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The Effect of Age on Drug Metabolism

Saskia N de Wildt
Dept of Paediatrics, Erasmus University & Sophia Childrens Hospital, Rotterdam, Netherlands

Trevor N Johnson
Academic Unit of Molecular Pharmacology & Pharmacogenetics, University of Sheffield and Pharmacy Department, Children's Hospital, Sheffield, UK

Imti Choonara Corresponding Author
Academic Division of Child Health, University of Nottingham, Derbyshire Children's Hospital, Uttoxeter Road, Derby, DE22 3NE, UK Email: imti.choonara@nottingham.ac.uk

We have reviewed the effect of age on drug metabolism in relation to four drugs: caffeine (CYP1A2), midazolam (CYP3A4), morphine (glucuronidation) and paracetamol (glucuronidation and sulphation). For all four drugs clearance is significantly reduced in the neonatal period. This reduced clearance remains present in infants and children under the age of two years for caffeine, midazolam and morphine but not for paracetamol. There is considerable inter-individual variation in clearance values for all ages and this appears to be greatest for midazolam. For children aged two years and older the median plasma clearance values for all four drugs are similar to adolescents and adults.

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Introduction

There are many factors that affect drug metabolism. There is currently considerable interest in the field of pharmacogenetics i.e. the effect of genetic make up in relation to the capacity to metabolise different drugs. We wish to give a brief overview of the effect of age on drug metabolism from birth through childhood to adolescence.

The major site of drug metabolism is within the liver. The gastrointestinal tract, blood cells and other organs are also involved in drug metabolism. The biological purpose of drug metabolism is to convert lipophilic (fat soluble) compounds into more polar and thus more water soluble substances that are more readily excreted into bile or urine. The enzymes involved in drug metabolism are not only involved in the breakdown of medicines but also the numerous other chemicals that humans ingest or inhale either deliberately or unwittingly.

The major pathways involved in drug metabolism are divided into phase 1 and phase 2 reactions. Phase 1 involves oxidation, reduction, hydrolysis and hydration reactions. The major pathway is oxidation which involves the cytochrome P450 dependent (CYP) enzymes. The major CYP enzymes are CYP1A2, CYP2B6, CYP2C8 – 10, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 and 5. The major pathways for phase 2 involve glucuronidation, sulphation, methylation, acetylation and glutathione conjugation.

We plan to highlight the changes that have been previously described in relation to some of the major metabolic pathways and review enzyme activity in paediatric patients of different ages. Specifically we will review the development of CYP1A2 and CYP3A4 as examples of phase 1 and glucuronidation and sulphation as examples of phase 2 metabolism.

We have used the age classification accepted by both the European Medicines Evaluation Agency

and also the recent International Conference on Harmonisation[1]. This classification divides paediatric patients into 5 age groups; preterm neonates, full term neonates, infants from 1 month up to 24 months of age, children between the ages of 2 and 11 years and adolescents from 12 to 17 years.

General trends in the development of phase 1 drug metabolism in children

Total cytochrome P450 content in the fetal liver is between 30 and 60% of adult values and approaches adult values by 10 years of age[2]. Different developmental patterns have been identified for CYPs involving activity in the fetal liver (CYP3A7), minimal activity in the fetal liver but with rapid increase hours after birth (CYP2D6 and CYP2E1) and development in infancy (CYP1A2)[3–6].

For many CYP drug substrates weight corrected clearance values are often low at birth but then increase rapidly reaching a maximum by 2 years of age. Hepatically metabolised drugs that exhibit a higher systemic weight normalised clearance in children compared to adults include theophylline[7], diclofenac[8], teniposide[9], phenytoin[10], carbamazepine[11] and omeprazole[12]. Possible reasons for increased hepatic clearance in children include an increased liver volume normalised to body weight[13,14] or a higher concentration of catalytically active CYPs. A recent study failed to detect increased intrinsic CYPs 1A2, 2C8, 2E1 and 3A4/5 activity in paediatric livers in comparison to adult livers[15].

CYP3A4

The CYP3A subfamily is the most abundantly expressed CYP subfamily in the human adult and newborn liver. Moreover, this subfamily is involved in the metabolism of more than half of all drugs, including cyclosporin, tacrolimus, cisapride, midazolam, fentanyl, lidocaine, nifedipine, indinavir and verapamil.

The CYP3A subfamily consists of at least 4 enzymes: CYP3A4, CYP3A5, CYP3A7 and CYP3A43. CYP3A4/CYP3A5 account for 30-40% of total CYP content in the adult liver and intestine. CYP3A4 and CYP3A5 are differentially expressed, but have largely overlapping substrate specificity. CYP3A7 is the main CYP isoform in the human fetal and newborn liver. From the few studies available, it appears that the substrate specificity of CYP3A7 is different from CYP3A4.

