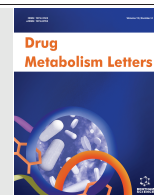
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Commentary

A Myriad Aberrations on Information of Ontogeny of Drug Metabolizing Enzymes in the Pediatric Population: An Obstacle for Personalizing Drug Therapy in the Pediatric Population



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Abstract: Major lacunae exist in our understanding of how developmental changes in drug biotransformation influence drug's exposure and thus its efficacy and toxicity in children. It is not just about smaller weight in children, which modifies the pattern of the drug's exposure. There are developmental, functional changes in organ systems, liver to body mass ratios, and changes in metabolism. Understanding these changes

and conducting studies to obtain data on ontogeny of drug metabolizing enzymes is essential for implementation of personalized dosing schedules in the pediatric population.

Keywords: Children, drug metabolism, enzyme, ontogeny.

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INTRODUCTION

The traditional method of treating children with medication includes administration of divided doses of the adult doses based on body weight or body surface area of a child. However, the ignorance of the fact that "children are not miniature adults" led to several therapeutic failures that resulted in unanticipated morbidity and mortality in pediatric patients [1, 2]. In the 1950s children were treated with an antibiotic, chloramphenicol, using doses simply extrapolated from adult doses based on body weight, following which many children suffered from symptoms of emesis, respiration and circulation problems referred to as the "grey baby syndrome [1]." Subsequent studies revealed that the affected children were incapable of effectively metabolizing the antibiotic to its glucuronide, due to an immature UDP glucuronosyltransferase system, resulting in excessive levels of the active drug and mitochondrial toxicity [3]. Though, increased drug sensitivity is not universal in children versus adults, children exhibited increased resistance to acetaminophen toxicity relative to adults, apparently because of increased capacity for sulfate conjugation early in life [2]. These two breakthrough incidences in the past had sensitized the scientific community about changes in the maturation, expression and function of drug metabolizing enzymes across the human life span, which can profoundly affect drug levels and thus its efficacy and safety, especially in pediatric and geriatric populations.

Adverse drug reactions (ADRs) in children represent a significant public health concern. A meta-analysis of pediatric ADRs concluded that 2.1% of pediatric admissions were due to ADRs, out of which 39% were severe [3]. These estimates might not reflect the actual incidences of ADRs, since there are no standard reporting systems available till recent days and primary data is derived from assessments conducted in individual pediatric hospitals. Despite knowing the burden of ADRs in children, the importance of the ontogeny of drug metabolizing enzymes (DME) was ignored in the past during the drug development process due to difficulty in obtaining fetal and neonatal tissue samples. Technological advances in medical research and mathematical modelling strategies helped the scientific world to generate the information on ontogeny or developmental patterns of drug metabolizing enzymes in humans. The physiologically based pharmacokinetic (PBPK) model is a multi-compartmental model where each compartment represents actual tissue and organ spaces and their volumes are the physical volumes of those organs and tissues. The PBPK models have been developed using *in vitro*, preclinical, clinical data to predict pharmacokinetics in infants and children of different ages. Pediatric PBPK models which consider time-varying system parameters may predict PK parameters in neonates and infants [4]. However, before implementing ontogeny of enzyme functions, it is important to consider potential pathological conditions that may influence the prediction of PK parameters by affecting physiological conditions of the patient [5]. The brief overview of DME maturation or activity in pediatric population is outlined in Table 1.

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Table 1. A brief overview of hepatic Phase I and II drug metabolizing enzymes ontogeny in Pediatric population*.

Pediatric Population	Duration	Enzymes in the Maturation Phase	Enzymes Already Matured	Enzymes with Higher Activity	Enzymes with Lower Activity	Absence of Enzyme Activity
Fetus & Preterm infants	<37 weeks gestation	CYP2C9, 19; CYP2E1 GSTA1 SULT1A1	CYP1A1 CYP2J2 SULT2A1 SULT1A3	CYP1A1 CYP2J2 GSTP1 SULT1E1 SULT1A3	CYP2D6 [†]	CYP1A2 CYP2A(all) CYP2B6 CYP3A4 [†] CYP2C9
Term newborn infants or newborns	0-28 days	CYP2D6 CYP2C19 CYP3A4 CYP2C9 GSTA1 SULT1A1	CYP2D6 CYP2E1	SULT2A1 -	SULT1A3 [†]	CYP1A2
Infants & toddlers	>28 days to 23 months	CYP1A2 CYP2B6 CYP2C19 CYP3A4	CYP2A6 CYP2C9 CYP2E1	CYP2A6 CYP2E1 SULT2A1	CYP1A2 SULT1E1	CYP1A1
Children	2-11 years	CYP2C19 GSTM1	CYP2D6 CYP2A6 GSTA1 SULT1A1	CYP2D6 CYP2A6 SULT2A1	SULT1E1-	CYP1A1
Adolescents	12 to 16/18 years	CYP2C19	CYP2D6 CYP1A2 GSTM1 SULT2A1 SULT1A1	CYP2D6 CYP1A2 CYP2A6 CYP2C9 CYP2C19 SULT2A1	CYP2B6 SULT1E1	CYP1A1 SULT1A3

