REVIEW ARTICLE

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Guidelines on Paediatric Dosing on the Basis of Developmental Physiology and Pharmacokinetic Considerations

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Abstract

The approach to paediatric drug dosing needs to be based on the physiological characteristics of the child and the pharmacokinetic parameters of the drug. This review summarises the current knowledge on developmental changes in absorption, distribution, metabolism and excretion and combines this knowledge with *in vivo* and *in vitro* pharmacokinetic data that are currently available. In addition, dosage adjustments based on practical problems, such as child-friendly formulations and feeding regimens, disease state, genetic make-up and environmental influences are presented.

Modification of a dosage based on absorption, depends on the route of absorption, the physico chemical properties of the drug and the age of the child. For oral drug absorption, a distinction should be made between the very young and children over a few weeks old. In the latter case, it is likely that practical considerations, like appropriate formulations, have much greater relevance to oral drug absorption.

The volume of distribution (V_d) may be altered in children. Hydrophilic drugs with a high V_d in adults should be normalised to bodyweight in young children (age <2 years), whereas hydrophilic drugs with a low V_d in adults should be normalised to body surface area (BSA) in these children. For drugs that are metabolised by the liver, the effect of the V_d becomes apparent in children <2 months of age. In general, only the first dose should be based on the V_d; subsequent doses should be determined by the clearance. Pharmacokinetic studies on renal and liver function clarify that a distinction should be made between maturation and growth of the organs. After the maturation process has finished, the main influences on the clearance of drugs are growth and changes in blood flow of the liver and kidney. Drugs that are primarily metabolised by the liver should be administered with extreme care until the age of 2 months. Modification of dosing should be based on response and on therapeutic drug monitoring. At the age of 2–6 months, a general guideline based on bodyweight may be used. After 6 months of age, BSA is a good marker as a basis for drug dosing. However, even at this age, drugs that are primarily metabolised by cytochrome P450 2D6 and uridine diphosphate glucuronosyltransferase should be normalised to bodyweight.

In the first 2 years of life, the renal excretion rate should be determined by markers of renal function, such as serum creatinine and p-aminohippuric acid clearance. A dosage guideline for drugs that are significantly excreted by the kidney should be based on the determination of renal function in first 2 years of life. After maturation, the dose should be normalised to BSA.

These guidelines are intended to be used in clinical practice and to form a basis for more research. The integration of these guidelines, and combining them with pharmacodynamic effects, should be considered and could form a basis for further study.

The pharmacokinetics and pharmacodynamics of drugs in children are different from those in adults. Many drugs administered to neonates show an intensified or even toxic effect; whereas in infants and children the same dosage, based on bodyweight, frequently results in decreased efficacy. The question this article addresses is whether and how a dosage can be adjusted in order to try to achieve comparable drug effects and comparable levels of safety in children as in adults.

1. Current Dosing Guidelines

The four main methods currently available to estimate the first drug dose for an infant are all based on the established dose for adults. The methods are: (i) identifying age-based categories on the basis of which the dosage adjustments can be made; (ii) normalisation of a dose to bodyweight; (iii) use of body surface area (BSA) as a guide to drug dosage; and (iv) use of an allometric method. All four approaches have a physiological basis, but all have some disadvantages.

1.1 Age-Based Dosing Regimens

Because neonates, infants, children and adolescents have distinct differences in physiological development, it seems reasonable to identify age-based dosing regimens. Potentially, the main advantage is the ease with which this approach can be used in practice. A distinct disadvantage is that this approach assumes that maturational effects on drug disposition are consistent within each of the age-based categories. This approach is imprecise in reflecting the substantial pharmacokinetic variability over wide age ranges.[1] In addition, it considers a standard paediatric patient. An adipose child, for instance, will not only have a different body composition, but also an aberrant physiological development compared with a slender child.

1.2 Bodyweight-Based Dosing Regimens

Age and bodyweight are obviously correlated, but pharmacokinetic parameters, normalised to bodyweight, may vary as a function of age. For many drugs, bodyweight-normalised drug clearance in children exceeds that of an adult. Therefore, an increase of the dosage based on bodyweight should be suggested for most drugs. Using this higher dosage, overdosing of adolescents and relatively heavy children can occur if no maximum dosage has been determined. Besides setting a maximum bodyweight, a minimum bodyweight must also be defined, since the bodyweight-normalised clearance in neonates is generally lower than in children.

1.3 Body Surface Area-Based Dosing Regimens

In 1950, Crawford et al.[2] introduced the concept of BSA in paediatrics based on the belief that many of the fundamental physiological processes of mammalian organisms are essentially constant when expressed per unit of body surface area. In addition, a relationship was established by Crawford et al.,[2] correlating the blood concentrations of two drugs with the dosage calculated based on BSA. The difference between the use of BSA and bodyweight is especially apparent for paediatric patients in the younger age range. At the age of 12 years, the BSA-based dose for a child with a normal body habitus is 1.2 times the adult-referenced bodyweight-based dosage. However, at the age of 2 years, the absolute dosage for children, adjusted based on BSA, is 1.7 times (70%) higher than the dosage adjusted based on bodyweight.[1] A dosage based on the BSA of children limits the risk of overdosing in older children, compared with a dosage based on bodyweight. The disadvantages of BSA-based dosing are: (i) the difficult way in which BSA is calculated (using length and bodyweight); (ii) the various formulas that can be used to calculate BSA; and (iii) neonates and infants being overdosed with certain drugs when BSA was used as a guideline (an example is an overdose of valganciclovir in neonates[3]).

1.4 Allometric Scaling

Allometric scaling is used extensively in evaluating preclinical pharmacokinetic data across animal species. Since 1940, it has been applied to adjust drug dosages in humans. It is based on relating physiological function and morphology to body size. This approach suggests that bodyweight$^{0.75}$ be used to scale clearance. It also suggests volume of distribution (V_d) be scaled to bodyweight^{1}.[4,5] The allometric approach (bodyweight$^{0.75}$) produces corresponding clearance values to scaling by BSA. Therefore, it has similar advantages and disadvantages as BSA, except for the advantage over BSA that no height measurement is needed.

Recently, Kearns et al.[6] stated that using simple dosage formulas and allometric scaling may have

potential clinical utility in children older than 8 years of age and in adolescents, whose organ function and body composition approximate that of young adults. These approaches have little value in very young infants and children, who show dramatic age-related differences in drug disposition.[6] Nevertheless, paediatricians and pharmacists are continuously forced to use these assumptions. Decisions regarding dosages are difficult to make, because there is a scarcity of data available to help paediatricians prescribe drugs.[7]

2. Physiology-Based Pharmacokinetics

The selection of an appropriate drug dosage for a neonate, infant, child or adolescent not only requires an understanding of the basic pharmacokinetic and pharmacodynamic properties of a given compound, but also the impact of the process of development upon each aspect of drug disposition.[8] In order to understand the impact of the developmental physiology, the four most important processes in pharmacokinetics: absorption, distribution, metabolism and renal excretion, should be studied individually. In this article paediatric pharmacokinetic studies, which deal with these processes, are reviewed. For each process a general recommendation for an age-related dosing schedule is provided.

