Essentials for starting a pediatric clinical study (1): Pharmacokinetics in children

Tsuyoshi Yokoi

Drug Metabolism and Toxicology, Division of Pharmaceutical Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

(Received February 17, 2009)

ABSTRACT — During childhood, as the body weight and its function changes drastically by age, drug therapy should be arranged according to the age-related changes in pharmacokinetics of its age. The gastric absorption of oral drugs is affected by the high pH of gastric juice in newborns and slow gastric emptying up to six months of age, resulting generally in poor absorption except for lipophilic drugs. Intestinal absorption is also poor in newborns. Due to the low serum protein level, the protein binding ratio is low in newborns, though the serum protein level increases to the adult level at one to three years after birth. Drug metabolism capability generally develops quickly after birth and reaches the adult level in two to three years, though there are many exceptions. The CYP3A7 activity is relatively high just after birth, which affects the clearance of its substrate drugs. In terms of conjugation enzyme activities, sulfate conjugation develops fast and glucuronate conjugation develops slowly. Among the glucuronosyltransferase (UGT) enzymes, UGT1A1 and UGT2B7 reach the adult level by 3 months of age, whereas UGT1A6, UGT1A9 and UGT2B7 take a few years to ten years. Although there is no definitive report on enzyme induction ability, both CYP and UGT are suggested to be more inducible in children than in adults. The hepatic drug metabolism of children is characterized by the fact that the relative liver weight and hepatic blood flow rate per unit liver weight is larger in children than in adults. Drug excretion from the kidney is undeveloped in newborns, below 50% of the adult level up to the age of two to three months. Therefore, the effective dose range and toxic dose range of drugs is closer in such young subjects, but reaches adult level by the age of one year. The glomerular filtration rate is low in newborns, and rapidly increases up to 200% of that in adults in one year, and then gradually decreases to the adult level. As mentioned above, newborns, infants and children show different pharmacokinetics for different drugs and therefore cannot always be discussed in the same way. For the safe use of drugs, the pharmacokinetics data of each drug should be considered.

Key words: Pharmacokinetics, Drug metabolism, Drug disposition, Drug interactions, Interindividual difference

INTRODUCTION

During childhood, as the body weight and its function changes drastically by age, drug therapy should be performed according to the age-related changes in pharmacokinetics of the age. In Japan, only 15.6% of prescribed drugs and 24.3% of injected drugs are officially provided with usage and dosage guidelines for children. Up to 80% of the drugs practically used for children are off-label drugs (drugs for which the indication, dosage and administration are not provided for the patient to be treated by the package insert). Most drugs have a warning that the indication for children has not been established. In addition, the relative risk of side effects for children is reported to be 3.4-fold higher than that for adults (Schmitt, et al., 2002).

Age classes

In the E11 session of ICH, “Clinical Investigation of Medicinal Products in the Pediatric Population” was discussed. Age class of children is extremely important, and ICH classifies pronatiss (preterm newborn) as gestational age less than 41 weeks, term newborn infants as 0 to 27 days of age, infants and toddlers as 28 days to 23 months, children as 2 to 11 years, adolescents as 12 to 16-18 years depending on the region. In addition, post natal age (PNA), gestational age (GA), and post conceptional age...
(PCA) were introduced as PCA = PNA + GA. In almost no package inserts has the concept of PCA been adopted, and descriptions such as “for one week old infants, use every 12 hr” are common. Accordingly, it is known that pronatits before 36 weeks of GA frequently shows an unexpected elevation of the serum concentration of vancomycin (Fig. 1 from http://merckmanual.banyu.co.jp/cgi-bin/diphthml.cgi?url=19/s258.html). Until the infant period, it is recommended to refer to the PCA for determination of the dosage. On the other hand, it has been reported that the expressions of hepatic drug-metabolizing enzymes are in accordance with the development of the infant after birth, and the half-life of drugs, such as phenytoin, diazepam, theophylline, antipyrine, carbamazepine, acetaminophen, gentamicin and digoxin are shortest at the infant period when the liver weight per body weight reaches the maximum (Klotz et al., 1975) (Fig. 2).

Factors influencing pharmacokinetics: absorption

The gastric pH of adults ranges from 1.4 to 2.0, whereas it is 6.0 to 8.0 for pronatis, 2.3 to 3.6 for full-term newborn, and reaches the adult range by the age of 1 to 2 years. The phenobarbital absorption rate from gastrointestinal (GI) tract is reported to be dependent on the gastric pH (Heimann et al., 1980) (Fig. 3). Gastric emptying is slow in infants, and reaches the adult rate (ca. 60 min) by 6 months of age. It should be noted that the peristalsis of newborns is irregular. Percutaneous absorption is high in newborns and goes down to the adult level by 3 to 5 years of age. Therefore, skin application of steroid drugs to newborns requires special attention.

Factors influencing pharmacokinetics: distribution

The body fat of pronatis ranges from 3 to 12% of the body weight, whereas it is 12% in full term in newborns and 18% in adults. Newborn liver has a high blood flow rate per liver weight, and goes down to the adult level by the age of 6 months. The serum protein level of infants is low and shows a low protein binding rate to drugs in serum. The serum protein binding rate for acidic drugs reaches the adult level by 1 year of age, and for basic drugs by 3 to 4 years. The extracellular water volume and total body water are 60% and 75% for neonates, 20% and 50% for adults, respectively. Therefore, it should be noted that the distribution volume of newborns is larger for hydrophilic drugs and smaller for lipophilic drugs than in adults, although they increase to the adult level at the age of 3 to 5 years.

