Special Article

Developmental Pattern of Hepatic Drug-Metabolizing Enzymes in Pediatric Population and its Role in Optimal Drug Treatment

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Abstract

Pediatric pharmacokinetics (PK) and pharmacodynamics (PD) differ from adults in multiple aspects. The extrapolation of PK/PD data from adults to children is not always simple because children are not small adults. Differential development of metabolic enzymes in children affects both PK and PD of a drug. Thus, the study of the developmental patterns of drug-metabolizing enzymes is essential to establish the PK and PD profile of drugs in the pediatric population. Further, these patterns may also aid to establish models for appropriate extrapolation of adult data for any newer drugs. We conducted a literature search on PubMed Central, Medline database, and Google Scholar with relevant search terms to obtain articles for this narrative review. The research on developing pattern of drug metabolizing enzymes is still evolving. This review presents an overview of the existing literature on developmental patterns of key metabolic enzymes in children. Greater emphasis needs to be given to study developmental pattern of metabolic enzymes as it not only helps drug development but also to optimize drug therapy in children.

Keywords: Adults, adverse drug reaction, children, dose, metabolism, ontogeny, pediatric population, pharmacokinetics

Introduction

Developmental changes in the expression of drug-metabolizing enzymes can profoundly affect the drug efficacy and safety, especially in the pediatric population. Children are not "small adults" with respect to drug therapy. However, overlooking this fact has led to several therapeutic failures, for example, the occurrence of "gray baby syndrome" in children who were treated with an antibiotic, chloramphenicol, using doses directly extrapolated from adult doses based on body weight. The affected had immature uridine 5′-diphospho-glucuronosyltransferase (UGT) to metabolize chloramphenicol efficiently causing mitochondrial toxicity due to higher plasma levels of the active drug.[1] However, drug-metabolizing capacities are not consistent in children, as they exhibit increased capacity for sulfate conjugation early in life resulting in resistance to acetaminophen toxicity.[2] Another example is UGT family member UGT2B7 which is immature at birth and in neonates <10 days of age. Thus, they require about a 25% of body weight correction in their morphine doses compared to infants to exhibit similar plasma levels. However, in practice, often children are administered with doses similar to that of adults to achieve comparable therapeutic levels.[3]

Adverse drug reactions (ADRs) in children represent a significant public health concern. A meta-analysis of pediatric ADRs concluded that 2.1% of admissions were due to ADRs, of which 39% were severe.[4] These estimates might not reflect the real scenario of ADRs as there are no standard reporting systems and the available primary data are derived from assessments conducted in individual pediatric hospitals. Several regulations such as European Union's Paediatric Regulation (2007) and the Best Pharmaceuticals for Children Act (last amended 2012) of the Food and Drug Administration have emphasized the need to progress further into translational research for drug use in children.[5,6] Drug disposition in the pediatric population is influenced by functional changes in multiple organs and organ systems, the ratio of the liver to body mass, changes in body composition, the relative size of the skin surface area, and maturation of metabolizing enzymes. Safe and effective treatment of children requires a fundamental

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understanding of the pharmacokinetics (PK) and dynamics of medicines in their dynamically developing systems.

This review presents an overview of the ontogeny of drug-metabolizing enzymes (DMEs) that are crucial in determining therapeutic dosing in children. We conducted a literature search on PubMed Central, Medline database, and Google Scholar. The combination of the following search term categories: "Pediatric population," "ontogeny," "enzyme development," "TDM," "children," "CYP450," "pharmacokinetics," and "adverse reactions" were used to obtain relevant articles for this narrative review.

The term pediatric population extends from the very small preterm newborn infants through to childhood and adolescents[7] as depicted in Table 1.

Developmental Pattern of Human Drug-Metabolizing Enzymes

The development of highly specific antibodies toward human DMEs, along with the identification of specific probe substrates, has permitted the elucidation of temporal-specific enzyme expression patterns or developmental trajectories[8] [Table 2].

Class I enzymes

These are expressed at their highest levels in the fetus during the first trimester, and expression levels either decrease or remain elevated during gestation. These are active toward endogenous substrates.

Class II enzymes

These express at relatively constant levels throughout gestation and in adulthood. Their expression may vary modestly within the 1st year after birth. For example, CYP2B6 and CYP2C19.