3. Developmental Changes in Absorptive Capacity and First-Pass Metabolism

The pH of the stomach is practically neutral at birth. The gastric pH decreases to around 3 within 48 hours following birth, then returns to neutral over the next 24 hours and remains neutral for the next 10 days.[9] Thereafter, it slowly declines again until it reaches adult values at about 2 years of age.

These initial changes do not occur in premature infants, who seem to have little or no free acid during the first 14 days of life.[9]

The time of gastric emptying is delayed in the period immediately after birth for both full term and pre-term neonates.[10] It approaches adult values within the first 6–8 months of life.[11]

Intestinal transit time is prolonged in neonates because of reduced motility and peristalsis, but appears to be reduced in older infants as a result of increased intestinal motility.[11,12] Other factors that may play a role in intestinal drug absorption are immaturity of the intestinal mucosa leading to increased permeability, immature biliary function, high levels of intestinal β-glucuronidase activity, reduced first-pass metabolism, maturation of carrier mechanisms and variable microbial colonisation.[12]

Intramuscular administration of drugs is unreliable in neonates since the blood flow to the muscles varies over the first 2–3 weeks of life.[11] Intramuscular injections have some disadvantages that prevent their use in children: the pain associated with an intramuscular injection is severe, the risk of complications is increased and the pharmacokinetics are unpredictable.[13]

The rectal route is not much modified by maturation. The local pH of the rectum is close to neutral in adults, but alkaline in most children.[14] The first-pass effect may have some effect on the bioavailability of rectal administrations.[11,15] The extent of first-pass metabolism with rectal administration is related to anatomical differences in venous drainage and in the site the drug is delivered to. Drugs administered high in the rectum are usually carried directly to the liver and therefore are subject to metabolism and the enterohepatic circle. Drugs administered low in the rectum are delivered systemically by the inferior and middle rectal veins, before passing through the liver.[15]

Percutaneous absorption can be faster and higher because neonates and infants, especially preterm infants, have a very thin, poorly keratinised skin, a more well-hydrated stratum corneum and a relatively large surface area.[9,11,12]

3.1 Pharmacokinetic Studies on Absorption and First-Pass Metabolism

The variability of pH in the first few days to weeks of life causes acid labile drugs (such as benzylpenicillin [penicillin G] and erythromycin) to be more efficiently absorbed when administered orally; whereas the absorption of weak organic acids

(phenobarbital [phenobarbitone], phenytoin) decreases.[11] Basic drugs are absorbed more rapidly at a higher pH of the stomach.[9]

The delay in gastric emptying may change the absorption of drugs.[11] This effect has been studied with several drugs. Anderson et al.[16] showed that the oral paracetamol (acetaminophen) absorption rate was significantly lower in the first days of life before stabilising after 1 week. Another study showed that the time to reach maximum concentration (t_{max}) of cisapride was significantly longer in preterm neonates compared with term neonates.[17] The short intestinal transit time in older infants may result in incomplete absorption of some sustained release products.[11] Developmental differences in the gastrointestinal disposition of lipids might alter the absorption of some drugs. A study with pleconaril (dissolved in a mixture of medium chain triglycerides) showed a dose dependent absorption of pleconaril in 16 neonates aged 7–32 days.[18]

An increased bioavailability of midazolam as a result of a low cytochrome P450 (CYP) 3A activity in the intestine has been reported in preterm infants.[19] Boucher et al.[20] showed that first-pass metabolism of zidovudine was decreased in the first 14 days of life. The bioavailability of oral zidovudine varied from 89% in infants younger than 15 days to a mean of 61% in older infants. This effect was not seen in premature infants.[21] The effect of maturation of carrier mechanisms on the absorption of drugs in children has not yet been studied in detail.

Practical issues may have a significant effect on the bioavailability of a drug, for example, infants need frequent feeding. Therefore, it is quite often impossible to prevent an interaction between a drug and food. The bioavailability of phenytoin was shown to be decreased by this interaction.[22] The bioavailability of an oral solution of itraconazole was lower in children with neoplastic disease than in adults, most likely because of either mucositis or vomiting.[23] For most drugs, the strength of the dosage form is not suitable for use in children; therefore, doses have to be divided into pieces, or non-registered forms (capsules, tablets or potions) and are prepared by the pharmacy. The stability and shakability of potions are generally difficult to establish. There is often a lack of an appropriate child-friendly way to administer the drug, for example, because of the taste of the medication. It was shown that the formulation of nizatidine (using apple juice or water as a solvent) instead of the age of child accounted for the differences observed in bioavailability in children,[24] most likely as a result of masking of the taste of nizatidine. Absorption parameters following ketoprofen administered rectally were similar in children and adults.[25,26] However, a prolonged absorption time of paracetamol was shown in preterm neonates in comparison with term neonates, possibly due to differences in rectal temperature.[27] The bioavailability of paracetamol seems to decrease with age, likely because of an increase in the first-pass effect of the liver by maturation of liver enzymes.[16] The bioavailability of the rectal administration of tramadol in children was shown in one study to be lower in children (age 1–6 years) than in adults, probably because of more alkaline pH of the rectal mucosa in children.[28]

Practical issues may affect absorption through the rectal route as well. Passing stools immediately after administration will affect the absorption, since the doses will be expelled by the child. In the first weeks of life, stooling may occur one to seven times daily. Stooling occurs more frequently in children than in adults, especially in breast-fed children.[29] Children dislike rectal administrations. Caution should be applied before giving significant amounts of rectal solutions. The bioavailability of a rectal solution of paracetamol in infants was shown to be decreased in comparison to suppository formulations, possibly due to loss of parts of the solution.[16]

Another route of administering drugs is percutaneous. Data of human skin from premature neonates indicate an inverse correlation between permeability and gestational age. Permeability rates were 100- to 1000-fold greater before 30 weeks gestation as compared with full-term neonates, with a 3- to 4-fold greater permeation rate seen beyond 32 weeks.[30] *In vivo* studies suggest that this increased dermal permeability in premature infants is a short-lived phe-

nomenon with the permeability barrier of even the most premature neonates similar to that of full-term neonates by 2 weeks of postnatal life.[30] Systemic toxicity can be seen with the percutaneous application of drugs, such as lidocaine (lignocaine) and corticosteroids during the first 8–12 months.[12] This toxicity is due to a relatively large surface area of the skin.

3.2 Conclusions on Drug Absorption and First-Pass Metabolism

Physiological changes in the gastrointestinal tract have a significant influence on the absorption of oral drugs. The major changes in the physiology of the gastrointestinal tract take place in the first weeks of life, as reported with paracetamol, cisapride and zidovudine.[16,17,20,21] In general, the bioavailability of drugs is decreased in neonates in comparison with adults. However, basic or acid-labile drugs are expected to have an increased absorption in neonates. The drugs in which first-pass metabolism or metabolism in the gastrointestinal tract play an important role in adults, should be administered to neonates with care. Dosage corrections should be considered in neonates in the first 2 weeks of life, based on these drug characteristics.

