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Pediatric pharmacokinetic considerations and implications for drug dosing

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Abstract

Optimizing the dosing of medicines for pediatric patients in routine clinical practice and determining the dose for clinical trials is still a challenging task. Children differ from adults in their response to drugs due to inherent differences in pharmacokinetics and/or pharmacodynamics, and responses may also vary among pediatric patients of different ages. However, the greatest disparities compared to adult pharmacokinetic profiles are observed in children below 2 years of age. The maturation of the liver and the kidneys, as well as the variation in body composition, are considered to be the main sources of pharmacokinetic variability. Hence, besides specific pharmacodynamic features, understanding age-related changes in drug absorption, distribution, and elimination is fundamental for optimizing drug efficacy and avoiding toxicity. This paper summarizes the pharmacokinetic changes throughout the childhood, along with the effect of developmental changes on drug dosage calculation. In clinical practice, age and body weight-based dosing regimens are usually used. In spite of dosing recommendations based on age and/or body weight, variabilities in pharmacokinetics and pharmacodynamic response remain, implying a need to monitor patients and optimize the dosing regimen according to physiological characteristics, disease characteristics and therapy.

Key words: children, maturation, development, pharmacokinetic variability, dosing regimen

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Introduction

The main challenge in pediatric pharmacotherapy is the optimization of dosing regimen in order to achieve effective and safe treatment. Differences among the pediatric and adult population are not just in size, but also due to physiological and biochemical processes. Many developmental changes during childhood can affect the pharmacokinetics and/or pharmacodynamics of drugs, causing different responses compared to adults. Understanding the characteristics of absorption, distribution, metabolism and excretion is important for rational dosing, since the effect and safety of a drug are largely dependent on the concentration in the body. The maturation of the liver and the kidneys, as well as the variation in body composition, are considered to be the main sources of age-related pharmacokinetic variability (1). In addition to differences between pediatric patients and adults, pharmacokinetics and pharmacodynamics of a drug can vary significantly among pediatric patients of different ages and stages of development. Hence, childhood can be divided into various groups of age, where each should be considered as a special population. Although some differences in the definition of pediatric age groups exist between organizations (Table 1), developmental stages of neonates, infants, children, and adolescents are widely familiar (2). In line with that, pediatric clinical trials are often requested according to specific age ranges (3). However, this may lead to the misleading conclusion that pharmacokinetic parameters are clustered into age ranges (4). Instead, they continuously change as a function of age and size, whereby age-related maturation is the most pronounced during the first 2 years of life (3, 4).

Table I Pediatric age groups based on Food and Drug Association (FDA) and National Institute of Child Health and Human Development (NICHD) (2).

Tabela I Pedijatrijske starosne grupe prema Upravi za hranu i lekove (FDA) i Nacionalnom institutu za zdravlje i razvoj (NICHD) (2).

Food and Drug Association (FDA)		**National Institute of Child Health and Human Development (NICHD)**	
Neonates	birth up to 1 month	Preterm neonatal	Birth at less than 37 weeks of postmenstrual age
		Term neonatal	Birth to 27 days
Infants	1 month to less than 2 years	Infants	28 days to 12 months
		Toddler	13 months to 2 years
Children	2 to less than 12 years	Early childhood	2 to 5 years
		Middle childhood	6 to 11 years
Adolescents	12 to less than 17 years	Early adolescence	12 to 18 years
		Late adolescence	19 to 21 years

Certain practical and ethical issues limits conducting clinical trials that involve pediatric subjects (5-7). That is why studies are usually performed after examining pharmacokinetics and efficacy/safety of the drugs in adults, having in consideration the physiological characteristics of a specific age group. Due to the absence of data or incomplete data in children, off-label or unlicensed use of drugs is common in pediatric clinical practice. In primary health care, the incidence of off-label prescription ranged from 29.5 to 51.7%, while the prevalence varied from 31.7 to 93.5% in relation to the total number of drugs prescribed (8). The most commonly off-label classes of drugs used in this population are antibiotics, dermatological, and anti-asthmatic drugs. Nevertheless, such a high percentage of prevalence is concerning, since off-label prescriptions are associated with an increased risk of adverse effects, particularly in patients younger than 2 years of age (7). Local registers of off-label drug use are developed in some countries, and they greatly support specific off-label drug use in pediatrics.