Factors influencing pharmacokinetics: excretion

Factors related to excretion differ largely between infants and adults. The glomerular filtration rate is 0.7 to 2 ml/min for pronatis, 2 to 4 ml/min for full-term newborns, and reaches the adult level (120 ml/min) by the age of 4 to 8 months. Renal tubular absorption and urine pH are low in newborns and reach the adult level by 2 to 3 months of age. Renal tubular secretion and renal blood flow rate of newborns are 20 to 30% of those of adults. Although the dose of digoxin for infants is twice that for adults, the blood concentration is equal to that in adults due to the high renal function of infants on a per body weight basis (Iisalo et al., 1973) (Fig. 4).
Pharmacokinetics in children

Factors influencing pharmacokinetics: metabolism

About 80% of drugs in clinical use undergo metabolic reactions in the body. Eighty percent of these are metabolized by cytochrome P450s (CYPs). P450 isofoms are expressed in an age-dependent manner. The total CYP contents in the liver are constant from the fetal period until the age of 1 year, remaining 25% to 50% of the adult level. Sulfate conjugation and acetyl conjugation activities increase rapidly after birth, whereas glucuronate conjugation activities increase slowly (Treluyer et al., 1997). CYP1A2 is undetectable in fetal liver and emerges from a few months after birth, requiring a few years to reach the adult expression level (Sonnier et al., 1998) (Fig. 5). Therefore, theophylline, which is metabolized by CYP1A2, shows high clearance after birth and is up to twice the adult level in infants (Fig. 6). Caution is needed with theophylline for infants, especially those under the age of 2 months.

CYP2C expression at the mRNA level for 2C8, 2C9,
2C18, and 2C19 in fetus is about 10% of that of adult, and reaches the adult level soon after birth. However, it is known that the expression level of protein and the enzyme activity are not correlated (Koukouritaki et al., 2004). The protein level of CYP2C9 increases rapidly after birth, whereas that of CYP2C19 increases slowly and takes 5 years to reach the adult level (Sonnier et al., 1998) (Fig. 7). S-warfarin, which is metabolized by CYP2C9, shows higher clearance rates in infants and toddlers than in adults. It is important to note that this difference is not significant when adjusted by the liver weight (Takahashi et al., 2000). The mRNA of CYP2D6 is highly expressed in fetus, but its activity is less than 5% of that in adults. In general, the mRNA levels are higher in infants than in adults, but the activities are considerably low, and the reason for this has not yet been determined.

![Graph showing developmental change of theophylline clearance](image1)

Fig. 6. Developmental change of theophylline clearance (Treluyer et al., 1997).

![Graph showing developmental change of CYP2C19 protein](image2)

Fig. 7. Developmental change of CYP2C19 protein (Koukouritaki et al., 2004). The coefficient of determination ($r^2$) was calculated after excluding nine outliers (open and hatched circles) based on a residual analysis.

![Graph showing developmental changes of hepatic CYP3A4 and CYP3A7 protein](image3)

Fig. 8. Developmental changes of hepatic CYP3A4 and CYP3A7 protein (Stevens et al., 2003).
Pharmacokinetics in children

(Treluys et al., 1991).

In terms of CYP3A, until the year 2000, it was believed that the total CYP3A level was rather constant during the transition from the fetal type CYP3A7 to the adult type CYP3A4. However, recent studies revealed that the expression of CYP3A7 protein is highest in the first trimester, and CYP3A4 protein gradually increases throughout the developmental period (Stevens et al., 2003) (Fig. 8). On the other hand, the expression of CYP3A5 is reported to be independent of age. At present, there is no definitive report on the induction capability of CYP enzymes. However, the possibility that enzyme induction is stronger in infants than in adults has been suggested by a study on clearance differences during the co-administration of carbamazepine and other antiepileptic drugs (Yukawa, 2007).

Other than CYPs, detailed reports are available on flavin-containing monooxygenases (FMO). A renal FMO1 is mainly expressed in the fetal period and diminishes after birth. In contrast, a hepatic FMO3 starts to appear 4 weeks after birth and requires 10 years to reach the adult level (Koukouritaki et al., 2002). Due to low FMO activities in infants, administration of FMO substrate drugs requires careful attention.

Among the glucuronosyltransferase (UGT) isoforms, UGT1A1 and UGT2B7 develop quickly, whereas UGT1A6, UGT1A9 and UGT2B7 develop slowly, and it is noted that UGT1A6 takes ten years to reach the adult level (Mirochnick et al., 1999) (Fig. 9).

In conclusion, although it is difficult to generalize this issue of pharmacokinetic of children, since each drug is involved differently in the developmental stages. Concerning drugs metabolized mainly in liver, it is known that an inverse correlation is demonstrated between age and hepatic drug clearance normalized by body weight, however, when normalized by liver weight or body surface area, a constant rate will be obtained between age and hepatic drug clearance. It is very important for the safety use of drugs to children to pay special attention to the characteristics of children’s pharmacokinetics.

![Fig. 9](image-url) Individual estimates of zidovudine clearance versus postconceptional age (Mirochnick et al., 1999). Open triangles, infants, solid circles, preterm infants.
SP312

T. Yokoi

ACKNOWLEDGMENT

This peer-reviewed article is based upon a lecture presented at the 35th Annual Meeting of Japanese Society of Toxicology, June 2008 in Tokyo under the theme of “Children's Toxicology”, June 2008 in Tokyo.

REFERENCES