Even though the amount and rate of drug delivery from absorption is a significant determinant of effect in infants older than a few weeks, practical problems may have a far greater effect. In these children, attention should be paid to the correct usage of oral drugs.

For rectal administration, no dosage correction has to be considered on the basis of bioavailability, except for the following three reasons: (i) practical problems could alter the bioavailability of the drug; (ii) in the first weeks of life a reduction of the enterohepatic clearance could alter the bioavailability of drugs in which this effect is important (as shown with paracetamol[16]); and (iii) the more alkaline pH of the rectum could alter the absorption of drugs.

Pain associated with the injections, the risk of complications and the unpredictable pharmacokinetics make intramuscular injection obsolete. Intramuscular injections should only be used in some cases of emergency.

The increased percutaneous absorption results in systemic concentrations of percutaneous application of drugs in the first 8–12 months of life. If a systemic effect is unwanted, percutaneous administration of drugs in pre-term and term infants in the first 2 weeks of life should be avoided.

Figure 1 can be used as a guideline to define a dosage based on drug absorption.

4. Developmental Changes in Distribution

In very young infants, the total body water is high (80–90% of the bodyweight) while fat content is low (10–15% of the bodyweight). The amount of total body water decreases to 55–60% by adulthood.[10] The extracellular water content is about 45% of the bodyweight in neonates, compared with 20% in adulthood.[10] The extracellular fluid volume is especially large in neonates with low birth weights.[31]

In children, the extracellular fluid volume correlates with the BSA. This is explained by the fixed, approximately linear relationship between the extracellular fluid space and the body surface.[32]

Protein binding tends to be reduced in neonates and infants for two reasons: (i) the concentration of binding proteins may be low; and (ii) the proteins generally have lower binding capacities in neonates.[11]

4.1 Pharmacokinetic Studies on Distribution

Several hydrophilic drugs, such as panipenem (a carbapenem), gentamicin and arbekacin (aminoglycosides) and linezolid have a significantly larger V_d in neonates than in infants or adults.[31,33-35] The larger V_d in neonates correlates with a larger extracellular water content. The pharmacokinetics of tramadol, a hydrophilic compound with a large V_d in adults, could be described with a two-compartment model. The V_d of the central compartment (a compartment more or less correlated to the extracellular water content) was increased in neonates compared with older children. The V_d of the peripheral compartment (in which the drug is bound to tissue)

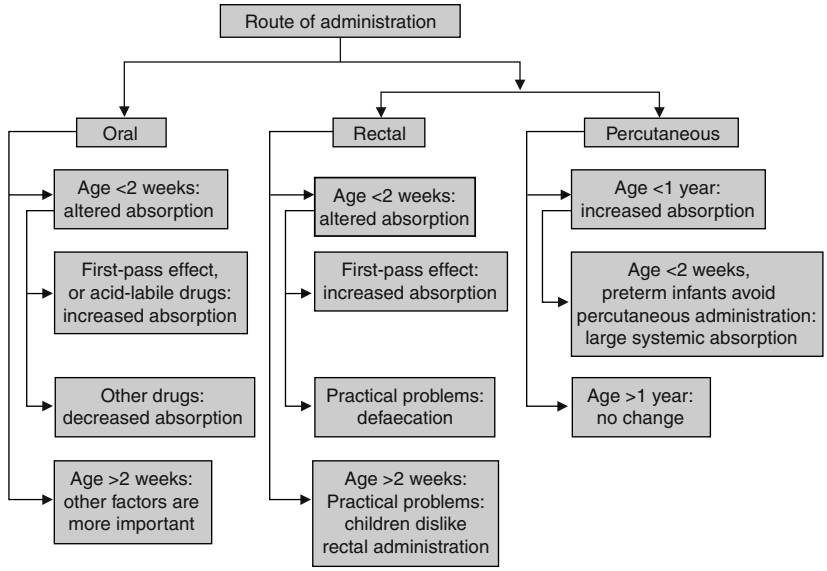

Fig. 1. Dosage guidelines based on drug absorption. Because of the scarcity of the literature, no exact guideline could be developed. However, if a drug is used when treating a child the differences in absorption compared with adults should be considered.

was not affected by age.[36] Other compounds, such as vancomycin, and lipophilic drugs such as diazepam and lorazepam, which have a relatively large V_d as well (>0.6 L/kg), show a similar V_d in infants and adults.[31,37,38]

Another factor which influences the V_d is the protein binding capacity of a drug. The low plasma protein binding capacity in neonates will increase the unbound fraction of the drug. This is possibly relevant for drugs that are extensively protein bound (>90%).[12] An enlargement of the free fraction may increase the V_d. This was shown by Kimura et al.[31] to be relevant in drugs with a small V_d (in adults).

4.2 Other Factors Related to Distribution

Other factors that could relate to differences in the drug distribution in children are the volume of the CNS and the permeability of the blood-brain barrier.

The volume of the CNS is relatively large in younger children and does not correlate well with BSA in the paediatric age range, since CNS volume reaches 80–90% of adult values by age 4–6 years; yet BSA does not reach adult values until about age 16–18 years.[10] These results have led to the use of dosing regimens for intrathecal methotrexate, which are selected on the basis of age rather than BSA.[10]

The blood-brain barrier, which is a determinant of distribution to the brain, is considered to be more permeable in newborns than in older children.[9] This could enlarge the effect of drugs that exert their effect in the brain, but can also enlarge the adverse effects if the effect in the brain is not wanted.

4.3 Conclusions on Changes in Distribution

Compounds with a small V_d (<0.4 L/kg in adults) distribute over the extracellular fluid. The extracellular fluid correlates with the BSA of the child. For this reason, BSA may be used as predictor for the dosage of these compounds (equation 1):

$$\text{Dose}_{\text{Infant}(V_d\text{Adult} < 0.4\ \text{L/kg})} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{BSA}_{\text{Infant}}}{\text{BSA}_{\text{Adult}}} \quad \text{(Eq. 1)}$$

Compounds with a large V_d in adults (>0.6 L/kg), some hydrophilic and all hydrophobic compounds, are extensively tissue bound. The tissue binding capacity does not seem to be altered in children, since the V_d of these drugs seems to be similar in children and adults. A dose should be proposed based on bodyweight (equation 2):

$$\text{Dose}_{\text{Infant}(V_d\text{Adult} > 0.6\ \text{L/kg})} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{Bodyweight}_{\text{Infant}}}{\text{Bodyweight}_{\text{Adult}}} \quad \text{(Eq. 2)}$$

Theoretically, the influence of an altered protein binding capacity in children becomes apparent for compounds with a high protein binding capacity and a small V_d in adults. An increase of the free fraction of the drug may show a larger V_d, but may also increase efficacy and toxicity, and may affect the renal excretion of drugs and the rate of metabolism of low-clearance drugs. An increase in clearance may result in stabilisation of the unbound drug concentration and therefore have no increase in drug effect. Because of these ambivalent effects, there seems to be no need to adjust the dosing schedule.