Pediatric dosing regimens are usually linearly extrapolated from adult data based on differences in body weight. That often leads to under or overdosing in children, since developmental changes are generally nonlinear processes (5). Hence, besides specific pharmacodynamic features, comprehensive pharmacokinetic consideration is a basis for rationale dosing. Therefore, the main aim of this article is to provide a basic understanding of developmental changes in pharmacokinetics in the pediatric population, as well as of the effect of developmental changes on drug dosage calculation.

Pharmacokinetic differences between children and adults

Growth and development are two specific features of children that can affect all pharmacokinetic processes. Pharmacokinetic profile of drugs differs between pediatrics and adults, but also can vary significantly depending on the age of the child and the stage of development. Thus, characteristics of absorption, distribution, metabolism and excretion in the pediatric population are described below.

Absorption

A number of age-dependent factors may influence the absorption of drugs after extravascular administration. In general, absorption of drugs in neonates and infants is slower and reduced than in older children or adults (1). Changes in the pH values of different parts of the gastrointestinal tract can directly affect important determinants of drug absorption, such as stability, dissolution, and ionization. Gastric pH is neutral at birth and drops to an acidic value (1-3) during the first 48 hours of life. In the following days, it increases again to a neutral value. Then, pH decreases gradually between 1 month and 2 years of age, and finally reaches adult levels at the age of 3 (9, 10). One example of increased bioavailability in neonates as compared with older children is acid labile penicillin G (11). Due to the changes of ionization, orally administered acidic drugs are less well-absorbed in an alkaline environment, while weak bases are absorbed faster (1, 9). Moreover, irregular gastric emptying and intestinal motility, as well as immature bacterial microflora, pancreatic and biliary functions in newborns may contribute to

variability in the rate and/or extent of absorption (1, 9, 10). Moreover, gastrointestinal disturbance and vomiting due to drug intake may limit the absorption of a drug from the gut and significantly reduce bioavailability. Finally, the development of intestinal metabolism and transport may be significant determinants of drug bioavailability. Cytochrome P450 (CYPs), specifically the CYP3A subfamily, are the predominant enzymes in the gut wall. Among many influx and efflux transporters, the most frequently studied one is P-glycoprotein, responsible for the movement of drugs back into the intestinal lumen. Unfortunately, there is insufficient evidence about the ontogeny of P-glycoprotein and CYP3A4 activity in the intestine, and the impact on drug disposition is not yet fully understood (3, 9, 10).

Besides oral administration, developmental changes can alter drug absorption by other extravascular routes. Thinner stratum corneum, greater cutaneous perfusion and hydration and higher ratio of body surface area to body weight may lead to higher percutaneous absorption in infants compared to adults (1, 9, 12).

Rectal drug administration is of high importance in pediatrics, as it allows fast absorption and consequently fast onset of drug action (e.g., paracetamol or diazepam). However, some practical issues, such as frequent stooling, especially in breast-fed infants, limits rectal administration. Furthermore, the first pass effect may be altered in neonates and infants if drugs are administered high in the rectum (12, 13).

Distribution and protein binding

Drug distribution in pediatric patients is determined by developmental changes in body composition, binding to plasma proteins and tissues and hemodynamic factors. Total body water ranges from 70-90% in preterm and term neonates to 55-60% in adults. Similarly, extracellular water makes up 45% of body weight in neonates, compared to 20% in adults (1, 3, 13). Hence, hydrophilic drugs, such as aminoglycoside antibiotics, display a higher volume of distribution in neonates than infants and children, or even adults (3, 9). On the other hand, body fat percentage increases from 10-15% at birth to 20-25% in infancy (3). In adults, body fat percentage ranges from 15 to 25%. These differences particularly affect the distribution of lipid-soluble compounds (9).