*Data presented here is ambiguous and concluded from studies which includes either measurement of mRNA expression [6] or Specific protein quantification [7] and probe drug metabolism in a limited number of samples [8]. [†]These enzymes are also absent or present at very low levels.

WHY WE HAVE LIMITED KNOWLEDGE AND WHAT ARE THE CHALLENGES TO FACE TO OBTAIN SUCH INFORMATION

Major lacunae exists in our understanding of how developmental changes in drug biotransformation influence drug levels subsequently its efficacy and toxicity in children. However, several obstacles must be addressed before we acquire the requisite data.

1. Ethical and logistical problems in obtaining suitable tissue samples from the pediatric population for *in vitro* studies.
2. Substantial species differences exist in both DME primary structure and regulatory mechanisms. This is raising a concern regarding extrapolation of data from animal model systems to humans especially at various developmental stages.
3. Dynamic changes in gene expression occur during different stages of human ontogeny. Thus, the common study design involving a small number of tissue samples representing a narrow time window, or the pooling of samples across large windows of time, might result in data from which definitive conclusions are difficult to make.
4. Difficulties in identifying specific probe substrates or developing enzyme specific antibodies. Questions

regarding the cross-reactivity of antibodies against animal model antigens have also been raised. Production of a similar metabolite from alternate enzymes, and involvement of multiple enzymes in the metabolic pathway is also a concern.

WHY IT IS IMPORTANT TO UNDERSTAND THE DEVELOPMENTAL PATTERN OF DME'S IN CHILDREN

It is not just about smaller weight in children, which modifies the pattern of the drug's effect *via* altering its exposure. There is development, functional changes in organ systems, liver to body mass ratios, changes in metabolism [9, 10], changes in body composition, diet, environment and relative size of the skin-surface area are few among several factors that affect the behavior of drugs in children [10]. In addition to the above mentioned factors, when a predominant or single enzyme is involved in drug metabolism generating a specific metabolite, genetic variations might have pronounced or limited effect in children subjected to the availability of the protein product. For example, Gideon Koren *et al.*, [11] reported a case where a neonate breastfed by a mother receiving codeine was dying of morphine toxicity. Genotyping of mother and child was found to be *CYP2D6**2×2 gene duplication (ultra rapid metabolizers)

and *CYP2D6**1/*2 genotypes (extensive metabolizer), respectively [11]. Independent of genotype, low expression of *CYP2D6* in neonates together with compromised glucuronidation results in the impaired elimination of morphine from breast feeding and increased toxicity. This in turn could have a profound effect on drug-drug interactions owing to the limited or increased activity of a specific DME. Understanding of ontogeny of DMEs involved in biotransformation of anti-cancer agents might help in optimal management of their toxicity in pediatric population [12]. Therefore, a safe and effective medication for children requires a fundamental understanding and integration of the role of ontogeny of essential physiological process and drug metabolizing enzymes in the disposition and actions of drugs and endogenous compounds. In addition to the traditional approaches of detecting specific enzymes at mRNA level or using a probe drug for identification of enzyme activity and quantification of specific enzyme at the protein level, recent advances such as relative quantification of protein fraction shall be considered in order to get accurate and precise data on several enzyme levels at once. Implementation of genetic markers as a predictor of enzyme function in pediatric patients is also possible only when the enzyme is predominantly expressed and involved to a greater extent in the metabolism of a specific drug. Effective implementation of personalized treatment is possible with the availability of precise information on DME ontogeny in the pediatric population, with the prediction of right dose, thus maintaining optimal drug levels, avoiding adverse events or loss of efficacy or minimizing drug interactions.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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