This will further exacerbate the variable rate and pattern of enzyme maturation. For example, newborns treated concomitantly with barbiturates, a CYP2C inducer \[114\], exhibited a marked reduction in diazepam (a CYP2C substrate) half-lives \(t_{1/2} = 18\pm1\ h\) as compared with newborns treated with diazepam alone \(t_{1/2} = 31\pm2\ h\) \[114,167\]. Furthermore genetic polymorphisms in CYP2D6, CYP2C9, CYP2C19, CYP2E1, UGT and NAT \[168\] may further enhance the interindividial variability in drug elimination characteristics observed in infants. Polymorphisms in drug metabolism and the potential for enzyme induction and/or inhibition complicate any assessment of elimination capacity in the newborn and young infant.

4.1.2. Hepatic first-pass effects

For many drugs subject to first-pass effects, hepatic metabolism results in a significant reduction in the oral bioavailability of a compound. Postnatal maturation of metabolic enzyme pathways and hepatocellular transport systems may result in significant differences in the oral bioavailability of compounds in the newborn and young infant relative to the adult. For all orally administered compounds, plasma protein binding and intrinsic clearance determine the extent of parent drug bioavailability \[99\]. Newborns generally exhibit lower plasma protein binding capacities. Higher unbound fractions of an absorbed compound may theoretically enhance oral clearance and result in lower oral bioavailability of the compound. For most drugs, intrinsic clearance has the most important effect on bioavailability. At birth, immature Phase I and Phase II metabolic enzyme pathways and hepatocellular transport processes may significantly reduce the extent of first-pass hepatic metabolism of an absorbed compound. Inefficient hepatic metabolism in the newborn may cause enhanced oral bioavailabilities relative to the adult. Maturation of the hepatic metabolic pathways will result in age-related reductions in oral bioavailability. As with hepatic clearance, interindividual differences in the rate and pattern of metabolic enzyme pathway maturation may cause significant interindividial variation in oral bioavailability during postnatal development. Hence, postnatal maturation of hepatic metabolism may greatly influence therapeutic efficacy and toxicant susceptibility because hepatic metabolism may determine the both the oral bioavailability of a compound and the efficiency with which the newborn or young infant may remove that compound from the body.

4.2. Renal clearance

Renal clearance mechanisms include glomerular filtration (GFR), tubular secretion and tubular reabsorption. At birth, these renal clearance mechanisms are incompletely developed and renal elimination capacity of the newborn is significantly compromised \[169–171\]. During late gestation and early
postnatal development profound anatomical and functional changes in the kidney greatly enhance renal elimination efficiency in the first few months of life [172,173]. Renal functions demonstrate a rapid maturation and generally reach adult levels before 1 year of age [174–176]. Maturation of glomerular filtration and renal tubular functions proceed at different rates and patterns resulting in marked interindividual variability in renal elimination efficiency.

The anatomical and functional development of the kidney continues throughout gestation into the early postnatal period. Nephrons increase in number until nephrogenesis is completed at 36 weeks of gestation [185]. Prior to 36 weeks gestation, then, changes in renal function principally correlate with increases in the number of nephrons [179–181]. Incomplete nephrogenesis in the pre-term newborn will compromise glomerular and tubular function [182]. Functional maturation and growth processes explain the changes in renal elimination capacity in the full-term infant [98,172]. In general, postnatal functional maturation of the kidney is associated with enhancements in renal blood flow, improvements in glomerular filtration efficiency and the growth and maturation of renal tubules and tubular processes [98].

4.2.1. Glomerular filtration

During the fetal stages, GFR capacity is significantly reduced [172]. Parturition triggers enhancements in both cardiac output and renal blood flow and a dramatic decrease in renal vascular resistance and a redistribution of blood flow within the kidney [172,183–185]. These hemodynamic changes cause a rapid increase in GFR during the early postnatal period [4,171,186–190]. At birth, GFR, normalized to body surface area, in the full-term infant is 10–15 ml/min/m² [169,171], but increases to 20–30 ml/min/m² within the first 2 weeks of life [171,191]. By 6 months of age, infant GFR, normalized to body surface area has approached adult levels (73 ml/min/m²) [192]. Rapid improvements in GFR result in rapid enhancements in the renal clearance of compounds principally eliminated by GFR.