Protein binding rate of acidic drugs to albumin reaches adult values by the first year of age. On the other hand, binding rate of basic drugs to α1-acid glycoprotein achieves adult levels at the age of 3 to 4 years (9). Lower concentrations of plasma proteins in neonates and infants lead to higher proportions of unbound drug (e.g. phenytoin, salicylates, ampicillin) and consequently higher distribution volumes (1, 3, 10, 13). Increased free fraction becomes apparent for highly bound drugs with small volume of distribution in adults, but clinical consideration should also account for the rate of elimination and clearance (13).

Finally, membrane permeability of natural barriers is a significant determinant of drug disposition, although evidence of a developmental pattern is still limited. It seems that the blood-brain barrier maturation includes an increase in tight junction capacity and P-glycoprotein expression and function (3). Hence, limited barrier function in neonates

may allow the drug to pass to the central nervous system, resulting in toxicity (13). Moreover, in certain conditions, such as meningitis, the permeability of blood brain barrier may be increased, which enables drug (such as ampicillin and aminoglycoside antibiotics) penetration to the site of action.

Metabolism

The kidney and liver have a central role in the elimination of many drugs. Fat-soluble drugs are usually first metabolized into a more polar form, and then easily excreted by the kidney. Metabolism pathways are commonly divided into either phase I or phase II reactions. Phase I is characterized by modification reactions, usually catalyzed by CYP450 isoenzymes. In phase II, the drug or metabolite is conjugated with polar endogenous molecules. Several enzymes are responsible for conjugation, such as UDP-glucuronosyltransferases (UGT), sulfotransferases, glutathione-S-transferases, N-acetyltransferases and methyl-transferases (14). Although metabolic biotransformation may occur at various sites in the body, the liver has the largest capacity. Hepatic clearance depends on intrinsic clearance primarily, but also hepatic blood flow, protein binding, and drug transporters (15).

Developmental changes in the expression and enzyme activity determine the intrinsic clearance of drugs. Hence, understanding the maturational profile (ontogeny) of enzymes is crucial for rational pediatric drug dosing. Three developmental patterns are proposed, mostly based on *in vitro* data. Prenatal pattern includes enzymes whose activity is high before and shortly after the birth (CYP3A7, some sulfotransferases and others). If enzyme activity remains stable throughout development, such as CYP3A5, it is classified as a constant pattern. The most common pattern is postnatal, characterized by low fetal activity that increases after birth, reaching adult values in a few weeks or months (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, many UGT and others) (3, 14).

In general, adult levels of CYP activity are largely achieved by the first year of life, though maturation is highly variable between isoenzymes (15). Among all CYP forms, CYP3A subfamily is the predominant hepatic enzyme responsible for the metabolism of approximately 50% of drugs. The most important form is CYP3A4 isoenzyme (3, 9). Its activity is low at birth and reaches 30-40% of the adult value after 1 month (16), and completely matures after the first year (15). On the other hand, CYP3A7 expression is maximal 1 week after birth, with a subsequent decrease through the first year of life, when the function is replaced by CYP3A4 (15, 16).

CYP2C subfamily maturation is characterized by the postnatal pattern, though 2C9 ontogeny is faster and earlier than 2C19. CYP2D6 is present in fetal liver tissue, with a subsequent increase after birth and early infancy (3). Genetic polymorphism of this isoenzyme has also been observed in children (9). CYP1A2 maturation is characterized by a slow developmental pattern (3), while CYP2E1 activity grows rapidly after birth, reaching adult values within the first year of life (15).