The dosing schedule based on V_d is shown in figure 2.

5. Developmental Changes in Metabolism

Hepatic blood flow, hepatic metabolism and hepatic transport systems determine hepatic clearance.[39] Birth results in dramatic changes in hepatic circulation and hepatic oxygen tension. This may affect hepatic function during the immediate postpartum period.[39]

Limited *in vivo* data suggest that the biliary excretory function and the carrier-mediated hepatocellular uptake are inefficient in infants.[39]

At birth, both phase I (primarily oxidation) and phase II (conjugation) metabolic enzymes may be immature. *In utero* exposure to enzyme-inducing drugs may reverse this pattern.[40,41]

The development of drug metabolising enzymes varies widely between neonates and may be delayed in premature infants.[42] Each individual isoform of phase I and phase II enzymes has unique maturational profiles. *In vitro* studies have been performed mainly with CYP enzymes and to a lesser extent, with uridine diphosphate glucuronosyltransferase (UGT) enzymes.[11,12,39,43,44] These *in vitro* data show the presence of significant amounts and activity of phase I and phase II enzymes at 2 months of age.[39] After the first year of life, most liver enzymes have matured.[11,12,38,43-45]

The most rapid elimination of drugs is found in school-age children and adolescents, and thereafter plasma clearance decreases with age.[42] Murry et al.[46] and Kanamori et al.[47] demonstrated that the liver volumes of children increase with age (studied in children aged between 1 year and 18 years) and were correlated with BSA; not with bodyweight. An *in vitro* study of several CYP enzymes in paediatric livers showed that the activity of matured hepatic enzymes is largely constant throughout childhood.[48]

5.1 Pharmacokinetic Studies on Metabolism: Immature Enzymes

The importance of hepatic enzyme activity in young infants has been acknowledged ever since the occurrence of serious adverse drug events associated with chloramphenicol toxicity (metabolised by UGT) in neonates. The maturation of the enzymes has a large influence on the rate of metabolism. For example, morphine clearance increases in time, with a maturation half-life of 88.3 days. Formation clearances of morphine, to its glucuronide metabolites

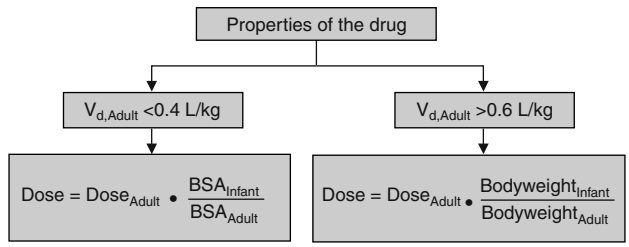

Fig. 2. Dosage guidelines based on volume of distribution (V_d). The calculation of the dosage of a compound in children should be based on the V_d in adults. **BSA** = body surface area.

morphine-3-glucuronide and morphine-6-glucuronide by UGT2B7, increases rapidly from 10.8 and 0.61 L/h/70kg, respectively, at birth to 64.3 and 3.63l/h/70kg, respectively, at 6 months.[45]

Björkman[49] showed that allometric scaling could not predict the clearance of two substrates (midazolam and alfentanil) in neonates because of the immaturity of the CYP enzyme system. This study showed that as soon as CYP activity approaches adult values the allometric method showed good estimates.[49]

A study on the pharmacokinetic data of 40 drugs in children of different age groups showed that the mean elimination half-life of these substrates approached adult levels at 2 months of life. At 6 months, the mean elimination half-life was increased in comparison with adult data. In this study, drugs were metabolised mainly via CYP liver enzymes.[30,50]

Another approach to study the rate of metabolism of a specific compound has been explained by Alcorn and MacNamara.[51] They developed a method to estimate the drug clearance by using *in vitro* hepatic microsomal activity data. *In vitro* data of the abundance and activity of microsomal proteins should be coupled with pharmacokinetic data of the drug in adults with the pathway of metabolism and the fraction of the dose eliminated by these routes. From these data the predominant elimination pathway and the drug clearance of infants can be calculated.

5.2 Pharmacokinetic Studies on Metabolism: Mature Enzymes

Propofol is a high-extraction drug and is therefore a good substrate to study hepatic blood flow.[43] The clearance of this anaesthetic agent, corrected for bodyweight, is 20–55% higher in healthy children aged 1–11 years, than in adults.[52-55] These results correlate with the BSA of children. Hepatic transport was studied using indocyanine green as a substrate. Indocyanine green is cleared by biliary secretion. The biliary secretion was best correlated with BSA.[56]

Several studies have been performed with drugs as markers for hepatic metabolic activity, which show age-related changes in drug clearance. In studies with phenazone (metabolised by CYP3A4, CYP1A2, CYP2C and CYP2B6), ciclosporin (CYP3A), theophylline (CYP1A2), phenytoin (CYP2C9), or anticancer drugs teniposide, etoposide and cytarabine (which are extensively metabolised by the liver) in children older than 1 year, clearances were more consistent when normalised to BSA instead of bodyweight.[10,46,47] Ginsberg et al.[50] studied substrates in a comparative child/adult pharmacokinetic database. This study showed a decrease in the elimination half-life of drugs (substrates for metabolism) from the age of 6 months to 12 years, which is also consistent with BSA and not with bodyweight.[50] However, the use of BSA instead of bodyweight has to be regarded with some caution as outlined in the following points:

1. These studies show a high interindividual variability in drug clearance.

2. The results are not consistently reproducible in other studies. For example, ciclosporin clearance by CYP3A was correlated in one study with the BSA in young children (age >1 year).[47] In other studies, ciclosporin plasma clearance related to BSA was shown to be considerably higher in paediatric patients younger than 8 years compared with adults.[44,57]

3. Pharmacokinetic studies of the same metabolic route with other compounds result in conflicting findings. The clearance of a substrate of CYP2C, phenytoin, was found to be correlated with BSA.[47] However, in a study using omeprazole as a CYP2C substrate, no relation was found between clearance and age.[58]

4. The rate of hepatic metabolism could depend on the pathway of metabolism. Crom et al.[59] clarified this in a study using phenazone and lorazepam as substrates. Fifty children (aged 2.3–17.8 years) with acute lymphocytic leukaemia in complete remission were compared with adult male volunteers. The clearance of phenazone, which is metabolised by CYP enzymes, normalised to bodyweight, was significantly greater in paediatric patients compared

with adults, while no difference was seen when normalising phenazone clearance to BSA. The bodyweight-normalised clearance of lorazepam (which is metabolised primarily by glucuronidation) in children was not significantly different from adults. The mean elimination half-life of UGT substrates lorazepam, morphine, oxazepam, trichloroethanol, valproic acid (sodium valproate) and zidovudine confirmed this finding.[50] Other studies with specific UGT substrates, such as morphine and zidovudine, have showed larger bodyweight-normalised clearances in children.[60,61] Tramadol is primarily metabolised by CYP2D6. Two pharmacokinetic studies of tramadol and its metabolite, *O*-desmethyl tramadol, showed no significant difference in clearance of tramadol between children (aged 1–12 years) and adults, when normalised to bodyweight.[62,63] The hepatic clearance of doxorubicin, which is metabolised via several routes, shows a correlation to bodyweight, instead of BSA.[10] Doxorubicin is metabolised via several routes, which are mainly unknown.