In vitro studies have shown that CYP3A7 activity is high directly after birth, while CYP3A4 activity is very low[3]. During the first days after birth a transition occurs from mainly CYP3A7 activity to CYP3A4 activity. Finally, adult levels of CYP3A4 are reached during the first years of life. This developmental pattern of CYP3A4 is reflected by the change in clearance rate of midazolam[16–19] at different ages (Table 1). Midazolam clearance is reduced in infants under the age of 2 years. Although the median plasma clearance reaches adult levels in children over the age of 2 years, it is important to recognise the considerable inter-individual variation[17] (up to 100 fold in one study)[18]. The exact developmental pattern of CYP3A4 activity during infancy remains to be elucidated. Studies of midazolam show a lower clearance (corrected for body weight) for CYP3A substrates in the first two years of life[18]. In contrast, the clearance of both cyclosporin and tacrolimus is higher in infants than older children and adults[20, 21]. Young children, therefore, require higher cyclosporin and tacrolimus dosages (in relation to body weight) than adults[22,23].

Interestingly, CYP3A is not only localised in the liver, but also in the intestine. Therefore, intestinal

Table 1. Age and midazolam clearance

Age group	Number of patients	Mean or median plasma clearance (ml/min/kg)	Range	Reference
Preterm neonates	24	1.8	0.7–6.7	16
	?	1.2	?	17
Term neonates	?	1.8	?	17
Infants 1–24 months	25	3.0	0.5–25.8	18
Children 2–11 years	12	9.2	0.5–66.7	18
Adolescents 12–17 years	20	10.0	?	19

*Data recalculated for modified age groups

drug metabolism also contributes to presystemic clearance of CYP3A substrates. A recent study showed *in vitro* that the ontogeny of intestinal CYP3A activity mirrors that of hepatic CYP3A activity[24]. Therefore, the oral bioavailability of CYP3A substrates may be increased consequent to reduced presystemic clearance in newborn infants. This assumption is supported by the finding that midazolam oral bioavailability is higher in preterm infants when compared to adults[25].

CYP1A2

CYP1A2 accounts for approximately 13% of the total cytochrome P450 enzyme expression in the livers of healthy adult humans[26]. Caffeine is a recognised probe to study the activity of CYP1A2 both *in vitro* and *in vivo*[27] (Figure 1).

In vitro caffeine metabolism
In vitro studies have shown that the rates of caffeine N1, N3 and N7 demethylation are significantly lower in the fetus, neonate and infant than the adult[28]. C-8 hydroxylation to 1,3,7 trimethyluric acid was not significantly different between age groups. The production of total dimethylxanthines increased significantly with age up to 300 days. Differences in the maturational profile of each pathway suggest that different CYP isozymes are involved with a delay in maturation of N1 demethylation in comparison with N3 and N7 demethylation.

In vivo caffeine metabolism
In one study total caffeine demethylation and N3 and N7 demethylation increase exponentially with postnatal age and reach a plateau by 120 days[29]. The maturation of N1 demethylation is delayed and does not occur until after 19 months of age. 8-hydroxylation is mature by as early as one month and may be higher in infants compared to adults. Because the N3 and N7-demethylation pathways account for 88% of the metabolism of caffeine in humans[30], caffeine clearance should give a reasonable estimate of *in vivo* CYP1A2 activity.

Studies in preterm neonates[31, 32] have shown reduced clearance of caffeine in comparison with term babies and infants[33, 34]. The overall changes in caffeine clearance with age are shown in Table 2. Pons and co-workers have demonstrated significant impairment of the 3N demethylation of caffeine by CYP1A2 in infants under the age of 6 months, thereafter the activity remains fairly constant[35, 36].

One study demonstrated an inverse relationship between weight adjusted body clearance and the molar fraction of caffeine excreted unchanged in the urine in neonates and infants aged 3 days to 9 months[37]. There have been relatively few studies of the pharmacokinetics of caffeine in children after the first year of life. In general most *in vivo* clearance results for caffeine in children mirror the *in vitro* development of CYP1A2 in the human liver[6].

Glucuronidation and sulphation

Many medicines undergo glucuronide conjugation after oxidation. Other medicines undergo direct conjugation with glucuronic acid as a primary metabolic pathway. An important group of phase 2 metabolising enzymes are the UDP-glucuronyltransferases (UGTs); to date at least 10 different UGTs have been identified. Several drugs are glucuronidated; e.g. morphine, paracetamol, codeine, lorazepam, naloxone, propofol and chloramphenicol[38]. As these drugs are metabolised by one or more different UGT isoforms, and some can also be sulphated, the effect of ontogeny on the pharmacokinetics of these drugs is not uniform.

Sulphation is the other major phase 2 metabolic pathway and results in formation of water soluble metabolites that can be excreted renally[39, 40]. Sulphotransferases are the enzymes involved in sulphation. The total number of sulphotransferase enzymes are unknown but are divided into two groups, catechol sulphotransferases and phenol sulphotransferases. The ontogeny of sulphation is different for different drugs. The developmental