Postnatal improvements in GFR correlate with gestational age rather than postnatal age [4,193–195]. Premature infants exhibit lower GFR values on average and a slower pattern of GFR development during the first 1–2 weeks postpartum as compared with the full-term infant [4,183,196]. With completion of nephrogenesis and maturation of glomerular function, enhancements in GFR in the preterm infant will proceed at the same rate as full-term infants [183]. However, even by 5 weeks of age the absolute value for GFR remains lower in preterm infants [183]. This functional delay in GFR in preterm infants is an important consideration in the estimation of an infant’s capacity for renal elimination. Interestingly, Fig. 4 illustrates infant GFR, on an ml/min/kg basis, is roughly comparable to the adult [185]. This implies adult renal clearance values normalized to a body weight may reasonably predict infant renal clearances on a body weight basis.

4.2.2. Renal tubular function

At birth, the renal tubules exhibit significant anatomic and functional immaturity [197]. Incomplete anatomical development of renal tubules compromises both passive reabsorption [188,198] and active secretion and reabsorption processes [199–201]. In addition to limited tubular size and functional maturity, poor peritubular blood flow, reduced urine concentrating ability, and lower urinary pH values further compromise renal tubule function in the newborn [202]. In general, renal tubular growth processes, maturation of renal tubular transport systems, and redistribution of blood flow to the secretory areas of the kidney account for the enhancements...
Numerous protein carrier systems mediate active renal excretion and reabsorption. Their postnatal development at the renal tubular epithelium and their impact on renal elimination efficiency in the newborn and infant remains largely unknown. Functionally, the kidney exhibits a reduced capacity to excrete weak organic acids like penicillins, sulfonamides, and cephalosporins [200,201]. Newborn kidneys excrete p-aminohippurate (PAH), a substrate for the organic anion transporters, at 20–30% adult levels [187], and adult excretion levels are approached by 7–8 months of age [176]. Premature and full-term infants excrete furosemide, a PAH transport pathway substrate, slowly with plasma half-lives of 19.9 and 7.7 h, respectively, as compared with 0.5 h in the adult [206,207]. In utero or infant exposure to certain agents may induce or inhibit renal tubular transport functions [174]. Transport induction or inhibition may compound the variability observed in renal clearance values in newborns and young infants. The low urinary pH values relative to the adult may influence the reabsorption of weak organic acids and bases, and differences in renal drug elimination may reflect a discrepancy in urinary pH values [166].

The anatomical and functional immaturity of the newborn kidney leads to reduced renal clearances of compounds during the early postnatal period. Differences in the rate of development of glomerular filtration and tubular function (i.e., the glomerulotubular imbalance) and the potential for the induction or inhibition of renal glomerular and tubule transport function [208] may have variable and complex effects on the renal elimination.

5. Conclusions

Postnatal maturation of pharmacokinetic processes has significant implications with respect to systemic exposure levels and the safety and/or efficacy of a compound in the newborn and young infant. Functional immaturity of absorption, distribution, metabolism and/or excretion processes contribute to the disparate responses observed between newborns, infants and adults. Premature infants present a further complication as the anatomical and functional immaturity of the organs and other biochemical and physiological processes involved in drug pharmacokinetics is further exacerbated. An assessment of the therapeutic efficacy or toxicant susceptibility of a newborn to an exposure will require a careful consideration of the developmental aspects of pharmacokinetic processes. In general, the combined effects of age-related changes in each pharmacokinetic process on plasma levels of a compound are poorly understood. Clinical studies encompassing newborns and infants within narrow postnatal age groups are needed to enhance our understanding of the pharmacokinetic and clinical consequences of postnatal maturation of absorption, distribution, metabolism and excretion processes. Such information will help to establish more effective guidelines to predict an exposure outcome in a newborn or young infant and to ensure safe exposures to therapeutic or inadvertent compounds.

References

[17] N.N. Huang, R.H. High, Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups, J. Pediatr. 42 (1953) 657–668.


[141] D.E. Rollins, C. von Bahr, H. Glauermann, P. Moldeus, A. Rane, Acetaminophen: potentially toxic metabolite formed...
by human fetal and adult liver microsomes and isolated fetal liver cells, Science 205 (1979) 1414–1416.