Class III enzymes

The expression of most of these enzymes reaches to adult levels from within a few weeks to 1 or 2 years, after birth (e.g., CYP1A2 and CYP3A4). However, for a few of the Class III enzymes (e.g. Flavin-containing monooxygenase 3 and CYP2C9), adult expression levels are not observed until post puberty.

Drugs undergo biotransformation through Phase I and II reactions. Phase I reactions are catalyzed by cytochrome P450 (CYP450) family and Phase II are by UGTs, sulfotransferase (SULTs), glutathione-S-transferase (GSTs), and N-acetyltransferase families. Isoenzymes within a family mature at distinct rates during the first several years of life.

Ontogeny of Phase I Drug-Metabolizing Enzymes and Adverse Drug Reactions

Phase I reactions include oxidation, reduction, and hydrolysis catalyzed by CYP450 superfamily of enzymes.

Cytochrome P450 Superfamily

CYP isoenzymes are heme-containing proteins that catalyze the metabolism of several lipophilic endogenous (e.g., steroids, fat-soluble vitamins, etc.) and exogenous compounds (e.g., drugs). Total CYP450 content in fetal liver is 30%–60% of adult values and reaches 100% adult levels during the first 10 years of life. Human CYP450 superfamily members are encoded by 59 functional genes, divided into 18 families and 42 subfamilies (list available at http://drnelson.uthsc.edu/human.P450.table.html). CYP450 1–4 families are mainly involved in xenobiotic metabolism.

Cytochrome P450 1A1

It is a crucial enzyme involved in the metabolic activation of polycyclic aromatic hydrocarbons to toxic metabolites in the lung.[9] Induction of CYP1A1 expression occurs upon exposure to polycyclic aromatic hydrocarbons from cigarette smoke.[10] CYP1A1 is neither inducible nor constitutively expressed in adult human liver.[11] However, the presence or absence of CYP1A family members in the human fetal liver is debatable.

Cytochrome P450 1A2

CYP1A2 is involved in caffeine and theophylline metabolism, and its ontogeny can be explained by imipramine metabolism.[12] The major metabolite of imipramine generated *in vitro* by adult liver microsomes is the demethylated derivative. The formation of desipramine by liver microsomes is very low when performed with fetal preparations and accounts for no more than 3%–4% of the adult activity. The rate of demethylation begins to rise in the group of infants aged 8–28 days and progressively increases to reach the adult levels in children aged 1 year or more. Children also require higher doses of theophylline to maintain the concentration in the therapeutic range.[13]

Dietary exposure influences the expression of the CYP1A2 enzyme. Studies have reported the rate of expression of CYP1A2 to be faster in formula milk-fed infants than in breast milk-fed infants. This could be because of inhibition or repression of the postnatal maturation process of CYP450-mediated caffeine metabolism by some components of human milk (free fatty acid, lipase activity, or other factors).[14]

Table 1: Developmental stages of pediatric population

Pediatric population	Duration	Stages of development
Preterm infants	<37 weeks gestation	Survival period
Term new-born infants or new-borns	0-28 days	Adaptation
Infants and toddlers	>28 days to 23 months	Rapid growth and maturation
Children	2-11 years	Language, socialization, and continued growth
Adolescents	12-16/18 years	Final growth and reproductive maturation

Table 2: Classification of enzymes based on developmental trajectories

Class I	Class II	Class III
ADH1A; CYP3A7; FMO1	CYP2C19; CYP2B6	ADH1B; ADH1C; AOX1
GSTP; SULT1E1; SULT1A3	CYP3A5; GSTA1; GSTA2	CES1; CES2; CYP1A2
	SULT1A	CYP2C9; CYP2D6; CYP2E1
		CYP3A4; EPHX1; EPHX2
		FMO3;GSTM1;GSTZ1
		SULT2A1;UGT1A1;UGT1A6
		UGT2B7

The numeral after the superfamily (CYP) represents the family (2), and the alphabet (C) after the numeral represents the subfamily, and the specific number (19) indicates the individual member of that family, for example, CYP2C19. ADH: Alcohol dehydrogenase, AOX: Aldehyde Oxidase, CES: Carboxylesterases, CYP: Cytochrome P450 enzymes, EPHX: epoxide hydrolase, FMO: Flavin-containing monooxygenase, GST: Glutathione S-transferases, SULT: sulfotransferase, UGT: Uridine 5′-diphospho-glucuronosyltransferase