5. The functionally most mature elimination pathway will be the predominant elimination pathway, as demonstrated with paracetamol and ritodrine.[16,43,64] These substrates are mainly glucuronidated in adults. However, the reduction in glucuronidation in childhood is compensated for by an increase in sulfotransferase activity.

5.2.1 Conclusions on Changes in Metabolism

Pharmacokinetic studies show that the grade of maturation of enzymes is the most important factor in determining the rate of metabolism in small infants. After maturation, hepatic blood flow, hepatic transport systems and hepatic metabolic capacity are important factors in the determination of a dose.

Immature Enzymes

The unique pattern of development of each enzyme and the pace of this development, makes it impossible to generalise data of young children. The clearance of a specific drug is highly dependent on the pace of development of the specific enzymes involved and on the pathway of metabolism. However, for clinical practice, some guidelines could be developed. In general, most drugs in neonates have a prolonged elimination half-life. Until the age of 2 months a very low dose should be administered at the start (equation 3). Subsequent dosages should be modified based on careful observation of response or adverse effects, and on therapeutic drug monitoring (TDM), if possible. [See section 9 for more details on TDM.]

$$\text{Dose}_{\text{Infant(age <2 months)}} = \text{low dose, based on response and TDM} \quad \text{(Eq. 3)}$$

At the age of 2–6 months the mean elimination half-life of most substrates approaches adult levels. *In vitro* data suggest that although liver enzymes in general have not matured fully, a significant amount and activity of enzymes is present at this age. Also, at this age range, one should be very careful when dosing drugs, but a general guideline based on bodyweight may be defined (equation 4).

$$\text{Dose}_{\text{Infant(age 2–6 months)}} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{Bodyweight}_{\text{Infant}}}{\text{Bodyweight}_{\text{Adult}}} \quad \text{(Eq. 4)}$$

In future, a dose could be predicted by studying the activity and content of all phase I and II enzyme pathways and renal excretion. These data should be compared with pharmacokinetic data of the specific drug in adults. From these data, the predominant elimination pathway and the clearance in infants may be calculated. However, caution is advised when using this guideline. The guideline is based on *in vitro* data and *in vivo* elimination half-life of drugs. Some drugs show an extreme deviation from the general pattern, which cannot be related to a specific pathway. Although it is impossible to include these extremes in a guideline, one has to consider this possibility when treating children.

Mature Enzymes

Pharmacokinetic and *in vitro* studies show that the rate of metabolism after the maturation of liver enzymes is mainly dependent on liver growth. The liver volume, blood flow and biliary function correlate well with BSA, whereas enzyme activity in general seems to be constant throughout childhood.

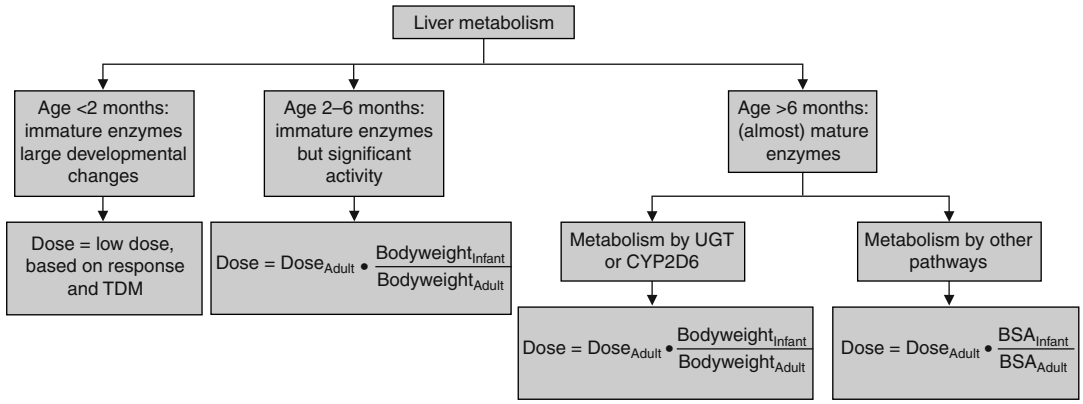

Fig. 3. Dosage guideline based on liver metabolism. Each individual isoform of phase I and phase II enzymes has unique maturational profiles. In general, the neonate has a prolonged elimination half-life for most drugs until the age of 2 months. *In vitro* data suggest that although liver enzymes in general have not matured fully at the age of 2–6 months, a significant amount and activity of enzymes is present. The mean elimination half-life of most substrates approach adult levels at 6 months of life. After maturation, the rate of clearance based on liver metabolism in children is generally greater than in adults, based on bodyweight; therefore, body surface area (BSA) should be used as a guideline. From *in vivo* data, the age of 6 months has been extracted as a boundary between immaturity and a clearance consistent with the liver volume. The exceptions are drugs that are metabolised by a few specific enzymes. Thus far, uridine diphosphate glucuronosyltransferase (UGT) enzymes and cytochrome P450 (CYP) 2D6 have been classified as such. In these cases the drug dosage should be based on bodyweight. **TDM** = therapeutic drug monitoring.

Based on many substrate studies, it seems reasonable to administer drugs that are metabolised by mature liver enzymes based on BSA. At the age of 1 year, maturation of most enzymes has occurred. As early as 6 months, the elimination half-life of drugs is generally consistent to the volume of the liver (equation 5).

$$\text{Dose}_{\text{Infant(age >6 months)}} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{BSA}_{\text{Infant}}}{\text{BSA}_{\text{Adult}}} \quad \text{(Eq. 5)}$$

An exception should be made for a few enzyme pathways. If a drug is mainly metabolised by UGT or CYP2D6, the plasma clearance seems to be correlated with bodyweight (equation 6):

$$\text{Dose}_{\text{Infant(drugs metabolised by UGT or CYP2D6)}} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{Bodyweight}_{\text{Infant}}}{\text{Bodyweight}_{\text{Adult}}} \quad \text{(Eq. 6)}$$

The predominance of these pathways should be considered with care, since another route of elimination, which seems secondary in adults, may take over as a predominant route in children.

A deficit of knowledge on the pathway of metabolism of drugs is a serious problem when dosing in children. If this route is unknown, no dosing schedule for children can be defined.

The response of dosing according to these guidelines should be considered carefully, since the substrate studies show a large interindividual variation.

The reason for the discrepancy between the rate of metabolism by UGT and CYP2D6 and liver growth needs additional study. The metabolic activity of each isoform of UGT enzymes needs to be elucidated. Other metabolic pathways, like drug transport by P-glycoprotein, need to be studied in more detail.

Figure 3 can be used as a guideline to define a dosage based on metabolism.

6. Developmental Changes in Renal Excretion

Maturation of renal function begins during fetal organogenesis and is completed by early childhood. Nephrogenesis begins at 9 weeks of gestation and is completed by 34 weeks of gestation, followed by postnatal changes in renal and intrarenal blood flow.

