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CYP3A drug metabolism in the developmental age: recent advances

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ABSTRACT

Introduction. The 3A subfamily of cytochrome P450 (CYP3A) accomplishes phase I metabolism for approximately half of the available medications. We aimed to review the recent advances in our understanding of CYP3A activity, which could apply to infants and toddlers.
Material and Methods. A literature review.
Results. The reviewed recent data cover: CYP3A7 expression and functions, changes of CYP3A4 function in the first two years of life, CYP3A intestinal metabolism and zonation, CYP3A metabolic programming, pediatric CYP3A pharmacogenetics, the impact of critical illness on CYP3A, phenotyping, and other clinical implications of a better comprehension of CYP3A biology.
Conclusions. Although the knowledge of CYP3A enzymes has already changed pediatric practice, much more is to be expected in the upcoming years. The areas to watch include: endogenous markers for phenotyping, new CYP3A7 substrates and products, pharmacogenetic interactions with transporter genes for non-immunomodulatory drugs, as well as interactions with microbiota and specific bioactive foodstuffs.

Keywords: CYP3A5, pharmacokinetics, children, pediatric, midazolam, omeprazole.

The 3A subfamily of cytochrome P450 (CYP3A) includes four monooxydases: CYP3A4, CYP3A5, CYP3A7, and CYP3A43. The first two of these enzymes are the most highly expressed of the P450 proteins and accomplish phase I metabolism for approximately half of the available medications. CYP3A activity is subject to ample interindividual variability and may also be affected by a wide range of factors including pharmaceuticals, xenobiotics, foodstuffs, and diseases. We aimed to review the recent advances in our understanding of CYP3A drug metabolism, which could apply to infants and toddlers.

CYP3A7

CYP3A7 constitutes 30–50% of P450 molecules in the fetal liver and may account for over 80% of CYP3A drug metabolism in term neonates [1]. Liver transcriptome analyses revealed that in infants CYP3A7 expression is 3-fold greater than in children aged 1–6 years and over 15-fold greater than in adolescents [2]. Curiously, CYP3A7 might be expressed in adults, but this usually is accompanied by very low CYP3A5 activity [3].

CYP3A7 has a known contribution to sex hormone metabolism, which probably underlies its

link with birthweight [4]. CYP3A7 metabolizes cyclosporine, dronedarone, tacrolimus, and to a small extent sildenafil. Yet, the list of CYP3A7 substrates is far from complete. Overall, CYP3A7 is a crucial, but unexplored contributor to P450 function in the first months of life.

CYP3A4 and CYP3A5

CYP3A4 and CYP3A5 activity profiles at the ages of 1 month–2 years were determined by Emoto et al. [5]. While CYP3A4 activity increases after birth, CYP3A5 is already at the target level, although subject to strong interindividual variation. Other studies suggested that CYP3A4 metabolic capacity continuously rises from birth to 16th month of life, when it reaches adult levels [6]. On the other hand, fentanyl CYP3A4 metabolism is subject to most considerable variation: the reported half-time in neonates may range from 6 (like in adults) to over 20 hours [7]. The elimination of another opioid, buprenorphine, which requires CYP3A4 and UGT1A1, seems to correspond to adult levels shortly after birth [8]. Sirolimus clearance increases with age, along CYP3A activity; in the first year the former augments two-fold [9], but varies greatly from patient to patient. The above examples demonstrate that it is challenging to predict the metabolism of CYP3A4 substrates.

Brussee et al. who investigated midazolam pharmacokinetics in 37 preterm neonates found that the oral bioavailability of midazolam was 92% as opposed to 30% in adults [10]. They concluded that CYP3A activity was poor not only in the liver, but also in the intestine. Currently we do not know when CYP3A4 commences intestinal metabolism. Experiments in a murine model revealed that CYP3A zonation — a selective increase of cytochrome expression in parts of liver exposed to xenobiotics to a greater degree — does not occur until the pre-weaning period. This raises questions: does zonation appear only after CYP3A7 slows down and if it is coupled with changes of CYP3A intestinal activity [11].