Cytochrome P450 2A subfamily

CYP2A family consists of CYP2A6, CYP2A7, and 2A13. None of the CYP2A enzymes appear to be expressed in fetal liver.[15] *CYP2A6* mRNA, protein, and activity levels reach adult levels by 1 year. CYP2A6 and CYP2A13 were readily detectable in seven of eight human fetal nasal mucosa samples from infants of 13 to 18 weeks,[16] suggesting that CYP2A6/2A13 expression would continue to increase from the third trimester. Expression of CYP2A13 mRNA was found to be at the highest level in the nasal mucosa, followed by lung and trachea[17] implicating the role of CYP2A13 in xenobiotic toxicity and tobacco-related carcinogenesis in the human respiratory tract.

Cytochrome P450 2C subfamily

This subfamily consists of CYP2C8, CYP2C18, CYP2C9, and CYP2C19. Among these, CYP2C9 and CYP2C19 are most abundant in adults liver, and ontogeny of CYP2C8 and CYP2C18 is not well known. Substrates of CYP2C9 are warfarin, phenytoin, diclofenac, ibuprofen, tolbutamide, losartan, and indomethacin. CYP2C19 substrates include mephenytoin, escitalopram, and most proton-pump inhibitors such as omeprazole and lansoprazole that are commonly used in children.[18]

A comparison of relative CYP2C9 and CYP2C19 expression levels in individual samples shows that CYP2C19 is the dominant CYP2C enzyme at the prenatal period with a transition to CYP2C9 as the dominant postnatal enzyme around birth.[19] CYP2C9 activity progressively reaches approximately 30% of adult values during the gestational period. CYP2C9 protein and activity level are less variable between 5 months and 18 years.[19] Ontogeny of CYP2C9 was explained with the use of phenytoin where its half-life was high in preterm infants (75 h) compared to term infants <1 week after birth (20 h) or term infants aged >2 weeks (8 h).[20] The elimination rate of phenytoin was higher for children than adults, and an inverse age relationship was found to exist.[21] Therefore, children might require higher doses than adults for drugs which are metabolized by CYP2C9 to achieve similar therapeutic concentrations.[3] Caution is required if these children are also carrying genetic variants affecting CYP2C9 function. Treluyer *et al*. reported an association between increased CYP2C9 expression and sudden infant death syndrome. A parallel increase in CYP2C8 and CYP2C9 mediated oxidation of arachidonic acid to epoxyeicosatrienoic acid (EET) and dihydroxyeicosatrienoic acid (HETE) was observed. Although unproven, this increase in EET and HETE may increase the risk of sudden infant death syndrome by decreasing vascular tone.[22]

CYP2C19 and its catalytic activities reach 12%–15% of adult values within 2 months of gestation. At birth, CYP2C19 activity is approximately 30% of adult activity and reaches adults values by 10 years of age.[19,23] In neonates, the clearance of proton-pump inhibitors (omeprazole and pantoprazole) metabolized by CYP2C19 is reduced, whereas, in children older than 1 year, the clearance is similar to adults.[24,25] Therefore, children may not require weight-adjusted dose correction for drugs metabolized by CYP2C19 to attain therapeutic concentrations, provided children are not carrying any genetic variants affecting its function.[3]

Cytochrome P450 2D subfamily

CYP2D6 is a major enzyme of this subclass and accounts for <2% of total adult hepatic CYP P450 content. CYP2D6 is essential for the oxidative metabolism of approximately 12% of clinically relevant drugs such as antihypertensive and tricyclic antidepressants. CYP2D6 also catalyzes the O-demethylation of codeine to the active moiety, morphine, and dextromethorphan to dextrorphan that have been used as both *in vitro* and *in vivo* CYP2D6 phenotypic probes. Measuring the extent of dextromethorphan O-demethylation is particularly useful in pediatric populations.