The glomerular filtration rate (GFR) is approximately 2–4 mL/min/1.73m^2 in term neonates, but may be as low as 0.6–0.8 mL/min/1.73m^2 in preterm

neonates.[6] The GFR increases rapidly to around 70 mL/min/1.73m^2 in full-term infants, and to 20 mL/min/1.73m^2 in preterm infants in the first 2 weeks.[12,65]

The renal function in preterm infants is reduced as a result of continued nephrogenesis.[65] The increase in GFR in the first weeks is mainly because of an increase in (renal) blood flow. Other factors that influence the GFR are vasoactive systems, such as the renin-angiotensin system, plasma protein concentration, the arteriolar resistance and the increase in surface area of the glomerular membrane.[65]

The renal weight is correlated with the BSA of the child.[66,67] However, studies on BSA or bodyweight to predict GFR have failed to uniformly show a correlation:[68] GFR divided by BSA seems to increase as a function of age in small children.[66,67] GFR may exceed adult values on a kg basis after the age of about 3 months.[67] Hayton[69] showed that maturation of GFR takes about 2 years. After 2 years, the capacity of glomerular filtration is similar in adults and children, when GFR is expressed in mL/min/1.73m^2.[66] This method, in which the GFR is correlated to adult values, uses BSA as an index to correlate GFR in children to adults. Studies in which the GFR is indexed to BSA and to extracellular fluid volume show that the latter is possibly a more valid parameter to describe the GFR.[67,70]

Tubular secretion is reduced at birth. In preterm infants, the tubular secretion may be different from term infants because of a limited tubular function.[71] Maturation of this tubular function takes about 1 year.[69] Sodium excretion in preterm neonates seems to be inverse to gestational age, possibly due to tubular immaturity.[72]

Renal reabsorption in newborns seems to be reasonably developed.[73] Some research suggests that further development and maturation of renal tubular reabsorption is a gradual and continuous process from birth to adolescence, but the key stage of maturation may be at about 3 years.[11]

6.1 Pharmacokinetic Studies on Renal Excretion

There is a high correlation between gestational age and renal excretion of drugs.[31,74,75] A method to determine the renal excretion, is to determine the GFR. The method mainly used by paediatricians to estimate the GFR in daily practice is the method of Schwartz, a formula which uses the creatinine plasma concentration (P_{CR}) and body length (L).[76,77] This formula correlates the GFR and serum creatinine (equation 7):

$$GFR = k \bullet \frac{L}{P_{CR}} \quad \text{(Eq. 7)}$$

GFR is expressed as mL/minute/1.73 m^2. The correction to 1.73m^2, a standard adult, has been performed in order to be able to correlate data of all patients. k is a constant that reflects the relationship between urinary creatinine excretion and body size. Estimations of k have been performed by Schwartz et al.,[76] Counahan et al.,[78] Morris et al.[79] and Leger et al.[80] Hellerstein et al.[81] and Pierrat et al.[82] evaluated the value of k in the formula of Schwartz in infants and concluded that Schwartz overestimated the GFR by 20%. However, in a study of children aged 4 days to 12 years, the GFR predicted by the method of Schwartz correlated well with the clearance of sotalol.[83] A study of the clearance of gentamicin in neonates showed a strong relationship to GFR calculated by the formula of Schwartz, even in preterm children.[75] This study shows that the value of k should be adjusted for term and premature neonates, as formulated by Schwartz et al.[76] According to Van Rossum et al.[84] and Hogg et al.,[77] the value of k is closely linked with the method used to measure the plasma concentration of creatinine. Therefore, the value of k should be assessed locally in each hospital.

There is some controversy regarding the use of serum creatinine to predict renal function in children. Serum creatinine depends on age, gender and muscle mass.[74] Residual maternally derived creatinine interferes with the assay in the first week of life in newborns.[38] Full-term infants excrete more urinary creatinine per minute per unit of body size than

premature infants.[75] A comparison of serum creatinine with inulin clearance in preterm neonates showed a good correlation and supported serum creatinine as an appropriate measure of GFR in preterm neonates.[85] Pierrat et al.[82] showed that the Cockcroft-Gault formula[86] predicts GFR in children older than 12 years more accurately than the formula of Schwartz, possibly because of factors such as gender and bodyweight.

Factors that have a negative influence on the use of plasma creatinine to predict renal function are: (i) disruption of the functional integrity of the renal tubule; and (ii) a GFR of under 20mL/min/1.73m^2.[65] In these patients, the GFR is possibly overestimated.[74] Creatinine is usually measured with the Jaffé reaction. With this method, high serum concentrations of serum bilirubin, ketoacids and cephalosporins interfere with the reaction. van den Anker et al.[85] showed that to measure serum creatinine an enzymatic method should be used since this method is much less influenced by these substances.

A more direct approach to estimate the GFR is to use a marker that is uncharged, biologically inert, freely permeable across the glomerular capillary and neither secreted nor reabsorbed by the tubulus.[65] Markers that have been mentioned to measure the GFR are inulin, polyfructosan S, cystatin C, ^{51}Cr-EDTA, ^{125}I-iothalamate or mannitol.[65,69,74] A marker to estimate the active tubular secretion in children is p-aminohippuric acid.[69]

The influence of other excretion pathways in the excretion of drugs in infants is unpredictable. This is mainly seen in preterm neonates, since the renal function in these infants is extremely low. An extrarenal pathway of excretion can become relatively greater. This is demonstrated with panipenem and imipenem in combination with cilastin.[31,87] The renal clearance and nonrenal clearance of imipenem for 41 premature infants averaged 16% and 80%, respectively, compared with adult values, which averaged 52% and 44%, respectively.[87] Another discrepancy in imipenem clearance was shown in infants, where an active tubular secretion component was shown to account for a greater fraction of the total renal clearance in children compared with adults.[88] Similar findings were seen with digoxin.[89] The higher clearance of both drugs in infants is possibly caused by a larger fraction of active tubular secretion.

6.1.1 Conclusions on Changes in Renal Excretion

The calculation of the drug dosage of a drug that is excreted by the kidneys should be based on the rate of the process that is primarily involved: glomerular filtration, tubular secretion or tubular reabsorption.

Although some controversy exists regarding the use of serum creatinine in infants to predict renal function, several studies show that there is a fair correlation between GFR and serum creatinine in children. In general, serum creatinine and the formula of Schwartz may be used to predict the GFR, even in preterm infants, from 1 week of age. The value of k should be estimated in different age groups and depends on the method of determination. In children older than 12 years, the formula of Cockcroft-Gault may be used to estimate GFR. The serum creatinine may in some cases under- or overestimate the GFR.[65,74,81] Using an inert marker to measure the GFR is more applicable when treating, for example, patients with an end stage renal impairment or when treating newborns in the first 7 days of life. In the first week of life, the gestational age may be used as a guide to prescribe drugs, which are primarily cleared by glomerular filtration. In this case, the serum creatinine values can be used to further adjust the dosage when creatinine is outside the normal range for that particular gestational age.