In addition, phase I covers non-CYP enzymes, such as flavin-containing monooxygenase (FMOs), alcohol and aldehyde dehydrogenases (ADHs) or esterases. It seems that the FMO-1 ontogeny pattern is prenatal, while FMO-3 activity increases after birth (postnatal pattern). Similarly, different patterns are detected for various forms of ADHs, while esterase function is probably stable throughout development (3).

Among phase II enzymes, the most important ones are UGTs. In general, UGT expression and activity is decreased in early life (up to 2 years) and different forms mature at different rates (3, 9, 15). Due to reduced glucuronidation capacity in neonates, chloramphenicol treatment results in drug accumulation and the development of grey-baby syndrome (3, 15). However, for drugs not exclusively metabolized by UGT, other pathways may compensate limited glucuronidation, highlighting the proper safety profile of the drug in small children. Indeed, there is evidence of increased sulfate conjugation of paracetamol and morphine in neonates as compared with adults (1, 15, 17), which represent an alternative metabolic pathway in small children. Interestingly, the activity of glutathione conjugation is even 65-70% of the adult level at birth (3).

Renal excretion

A major route of excretion for many drugs and metabolites is renal, though the bile, feces or lungs may also contribute significantly. The mechanism of renal elimination involves glomerular filtration (GF), tubular secretion, and active or passive tubular reabsorption. These processes are immature at birth and each exhibits an independent developmental pattern, but in general, renal function maturation is completed by 2 years of age (9).

The glomerular filtration rate (GFR) in neonates is only 30-40% of the adult value. GFR increases rapidly after the birth, and usually reaches 50-60% of the adult value by the end of the third week. After that, it rises steadily and achieves adult values by the first year (1). However, GFR values in children are still lower than in adults, considering the differences in body size (5). In contrast to GFR, tubular secretion and reabsorption have a slightly slower maturation trend (3, 9). Tubular secretion reaches mature values at 15 months of age, while the process of reabsorption requires as long as 2 years to develop (3). Consequently, a higher elimination half-life of gentamicin in neonates has been observed, leading to an extended dosing interval in neonates compared to adults.

Parameters of growth and development as a basis for drug dosing

Defining effective and safe dosing regimens in pediatric patients is a complex issue, due to specific physiological and anatomical characteristics. Besides the described developmental characteristics of absorption, distribution, and elimination, children also differ from adults in response to drugs due to alterations in pharmacodynamics (5). Moreover, developmental changes can be further impacted by disease state, drug-drug interactions, or genetic polymorphisms (14, 18). In general, the selection of appropriate dosing strategy requires a detailed consideration of pharmacokinetic and pharmacodynamic information in children, as well as additional influences. However, due

to the lack or incomplete specific pediatric data, dosing regimens are often extrapolated from adults. Pharmacokinetic parameters are usually correlated with age, body weight or surface area as descriptors of development and growth. The relation to clearance is particularly important for defining the maintenance dose rate, while the volume of distribution is significant only for loading dose (15, 19). Thus, there are several methods for dosage calculation in children based on age, body weight, body surface and allometric scaling (9, 13).

Simple age-based dosing seems appealing for clinical practice, and reasonable considering age-related alterations in pharmacokinetic parameters. However, dosing based entirely on age is inadequate and generally not recommended (9). This method assumes that maturational profiles of organs that contribute to pharmacokinetic processes are consistent within each of the ages. In addition, it defines the dosing regimen for the standard patient for each of the age categories, which may not be adequate for child weighing outside of the typical values (13).

Weight-based linear scaling of an adult to pediatric dose is a widely used method. Although size-related differences in pharmacokinetic parameters are accounted for, pediatric growth and development are not linear processes. Accordingly, this method does not take into account age-related organ maturation in youngest children (1, 9). Thus, a simple linear scaling of pharmacokinetic parameters and doses from adults to children has some limitations (18). This method often leads to underdosing in infants and children, since elimination doesn't change in proportion to weight, and overdosing in neonates due to immature elimination (13, 18, 20).