The expression of CYP2D6 in fetal liver is debatable. Ladona *et al*. suggested the absence of CYP2D6 expression in fetal liver.[26] In contrast, Treluyer *et al*. reported both CYP2D6 protein and mRNA expression at only 5% of adult levels in 30% of the total fetal liver specimens (at <30 weeks of gestational age) examined. Expression was detectable in about 50% of the samples >30 weeks of gestational age, but still at only 15% of adult levels. Interindividual variability in expression of CYP2D6 can be due to the polymorphic nature of this enzyme in adults but may also reflect polymorphisms of regulatory elements controlling developmental expression. CYP2D6 protein expression is increased significantly after birth and reaches 50%–75% of adult values during the neonatal period.[27]

A syndrome of irritability, tachypnea, tremors, jitteriness, increased muscle tone, and temperature instability was observed in infants born to mothers receiving selective serotonin reuptake inhibitors (SSRI). However, it is unclear whether the symptoms result from neonatal withdrawal, from serotoninergic toxicity after *in utero* exposure or from a combination of both. The delayed *in vivo* ontogeny of CYP2D6 and CYP3A4 in neonates suggests that the syndrome is because of hyperserotonergic state due to delayed clearance

of SSRI (paroxetine) by CYP2D6. The symptoms disappear along time-dependent lines consistent with the maturational patterns of CYP2D6. Caution is required while administering CYP2D6 substrates to children, irrespective of whether they carry functional variants or not.

Cytochrome P450 2E subfamily

CYP2E1 metabolizes short chain dialkyl nitrosamines, organic solvents, and therapeutic drugs including many anesthetics. Many of CYP2E1 substrates induce it. Detectable levels of CYP2E1 protein are found in fetal liver samples as early as in the second trimester. Expression of CYP2E1 mRNA, protein, and enzyme activity rises immediately after birth, and levels increase gradually to approach adult levels by 1 year of age.[28]

CYP2E1s' ability to activate various neurotoxicants, known for their teratogenic activity (e.g., ethanol and toluene) provoked considerable interest in the scientific community to probe the ontogeny of this enzyme in the developing brain. The catalytic activity of CYP2E1 appeared in the human fetal brain within 2 months of gestation. Thus, it would appear that CYP2E1 present in the fetal brain may play a role in the neurotoxicity caused by *in utero* exposure to neurotoxicants such as ethanol.

Cytochrome P450 3A family

The human CYP3A consists primarily of four enzymes (3A4, 3A5, 3A7, and 3A43) involved in the metabolism of many clinically used drugs, several of which are of potential significance to pediatric practice. These isoforms are located primarily in the liver, small intestine, and kidney.

CYP3A7 is the major CYP isoform in fetal liver. CYP3A4 is absent in fetal liver but increases progressively throughout childhood. It was demonstrated that CYP3A7 enzyme is differentially expressed in the fetus with a transition to CYP3A4/3A5 in the adult.[29] Research on the PK and pharmacodynamics (PD) of cisapride was used to prove the clinical implications of the CYP3A7/3A4 transition. In adult patients, QT prolongation was found to be associated with an excessive dose of cisapride or high plasma levels of the parent drug. Except through a limited access program for specific diseases such as feeding intolerance in neonates, cisapride was banned from the market. Based on the fact that cisapride was metabolized mainly by CYP3A4 and not CYP3A5 or CYP3A7, neonates were assumed to demonstrate deficient metabolic ability. Supporting this hypothesis of the seven microsomal preparations from fetal or neonatal liver aged <7 days, low cisapride metabolism was detectable in four preparations. Kearns *et al*.[30] further confirmed this hypothesis and showed that terminal elimination rate constant of cisapride increased in patients at 30-week postconception from approximately by tenfold in 52 weeks postconception. The differential substrate specificity of CYP3A4 and CYP3A7 together with a developmental transition demonstrated to have a significant influence on the risk of ADR in neonates, especially those born prematurely. The maturation of CYP3A4 in children is better explained with the use of carbamazepine metabolism.[31] Reports from PK studies and therapeutic drug monitoring (TDM) databases suggest that carbamazepine clearance is higher in children than in adults, thereby necessitating higher doses of the drug on a mg/kg basis to achieve and maintain therapeutic concentrations.