Based on serum creatinine or an inert marker to measure the GFR in the child, a dosing guideline for drugs with significant excretion (>50%) by glomerular filtration can be developed. If the GFR is expressed in clearance in mL/min, not in mL/min/1.73m^2, the following guideline should be used (equation 8):

$$\text{Dose}_{\text{Infant(age >1 week)}} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{GFR}_{\text{Infant(mL/min)}}}{\text{GFR}_{\text{Adult(mL/min)}}} \quad \text{(Eq. 8)}$$

If the GFR is estimated in mL/min/1.73m^2, the estimated GFR should be adjusted with the factor:

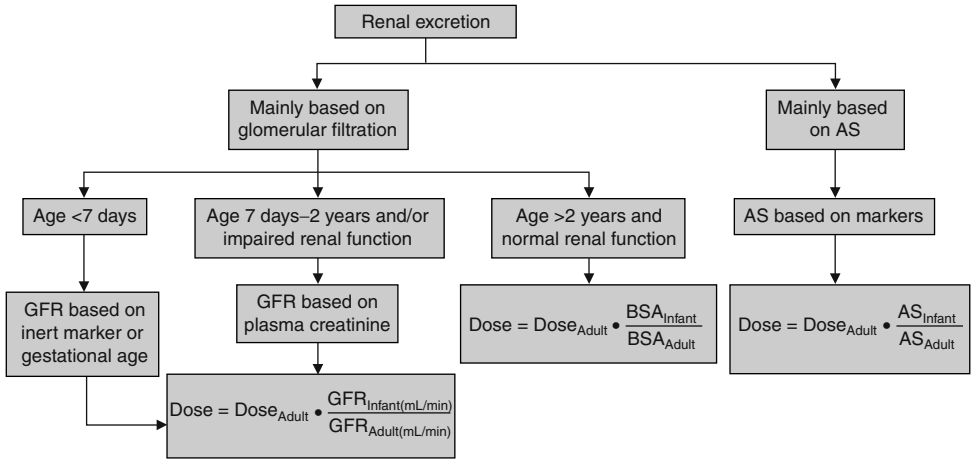

Fig. 4. Dosage guideline based on renal excretion. In general, the rate of clearance based on the glomerular filtration rate (GFR) in children older than 3 months is greater than in adults, based on bodyweight. Drug dosing should be based on GFR, active tubular secretion (AS) or tubular reabsorption. In neonates <7 days old and in children with, for example, an end stage renal function, the GFR should be estimated with an inert marker. For the estimation of the GFR in other children, serum creatinine can be used as a marker. Since there is a good correlation between body surface area (BSA) and GFR in children >2 years old without renal insufficiency, BSA can be used in these infants to calculate the dose. A marker for AS is p-aminohippuric acid.

$BSA_{child}/1.73m^2$. A standard GFR in adults is approximately 125 mL/min/1.73m^2. Therefore, the factor with which the GFR (in mL/min/1.73m^2) of the infant should be adjusted is $1.73m^2 \times 125$ mL/min/1.73m$^2 \approx 215$ (mL/minute) [equation 9]:

$$\text{Dose}_{\text{Infant(age >1 week)}} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{GFR}_{\text{Infant(mL/min/1.73m}^2\text{)}} \bullet \text{BSA}_{\text{Infant}}}{215} \quad \text{(Eq. 9)}$$

After maturation of the renal function at the age of approximately 2 years, the GFR correlates well with the BSA of the child in patients with a normal renal function. Extracellular fluid volume has been proven to be an even better parameter, but this parameter is not useful for the estimation of a dose for the clinical practice. Renal insufficiency in children does not occur often. Therefore, in general it seems reasonable to determine the dose of drugs that are excreted by glomerular filtration indexed to BSA in children >2 years of age (equation 10).

$$\text{Dose}_{\text{Infant(age >2 years)}} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{BSA}_{\text{Infant}}}{\text{BSA}_{\text{Adult}}} \quad \text{(Eq. 10)}$$

The rate of active tubular secretion can be measured by using two markers: a marker of the GFR (mannitol, inulin, creatinine, etc.) and of the active tubular secretion and GFR (p-aminohippuric acid). The elimination of the marker of active tubular secretion and GFR should be subtracted by the excretion of the marker of GFR to give active tubular secretion.[69]

From these data a dosing guideline for drugs with a significant excretion (>50%) by active tubular secretion (AS) can be developed (equation 11):

$$\text{Dose}_{\text{Infant}} = \text{Dose}_{\text{Adult}} \bullet \frac{\text{AS}_{\text{Infant}}}{\text{AS}_{\text{Adult}}} \quad \text{(Eq. 11)}$$

A higher fraction of active tubular secretion should be considered in infants. These factors should be included in the model in order to optimise the dosing guidelines further. A substrate to measure reabsorption has not yet been defined. Reabsorption should be quantified as well. Data of adult patients with severe renal impairment could reveal a dependence on nonrenal elimination pathways for drugs, which could prevail in infants.

Figure 4 can be used to define a dosage based on renal excretion.

7. Integration of Pharmacokinetic Processes

After the unravelling of the developmental changes in absorption, distribution, metabolism and elimination, it is crucial to integrate this newly acquired knowledge into one model. The four schedules should be combined to construct a dosing regimen.

The V_d cannot be seen in isolation. The maximum plasma concentration of a drug in the body depends on the V_d. The clearance of the drug determines the steady-state concentration of the drug. The steady-state concentration is reached after a period of time equivalent to 4–5 times the elimination half-life of the drug. When steady state is reached, the V_d loses its importance, as shown in figure 5.

For this reason, only the first doses of a drug in infants should be based on the presumptions of the V_d in order to reach the therapeutic range. After the design of the first dose, the regimen of the maintenance dose should be defined by the clearance of the drug.

Exceptions to this rule are compounds in which the steady-state concentration is never reached. A reason could be a very short elimination half-life or a wash out period after every dose in order to prevent accumulation. Antibacterial agents like aminoglycosides are an example.[90] In these situations, a dose based on V_d should be given at each administration.

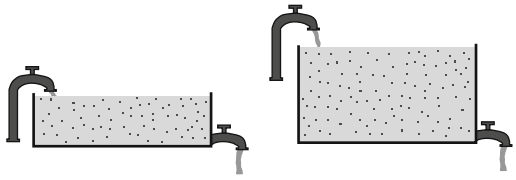

Fig. 5. A small and a large bathtub have been filled with water. In order to reach the same concentration of soap in the two baths, the amount of soap that should be added will be much greater in the large bathtub. After reaching the same concentration the plug is pulled out while the tap keeps on running. The flow into the bathtub is the same as the flow out of the bath. In order to keep the same (steady state) concentration in both bathtubs, the same doses of soap should be added into both bathtubs.

Another exception is when the calculated maintenance dose (the dose based on excretion) exceeds the calculated first dose (the dose based on V_d). This applies to renally excreted drugs in children over 2 years of age and to drugs that are metabolised by the liver in children over 2 months of age. In these cases, only a dose based on clearance is used.