Interestingly, there is evidence for metabolic programming with regard to CYP3A. In a murine model provision of high doses of phenobarbital early in life produced an effect of Cyp3a induction that persisted into the adulthood [12]. Exposure of rats with low birth weight to high-fat and high-energy diet led to a longer-term increase in CYP3A1 mRNA expression [13]. Moreover, in rats CYP3A activity shortly after birth might be induced by malnutrition during pregnancy [14]. It might be that programming underlies the large interindividual differences observed in the clinical setting.

Pediatric CYP3A pharmacogenetics

In the last five years a series of articles regarding tacrolimus metabolism in transplant recipients have been published with very similar results. For instance, in a study of over 100 pediatric liver transplant recipients, carriers of CYP3A5*1 allele (yielding large amounts of full-length enzyme), who received liver from CYP3A5*1-positive donors, required over 70% larger doses of tacrolimus [15]. In the work by Uesugi et al. CYP3A5*1 genotype of the transplanted liver associated with a relative risk of acute cellular rejection equaling 2.6 [16]. Moreover, steroid-free kidney transplant recipients who did not carry CYP3A5*1 had higher tacrolimus concentrations [17].

Pharmacogenetic analyses regarding other CYP3A substrates in infants or children are less abundant. In one such study, the lack of CYP3A4*1B (normal AA genotype of rs2740574) associated with the resistance to antiepileptic medication [18]. In various groups, CYP3A5*3 inconsistently associated with vincristine neurotoxicity. CYP3A5 and CYP3A7 polymorphisms seemed to modify the relationship between *in utero* mercury exposure and neurodevelopment [19].

Clinical context

Midazolam pharmacokinetics in infants indicated that CYP3A activity was reduced by two-thirds when CRP values reached 300 mg/L and by one-third when insufficiency of three organs was stated (as compared with one) [20]. Critical illness was found to be the most significant factor to affect CYP3A4 and CYP3A5 function in a group of children aged from 1 month to 17 years [21]. Such severe conditions are one of many examples for how drug metabolism may be altered, further rising uncertainty regarding CYP3A function in individuals.

The possible answer to large variation could be CYP3A phenotyping. However, the use of an endogenous marker would be more convenient than the application of midazolam, alfentanil or buspirone [22]. One such compound could be 4β-hydroxycholesterol [23]; however, its specificity is contested by data, which suggest that its levels depend to a large degree on other factors. Introduction of CYP3A phenotyping into pediatric practice would augment the availability of some classes of drugs, for instance, prokinetic agents, such as domperidone [24].

An example of the impact of the new knowledge of CYP3A4 interactions was provided by Bernard et al. who used lacidipine as a calcium inhibitor with no effect on CYP3A4 in pediatric oncohematology patients receiving other medication e.g., cyclosporine [25]. As was recently noted, CYP3A inhibitors might pose a risk of patent ductus arteriosus in critically ill neonates [26]. A recently published case report highlighted the potential of dexmedetomidine to inhibit tacrolimus metabolism by 75% [27]. CYP3A4 immaturity was hypothesized to be the cause of transient neutropenia in rifabutin-treated children with concomitant human immunodeficiency virus infection and tuberculosis [28]. Finally, CYP3A4 seems to be an alternative route for the inactivation of metabolites of vitamin D: its induction with rifampin in children with infantile hypercalcemia was successful [29]. Our growing comprehension of CYP3A roles and interactions will likely provide further vital data, similar to the above.

Conclusion

Although the knowledge of CYP3A enzymes has already changed pediatric practice, much more is to be expected in the upcoming years. The areas to watch include: endogenous markers for phenotyping, new CYP3A7 substrates and products, pharmacogenetic interactions with transporter genes for non-immunomodulatory drugs, as well as interactions with microbiota and specific bioactive foodstuffs.

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BB — interpretation of data for the work, information acquisition, revising manuscript for important content, final approval and agreement to be accountable.
ABŚ — study concept, design, and supervision; information analysis and interpretation, revising manuscript for important content, final approval and agreement to be accountable.

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