Developmental patterns for the ontogeny of important Phase I DMEs in humans are summarized in Table 3 (Modified from Leeder and Kearns).[32]

Ontogeny of Phase II Metabolizing Enzymes

Change in expression of Phase II drug-metabolizing enzymes and their balance during development can considerably alter

Table 3: Developmental patterns of important Phase I drug-metabolizing enzymes in humans

Phase I enzymes	Substrates	Known developmental patterns
CYP2D6	Antiarrhythmic drugs, codeine Dextromethorphan, ethylmorphine, ondansetron, perphenazine Serotonin reuptake inhibitors S-mianserin, tolterodine Tricyclic antidepressants Zuclopenthixol	Low to absent in fetal liver but appears at 1 week of age; activity (i.e., 20% of an adult) by 1 month; adult competence by 3-5 years of age
CYP2C9	Losartan, NSAIDs (celecoxib, ibuprofen, indomethacin, naproxen) Phenytoin	Apparently absent in fetal liver; low activity in first one month of life, with adult activity reached by approximately 6 months; activity may exceed adult levels during childhood and decline to adult levels after puberty
CYP1A2	Theophylline, imipramine	Apparently absent in fetal liver; adult levels reached by approximately 4 months and exceeded in children at 1-2 years of age; adult activity reached after puberty
CYP3A7	Dehydroepiandrosterone Ethinylestradiol	A fetal form of CYP3A that is functionally active (and inducible) during gestation; virtually disappears by 1-4 weeks of postnatal when CYP3A4 activity predominates but remains present in approximately 5% of individuals
CYP3A4	Cisapride, cortisol, cyclosporine Diazepam, erythromycin, ethosuximide, midazolam Nifedipine, ritonavir, tacrolimus	Extremely low activity at birth, reaching approximately 30%-40% of adult activity by 1 month and full adult activity by 6 months; may exceed adult activity between 1 and 4 years of age, decreasing to adult levels after puberty

NSAIDs: Nonsteroidal anti-inflammatory drugs

the PK of a given drug. The Phase II drug-metabolizing enzymes catalyze the reactions which result in pharmacological inactivation or activation or detoxification.

Glutathione S-transferases

There are three families of GST enzymes: microsomal, cytosolic, and mitochondrial. The cytosolic GST enzyme family consists of six subfamilies: GSTA (alpha), GSTM (mu), GSTO (omega), GSTP (pi), GSTT (theta), and GSTZ (zeta). The enzymes of GST family show overlapping substrate specificities. Hence, it is difficult to characterize the developmental pattern of individual enzyme based on catalytic activity. The advancements in research enabled differentiation between GST enzymes[33] that allowed to study the GSTM, GSTA, and GSTP ontogeny. GSTP expressed at the highest levels in early gestation (20 weeks), and its expression declined progressively with age to nearly non-detectable levels in adults. GSTA1 and A2 expressed in the fetal lung, but at levels, 0.5%–1% of that observed in the liver. GSTA exhibits higher activity rates in children below 2 years of age and lower activity rates in children above 6 years of age. Older children have high levels of hepatic GTSM activity similar to adults. The levels of GSTM and GSTP in both fetal and postnatal kidney samples were similar to those observed in the liver suggesting uniform expression levels.[34] Although no specific information is available in the literature, administration of electrophilic drugs such as chemotherapeutic agents requires caution in children. Polymorphic variants in GSTs also influence the elimination, increasing the level of complexity to the drug dosing decision process. TDM process is advantageous in such situation to make decisions on dosing to avoid ADRs.

Sulfotransferases

The SULTs are composed of at least 11 distinct isoforms that catalyze sulfate conjugation of a variety of compounds using 3′-phosphoadenosine-5′-phosphosulfate as a donor. Sulfation results in a reduction in the biological activity of endogenous and exogenous compounds. SULTs play a key role in steroid hormone biosynthesis, catecholamine metabolism, and thyroid hormone homeostasis.[35] SULT1A1, SULT1A3, SULT1A6, SULT1B1, SULT1E1, and SULT2A1 are most important for xenobiotic metabolism in humans. SULT1A1 accounts for more than 50% of total SULT protein in the liver. SULT1A1 protein and activities are present in the liver of 10-week-old fetus and do not vary during development. However, fetal SULT1A1 was found to be more sensitive to the inhibitory effects of mefenamic acid and salicylic acid than adult SULT1A1.[36] This suggests that differences between fetal and adult SULT activities could have an influence on drug and hormone metabolism in the fetus. SULT1A3 conjugates circulating catecholamines. Salbutamol and apomorphine are substrates of this enzyme. Expression of SULT1A3 mRNA, protein, and activity (responsible for the metabolism of catecholamines) is high in the liver during early fetal development and decreases substantially in the late fetal development to reach the low levels in adults.[35] High levels of SULT1A3 protect the developing fetus from the adverse effects of circulating catecholamines, whereas the decline in activity during the perinatal period ensures availability of these hormones for the regulation of blood pressure and glucose homeostasis for a successful transition to postnatal life. SULT1E1 has high selectivity and affinity for endogenous estrogens. Endometrium uses sulfation as a specific mechanism of controlling estrogenic stimulation. This enzyme sulfates steroid medication including 17α-ethinylestradiol and is assumed to play a vital role in regulating the biological function of these hormones. SULT1E1 is expressed at higher levels in the fetus, suggesting its role in protecting the developing fetus from the actions of 17-estradiol.[37] SULT2A1 is involved in the biosynthesis of sex steroids and bile acids. SULT2A1 also metabolizes alcohol. SULT2A1 is a second major form of SULT in the liver, but its levels in the extrahepatic tissues are lower compared to other SULTs, which suggests that SULT2A1 substrates do undergo metabolism in the liver. Expression of this enzyme at its higher levels in the liver also suggests that it plays a major role in bile acid homeostasis and protection of the neonate from the toxic effects of bile acids.[38]