Concept of surface-area-based dosing relies on the theory that fundamental physiological processes are essentially constant when expressed per unit of body surface area. However, studies indicate that this approach could lead to overdosing with certain drugs in neonates and infants. In addition, the disadvantages of this method are the existence of various formulas and difficulties in calculation (13). With the exception of many chemotherapeutic agents, this parameter is not often used for either adult or pediatric dosing calculation.

Allometry relates physiological processes and morphology to body size. It is widely used to predict pharmacokinetic parameters, not only from animals to humans but also from adults to the pediatric population. This approach describes the nonlinear relationship between body weight and parameters of interest, such as clearance or distribution volume, using power function or an exponent (1, 9). Over the years, several allometric models have been proposed, based on variable or fixed exponents (usually 0.75 for basal metabolic rate, also called "theory based allometry"). These models were recently reviewed, and the author concluded that at best the mean clearance or dose can be predicted (1). In general, theory based allometric scaling can be used to adequately predict clearance for children over 2 years of age, but it does not account for age-related maturational effects important for neonates and infants. In population pharmacokinetic studies, this is resolved by adding maturation function (20, 21).

Regardless of limitations, all the described methods are still in use in clinical practice, and there are no consistent recommendations about the preferred approach. In addition, one comprehensive algorithm for dose calculation has been prepared based on the physiology of the child and *in vivo* and *in vitro* data of drugs. It is based on recommended doses in adults, taking into account the pharmacokinetic characteristics of a drug, and age, weight or body surface area of the child (13).

In the reference literature and guidance, dosage regimens for children are usually presented according to age or body weight. Although those factors are correlated, it has been observed that the values of pharmacokinetic parameters adjusted to body weight can still vary as a consequence of years. Therefore, the values of parameters and recommended drug dosing regimens are usually defined according to body weight for each of the age categories. However, the lack of standardization about the age or weight based or banded approaches has resulted in heterogeneous recommendations. Mathur et al. compared five pediatric guidelines for antibiotic use and found a substantial variation in recommended doses for each of the drugs. For instance, the recommended dose of oral amoxicillin for a child with suspected nonsevere pneumonia (5 years of age, body weight of 18 kg) ranged from 360 to 1620 mg per day (22). An additional concern in pediatric pharmacotherapy is drug dosing to obese children. Weight-based recommendations reflecting the use of total body weight may not be justifiable in these patients. However, there are still opposite opinions regarding the appropriate size descriptors. Nevertheless, it is clear that clearance does not change proportionally with total body weight. Dosing consideration should be based on the degree of obesity, changes in pharmacokinetics, recommended dose in obese adults, and the available results of pediatric studies (1, 23).

Finally, therapeutic drug monitoring (TDM) in conjunction with clinical monitoring should be considered in some patients to individualize dosing regimen. It is justified only when the concentration-effect relationship has been proven, when drug has high pharmacokinetics variability and narrow therapeutic range. TDM of some antibacterials, immunosuppressants, antiepileptics and chemotherapeutics is routinely performed in pediatric patients (13). However, information about the safe and effective concentrations in children is not available for numerous drugs (24).

Innovative methods for pharmacokinetic modeling of maturation

Dosing information is difficult to determine in children, as traditional pharmacokinetic studies are subject to a range of practical and ethical constrains. Study design requires sampling frequently from each individual over a time period of several half-lives, which is a significant burden for children (6). On the other hand, the development of the population pharmacokinetic approach has allowed simultaneous analysis of sparse and unbalanced data from multiple subjects. The non-linear mixed effects method enables the quantification of covariates contributing to variability, as well as unexplained interindividual and residual variability (6, 10, 25-28). Moreover, it allows the exploration of developmental characteristics in childhood, primarily by using size and/or age as covariates. Allometric weight scaling with a single exponent usually

describes clearance in children over 2 years of age well, but not in neonates and infants, due to immature elimination. To overcome this, allometric scaling with a single fixed or estimated exponent is combined with the maturation factor to adjust for age. Maturation is usually described by sigmoidal function based on postmenstrual age or some other age descriptor (5, 6, 20, 21, 29-31). Another way is to use or estimate an allometric exponent which changes with either weight or age (30, 32). Considering its numerous advantages, regulatory documents support this approach for pediatric pharmacokinetic analysis of clinical data (33, 34). In addition to drug development, population models are useful in clinical practice for dosage individualization in conjunction with TDM of drugs (18).

