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The ontogeny of drug metabolism enzymes and implications for adverse drug events

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Abbreviations:
bZIP, basic/leucine zipper
C/EBP, CCAAT/enhancer binding protein
DBP, D-element binding protein
DHEA, dehydroepiandrosterone
DM, dextromethorphan
DME, drug metabolizing enzyme
DX, dextrorphan
GFR, glomerular filtration rate
HNF1, hepatic nuclear factor 1
LAP, liver activator protein
LIP, liver inhibitory protein
PAR, proline and acidic acid rich
RT-PCR, reverse transcriptase-coupled polymerase chain reaction.

ABSTRACT

Profound changes in drug metabolizing enzyme (DME) expression occurs during development that impacts the risk of adverse drug events in the fetus and child. A review of our current knowledge suggests individual hepatic DME ontogeny can be categorized into one of three groups. Some enzymes, *e.g.*, CYP3A7, are expressed at their highest level during the first trimester and either remain at high concentrations or decrease during gestation, but are silenced or expressed at low levels within one to two years after birth. SULT1A1 is an example of the second group of DME. These enzymes are expressed at relatively constant levels throughout gestation and minimal changes are observed postnatally. ADH1C is typical of the third DME group that are not expressed or are expressed at low levels in the fetus, usually during the second or third trimester. Substantial increases in enzyme levels are observed within the first one to two years after birth. Combined with our knowledge of other physiological factors during early life stages, knowledge regarding DME ontogeny has permitted the development of robust physiological based pharmacokinetic models and an improved capability to predict drug disposition in pediatric patients. This review will provide an overview of DME developmental expression patterns and discuss some implications of the data with regards to drug therapy. Common themes emerging from our current knowledge also will be discussed. Finally, the review will highlight gaps in knowledge that will be important to advance this field.

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1. Introduction

1.1. Historical perspective

There is ample historical evidence from therapeutic misadventures that drug disposition and response are substantially different in children versus adults. Often cited is the administration of chloramphenicol to neonates at doses that were extrapolated from those found effective and safe in adult patients. These children exhibited symptoms referred to as grey baby syndrome consisting of emesis, abdominal distension, abnormal respiration, cyanosis, cardiovascular collapse and death. Studies subsequently demonstrated that an immature UDP glucuronosyl transferase system, resulting in impaired metabolism and clearance, was primarily responsible (Weiss et al., 1960). However, increased drug sensitivity is not universal in children versus adults. Thus, children exhibit increased resistance to acetaminophen toxicity relative to adults, apparently because of an increased capacity for sulfate conjugation early in life (Alam et al., 1977). Nevertheless, the example of chloramphenicol-induced grey baby syndrome, as well as other age-specific adverse drug events, were major impetuses for legislative changes to encourage pediatric clinical trials both in the United States (1997 FDA Modernization Act; 2002 Best Pharmaceuticals for Children Act; and the 2007 FDA Revitalization Act) and in Europe (Regulation EC No. 1901/2006 on Medicinal Products for Paediatric Use). There also has been a concerted effort to better understand life-stage-dependent changes in drug metabolism and disposition.

1.2. The challenge

Changes in pharmacokinetic parameters during development (Alcorn & McNamara, 2003) contribute substantially to the differences in therapeutic efficacy and adverse drug reactions observed in children (Kearns et al., 2003a). Of these parameters, changes in drug metabolizing enzyme (DME) expression, as exemplified by the example of grey baby syndrome described above, are recognized as making a major contribution to the overall pharmacokinetic differences between adults and children (Hines & McCarver, 2002; McCarver & Hines, 2002). However, the knowledge needed to better understand and more importantly, predict therapeutic dosing and avoidance of adverse reactions during maturation remains incomplete. This gap in knowledge is despite the increasing prescription of off-label medications for pediatric diseases based on adult efficacy data, particularly in the neonatal and pediatric intensive care settings (Cuzzolin et al., 2006). Advances in human developmental pharmacology that would address this knowledge gap have faced several challenges. Of major importance have been ethical and logistical problems in obtaining suitable tissue samples for *in vitro* studies. Increasing the significance of these problems was the realization that substantial species differences exist in both DME primary structure and regulatory mechanisms, causing concern regarding the ability to readily extrapolate data from animal model systems to humans. Furthermore, dynamic changes in gene expression occur during different stages of 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, has lead to data from which definitive conclusions are difficult to make. The science also has been hampered by the promiscuous nature of many of the DME making it difficult to identify specific probe substrates or develop highly specific antibodies. Questions regarding the cross-reactivity of antibodies raised against animal model antigens also have been raised. In addition, the lack of appreciation of the complexity of some of the loci encoding human DMEs has lead to the utilization of non-specific probes, and the mis-belief that transcript levels would correlate well with protein and activity levels [see Rich and Boobis (1997) for a discussion of many of these latter points].

The objective of this review is to summarize our current knowledge regarding the ontogeny of key human hepatic enzymes that potentially impact xenobiotic pharmacokinetics and indirectly, pharmacodynamics. The review also will try to put this knowledge into the context of other developmental changes that have a significant impact on pharmacokinetics.

2. Physiological factors impacting drug disposition during development

Several physiological parameters undergo changes during development that can impact drug disposition [see Kearns et al. (2003a) for a recent review]. For example, intragastric pH is elevated in the neonate relative to later life stages resulting in lower bioavailability of weakly acidic drugs. Maturation of intestinal motor activity takes place during early infancy and also impacts drug absorption. Similar to what has been observed in the liver, intestinal enzymes and transporters that influence drug absorption are likely to undergo developmental changes and alter bioavailability, although this is an understudied area. There also are age-dependent changes in body composition that will impact the volume of drug distribution and thus, overall disposition. Furthermore, changes in the major drug binding plasma proteins occur with age (McNamara & Alcorn, 2002). However, anatomical and functional changes in the liver and kidney appear to have a quantitatively more important influence on pharmacokinetics,