Uridine 5′-diphospho-glucuronosyltransferase

The family of UGT catalyzes glucuronidation of hundreds of hydrophobic endogenous molecules (e.g. bilirubin, bile acids, thyroxine, and steroids) and exogenous chemicals including potentially carcinogenic or teratogenic compounds entering the body through diet or air. UGT1, UGT2, UGT3, and UGT8 are members of this family.

The UGT1 and UGT2 gene families are important in the metabolism of many xenobiotics such as morphine, paracetamol, and capable of metabolizing important endogenous compounds (e.g., bilirubin and ethinylestradiol). UGT1A1 is most active towards bilirubin and is absent in the fetal liver. The expression of UGT1A1 is probably triggered by processes associated with birth and mRNA reaches adult levels by 3–6 months of age.[39] UGT1A6 is an important enzyme involved in acetaminophen glucuronidation. It is absent in the fetus, expressed at very low levels in the neonate but reaches adult levels after10 years of age.

Although the precise UGT enzyme responsible for gray baby syndrome remains unknown, it appears to be a member of the UGT2B subfamily. UGT2B7 expression was studied using morphine as a substrate and found to be expressed in fetal liver (15–27 weeks) at 10%–20% of adult levels and its expression increases at birth, reaching adult levels by 2–6 months of age.[40] UGT2B17 is involved in the metabolism of androgenic steroids. In the fetal liver, UGT2B17 is only 3% of adult levels, increasing to 13% in the neonate. No information is available on when the expression reaches to adult levels. Caution is required with implementation of TDM while administering substrates of UGT.

The developmental patterns for the ontogeny of important Phase-II drug-metabolizing enzymes in humans are summarized in Table 4.

Table 4: Developmental patterns of important Phase II drug-metabolizing enzymes in humans

Phase II enzymes	Substrates	Known developmental patterns
GST	Environmental toxins, pesticides, epoxides from aflatoxins B1	GSTP is found to be expressed at the highest levels in early gestation (20 weeks) and declineds progressively with age to nearly non-detectable levels in adults
SULT	dopamine, adrenaline, noradrenaline, salbutamol, and apomorphine	SULT1A3 mRNA, protein, and activity (responsible for the metabolism of catecholamines) are high in liver during early fetal development and decreases substantially in the late fetal development to reach the low levels in adults
UGT	Bilirubin, bile acids, thyroxine, and steroids	Processes associated with birth probably trigger the expression of UGT1A1 and mRNA reaches adult levels by 3-6 months of age UGT1A6 is absent in the fetus, expressed at very low levels in the neonate, but reaches adult levels after10 years of age UGT2B7 is expressed in fetal liver (15-27 weeks) at 10%-20% of adult levels and do not change with increasing gestational age

GST: Glutathione S-transferases, SULT: Sulfotransferase, UGT: Uridine 5′-diphospho-glucuronosyltransferase

Impact of Developing Drug-Metabolizing Enzymes on Drug–Drug Interactions in Children