Physiologically-based pharmacokinetic (PBPK) modeling has recently gained much broader applications in drug development (35, 36). This complex approach is designed to work with little or no clinical data, but it provides a useful insight into the mechanistic understanding of the disposition of drugs. The inclusion of population-specific physiological data and drug-specific data facilitates the prediction of drug disposition in special populations (1, 37). These models have a role in predicting first-in-man doses, first-in-children doses, drug-drug interactions, but also in scaling to children (31, 38, 39). The combination of 'bottom-up' PBPK and 'top-down' (population) approaches may be useful to compare results and further optimize different models (6, 31).

Conclusion

Determining dosing regimens in pediatric populations is challenging due to complex physiological and anatomical alterations during childhood. Children differ from adults in their response to drugs as a result of changes in pharmacokinetics and/or pharmacodynamics. Due to a limited number of pediatric trials, dosing regimens are usually defined after obtaining results of pharmacokinetic studies on the efficacy and safety in adults. In order to better extrapolate data from adults to pediatric patients or within pediatric populations, understanding developmental and pharmacokinetic alterations is crucial. Of major importance is the consideration of elimination organ maturation in infants. Pharmacokinetic parameters are usually correlated with age, body weight or body surface. Thus, in the reference guidance, dosing regimens are usually defined by kilograms of body weight for each of the age categories. In spite of the dosing recommendations, a great variability in pharmacokinetic and pharmacodynamic response remains, implying a clear need to monitor patients and adjust the dosing regimen individually to each patient, according to physiological characteristics, disease characteristics and therapy.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Značaj farmakokinetike u doziranju lekova kod pedijatrijskih pacijenata

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Kratak sadržaj

Optimizacija doziranja lekova kod pedijatrijskih pacijenata u rutinskoj kliničkoj praksi i procena doze pre započinjanja kliničkih studija je i dalje značajan izazov. Pedijatrijska populacija se razlikuje od odraslih pacijenata u odgovoru na lekove, što je uzrokovano izmenjenom farmakokinetikom i/ili farmakodinamikom, a odgovor može varirati i među decom različitog uzrasta. Međutim, najveće razlike u odnosu na farmakokinetičke profile odraslih pacijenata primećuju se kod dece mlađe od 2 godine. Sazrevanje jetre i bubrega, kao i promene u udelu telesnih tečenosti i masnog tkiva u odnosu na ukupnu telesnu masu, smatraju se glavnim izvorima farmakokinetičke varijabilnosti. Dakle, pored specifičnih farmakodinamičkih karakteristika, razumevanje razvojnih promena u resorpciji, raspodeli i eliminaciji leka je fundamentalno za optimizaciju efikasnosti i bezbednosti terapije. Ovaj rad sumira farmakokinetičke promene tokom detinjstva, zajedno sa uticajem razvojnih promena na izračunavanje doze leka. U kliničkoj praksi se obično koriste režimi doziranja zasnovani na starosti i telesnoj masi. Uprkos preporukama za doziranje na osnovu godina i/ili telesne mase, i dalje se uočava varijabilnost u farmakokinetici i farmakodinamičkom odgovoru, što ukazuje na potrebu za praćenjem pacijenata i optimizacijom režima doziranja prema fiziološkim karakteristikama, karakteristikama bolesti i terapiji.

Ključne reči: deca, sazrevanje, razvoj, farmakokinetička varijabilnost, režim doziranja