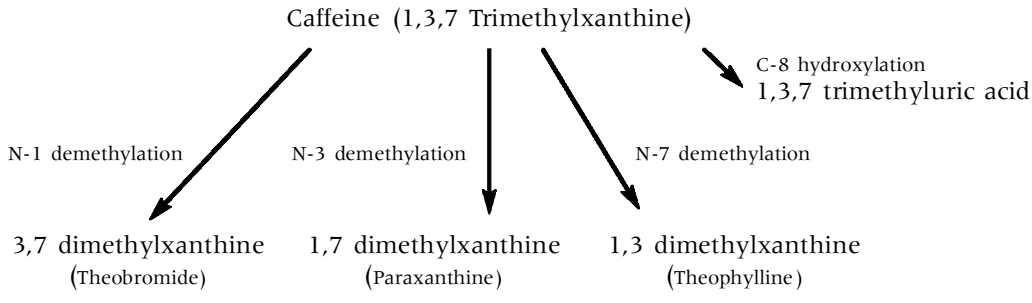

Figure 1. The major pathways of caffeine metabolism

Table 2. Age and caffeine clearance				
Age group	**Number of patients**	**Mean or median plasma clearance (ml/min/kg)**	**Range**	**Reference**
Preterm neonates	89	4.9	3–17	31
Term neonates	1	20	-	33
Infants 1–24 months	12	72.4	22.3–153	34
Children 2–11 years	9	81.6	21–132	35
Adolescents 12–17 years	_	_	_	_
Adults	?	94	21–270	36

Table 3. Age and morphine clearance				
Age group	**Number of patients**	**Mean or median plasma clearance (ml/min/kg)**	**Range**	**Reference**
Preterm neonates	72	3.5	0.5–9.6	42
Term neonates	44	6.3	0.6–39	42
Infants 1–24 months	11	13.9	8.3–24.1	43
Children 2–11 years	18	37.4	20.1–48.5	44
Adolescents 12–17 years	6	25.4	9–53.4	45

Table 4. Age and paracetamol metabolism				
Age group	**Number of patients**	**Mean or median plasma half life (h)**	**Range**	**Reference**
Preterm neonates	21	5.7	3.5–25.2	47
Term neonates	12	3.5	2.2–5.0	48
Infants 1–24 months	15	1.6	0.8–2.4	49
Children 2–11 years	18	1.7	?	50
Adolescents 12–17 years	10	1.5	0.8–1.9	51

profiles of glucuronidation and sulphation are illustrated by the examples of morphine and paracetamol, which are markedly different.

Morphine

Morphine undergoes conjugation (UGT2B7) to both morphine 3-glucuronide and morphine 6-glucuronide. The former is the major metabolite and is inactive, whereas morphine 6-glucuronide has considerable analgesic activity. Studies have shown that the sulphation of morphine is a minor metabolic pathway that does not contribute to the overall clearance[41]. The changes in plasma clearance, therefore, reflect the development of glucuronidation. This is markedly reduced in prematurity and after infancy reaches adult levels[42–45] (Table 3). Inter-individual variation is greatest in the neonatal period[42].

Paracetamol

Paracetamol undergoes metabolism by glucuronidation (UGT 1A6 and to a lesser extent UGT 1A9) and sulphation[46]. Glucuronidation is reduced but there is, however, compensatory sulphation which has a significant impact on the clearance of paracetamol in prepubertal children. There have been relatively few studies looking at the clearance of paracetamol and we have therefore summarised the studies that have determined the plasma half-life[47–51] (Table 4). This is increased in neonates and especially in preterm neonates[47,48]. In infancy and childhood the half-life is the same as in adolescents and adults[49–51]. The ratio of glucuronidation to sulphation, however, changes with development[52]. In contrast to morphine the sulphation of paracetamol plays a significant role in drug metabolism.

Table 5. Glucuronide to sulphate ratios		
Age group	**Morphine**	**Paracetamol**
Preterm neonates	36	
Term neonates		0.34
Infants 1–24 months		
Children 2–11 years	629	0.75
Adolescents 12–17 years		1.61

The relative contributions of glucuronidation and sulphation to the metabolism of morphine[41] and paracetamol[46] are shown in Table 5. In contrast to paracetamol, sulphation is not always available as an alternative metabolic pathway when glucuronidation activity is developmentally low. This is illustrated by the well-known toxicity of chloramphenicol in neonates, which is attributed to accumulation of drug due to low glucuronidation activity and the lack of alternative metabolic pathways[53].

In summary, due to differences in the ontogeny of the individual UGT isoforms, the different substrate specificity of the individual UGT isoforms and the variations in availability of alternative metabolic pathways, a single ontogenic pattern for glucuronidation is not available. Therefore, up to now, age-related adjustments in dosing of UGT substrates can only be done per individual drug.

Conclusions

We have used the data for four drugs that are extensively used in children and hence there is considerable information regarding the pharmacokinetics. These four drugs involve both phase 1 (CYP1A2 and CYP3A4) and phase 2 (glucuronidation and sulphation) pathways. We have demonstrated that for all four drugs plasma clearance is reduced in the neonatal period (paracetamol: only prolonged plasma half-life has been documented). This reduction in clearance appears to be greater in preterm infants. Adult clearance values appear to be reached within the first two years of life for caffeine, midazolam and morphine. It is important not to extrapolate these findings to all medicines and to all metabolic pathways. For instance studies of cyclosporin and tacrolimus, which undergo metabolism by CYP3A4 show increased clearance in infants. Further studies are required in relation to drug metabolism in infants between the ages of one and twenty four months.

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