Drug–drug interactions are well documented in adults, but the studies are often lacking in children due to ethical issues. Hence, we solely depend on case reports. The effect of drug–drug interactions in children alters as DMEs mature. The impact of these interactions is immense in the case of chemotherapy due to the narrow therapeutic window of many chemotherapeutic drugs. For example, cyclosporine (substrate of CYP3A4) is routinely used as an immunosuppressant in solid organ and allogeneic bone marrow transplant patients. When cyclosporine (CYP3A4 substrate) was administered along with voriconazole (CYP3A4 inhibitor), a 2·48-fold rise in the trough concentration of cyclosporine was observed in renal transplant patients aged between 20 and 71 years, and therefore, a reduction in the dose and monitoring of cyclosporine concentration were suggested.[41] However, in children, cyclosporine levels might not rise as expected in adults due to the possible increased activity of CYP3A4 compared to adults.[42] Hence, reducing the dose of cyclosporine when given along with voriconazole in children might compromise its efficacy. Thus, the impact of the developmental pattern of enzymes has to be taken into account while assessing consequences of drug–drug interactions in children.

Role of Therapeutic Drug Monitoring in Optimizing Therapy

As the DMEs are still in the process of development in children, it becomes necessary to monitor the drug levels with respect to their effects. As an example, TDM is in use for monitoring busulfan levels during administration of the conditioning regimen in children receiving hematopoietic stem cell transplantation. The adverse effects of busulfan include interstitial pulmonary fibrosis, hyperpigmentation, hepatic sinusoidal obstruction syndrome, and seizures. Busulfan undergoes glutathione conjugation by GST, which is liable for variability with the age of the children. Similarly, younger children receiving ifosfamide, an anticancer drug, might be at higher risk of developing nephrotoxicity through increased production of chloroacetaldehyde by CYP3A enzyme (a nephrotoxic metabolite of ifosfamide). TDM can help in such case to monitor the levels of parent drug and metabolite to control dosing. TDM may be especially useful in monitoring pharmacological effects of immunosuppressant drugs in children.[43] However, for drugs such as voriconazole, patients <12-year-old required higher dosages to maintain drug levels within the targeted therapeutic range than older patients.[44] Similarly, there is a need for TDM in children receiving antiretroviral therapy.[45] Application of TDM in individualizing therapy for epilepsy among children could be especially useful in minimizing ADRs.[46] In this direction, the German-Swiss-Austrian competence network for TDM in child and adolescent psychiatry has been initiated to collect and collate demographic, safety, and efficacy data along with blood concentrations of psychotropic drugs in children and adolescents.[47]

Future Perspectives

Understanding the developmental patterns of DMEs helps in the development of more appropriate PK models for pediatric drug development. As these age-associated differences are enzyme specific, all studies in developmental pharmacology should use specific validated phenotypic markers along with pharmacogenetic markers. Further, it is validated that pediatric PK is not just an extrapolation of adult PK indicating that no single method could predict dosing in children. Thus, more studies including both *in vitro* and clinical studies are essential for establishing PK models for important drugs used in children.[48] *In vitro* characterization of metabolic enzymes is pivotal.[49] As drugs are substrates for many enzymes, clinically significant role of these age-associated changes in the enzyme activity can be obtained only by clinical PK investigations. Thus, both *in vitro* and *in vivo* understanding of developmental patterns of the enzymes are mandated in future studies. Sophisticated software (SimCYP®, NONMEM, PK-Sim®, and MoBi®) have enabled us to apply population and physiology-based PK modeling based on ontogeny functions to develop appropriate pediatric dosing guidelines.

Recently, another dimension has been added to the existing complexity, with the accumulated data on the role of gut microbiota on drug metabolism.[50] Gut microbiota plays a role in the metabolism of important drugs. Thus, microbiota can influence drug metabolism through diet, environment, and route of administration. Recent evidence attributed pediatric gut microbiome to various diseases from diabetes to asthma.[51] Thus, emphasis on investigating the role of gut microbiome on PK and PD of drugs in children warranted in the near future.

Conclusion

Expression of many DMEs alters during the developmental phases in children that markedly affect drug response. Although overlooking these changes has led to several therapeutic misadventures with consequent adverse effects, we hope that a greater awareness and the application of tools such as physiologically based PK modeling will prevent such complications in the future. Further, as we gain more knowledge regarding the mechanisms regulating DME ontogeny, we will be able to understand better and predict an individual's metabolic capacity and drug response which permit adjustment of therapies accordingly.

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Conflicts of interest

There are no conflicts of interest.

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