The predominance of renal elimination, or excretion by liver metabolism, should be studied with care. In very young children especially, the possible influences of secondary pathways could become much more important in comparison with adults. For example, 86% of caffeine in infants is eliminated by renal excretion, whereas in adults, caffeine is extensively metabolised by the liver.[91]

Another warning results from metabolites, which may be pharmacologically active or may cause adverse events. Morphine-6-glucuronide, for example, is approximately 100 times more potent as an analgesic than morphine. Reduced clearance of this metabolite due to a reduced renal eliminating capacity, may therefore lead to a prolonged analgesic effect, with an increased risk of adverse effects.[92] The immaturity of epoxide hydrolase in neonates may cause adverse effects when treating neonates with carbamazepine. The metabolite carbamazepine-epoxide accumulates in the neonate because of this immaturity.[30]

After the design of the dosage based on these considerations of V_d and elimination, modifications should be considered based on the absorption parameters. These modifications are explained in figure 1.

Figure 6 explains the dosage guideline based on this integration of pharmacokinetic processes.

8. Other Factors Influencing the Disposition of Drugs

Disturbances in the child, such as diseases, can have a large influence on metabolism and renal excretion. Hypoxic episodes and poor perfusion, both of which are common in ill newborns, might be expected to reduce the rate and amount of drug absorption. Hypoxaemia decreases the glomerular and tubular functions in neonates.[93] Severe cardiac

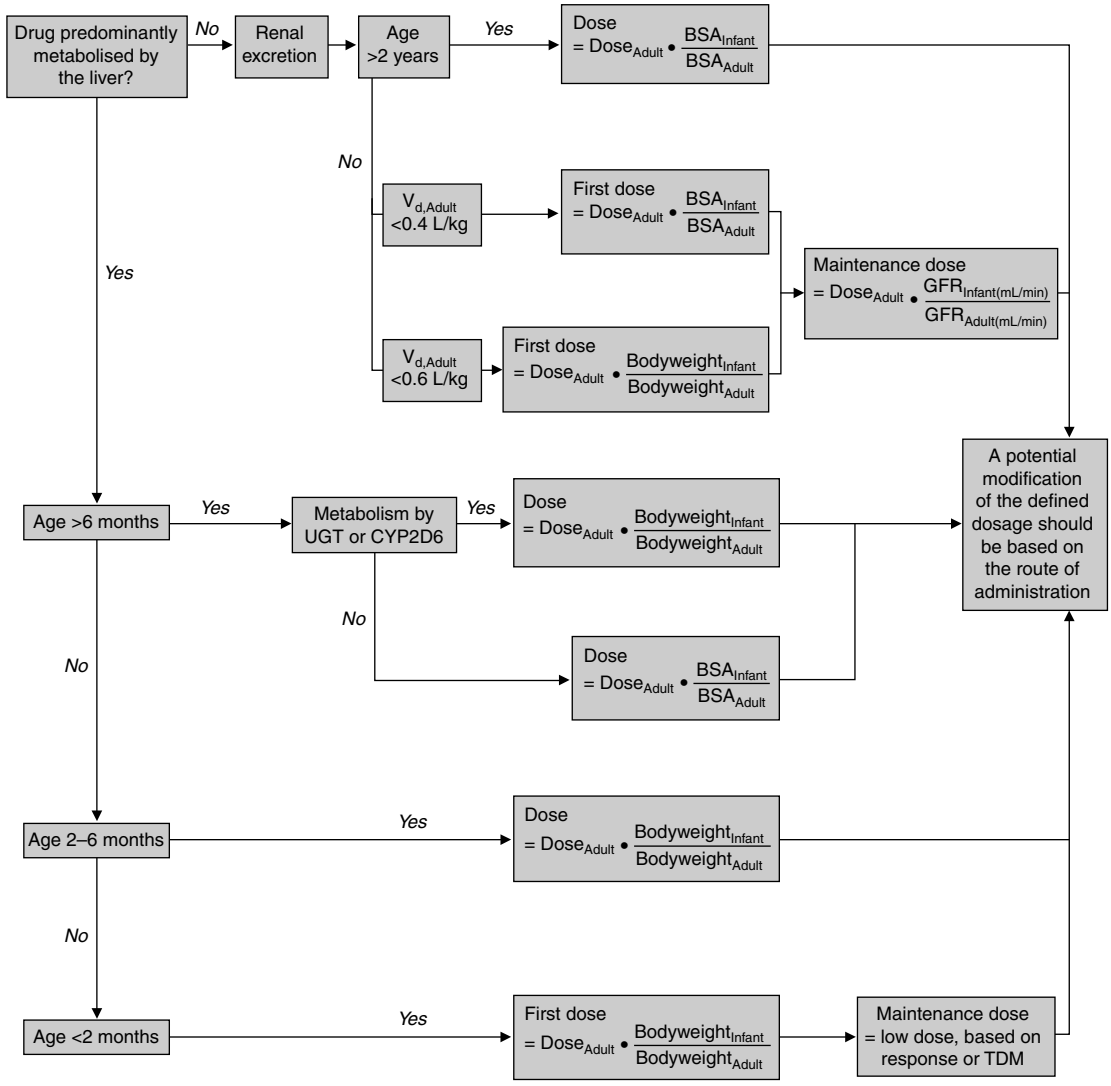

Fig. 6. Dosing guideline based on the integration of the pharmacokinetic processes in the absence of pharmacokinetic data in children. This guideline is based on the current knowledge of the physiology of the child and *in vivo* and *in vitro* data of drugs. A drug dosage should be based on the characteristics of the drug and the age of the child. A modification of the dosage should be based on the route of administration. These modifications have been explained in the main text and developmental changes in absorptive capacity and first-pass metabolism in figure 1. Especially when treating children <6 months old the possible influences of secondary pathways could become much more important in comparison to adults. Therefore, in these patients, different routes of metabolism and renal excretion (of metabolites) should be considered. **BSA** = body surface area; **CYP** = cytochrome P450; **GFR** = glomerular filtration rate; **TDM** = therapeutic drug monitoring; **UGT** = uridine diphosphate glucuronosyltransferase; $\mathbf{V_d}$ = volume of distribution.

insufficiency in children reduces the perfusion of the splanchnic area and so reduces and delays absorption.[9] Portal blood steals through the ductus venosus, impairing hepatic and renal flow in neonates. The V_d may also be altered in these neonates.[4] Distribution and elimination can therefore not be predicted in patients with a patent ductus arteriosus.[4,49]

Alteration of hepatic blood flow by diseases is seen when using propofol as a substrate. Rigby-

Jones et al.[94] concluded that in critically ill infants, increased peripheral V_d and reduced metabolic clearance following surgery causes prolonged clearance of propofol. Other examples are leukaemic infiltration of the liver in children with acute lymphoblastic leukaemia and viral hepatic infections, which will alter the pharmacokinetics of hepatically metabolised drugs.

Protein binding in patients with acute leukaemia and in acutely ill patients may be altered as a result of poor nutrition.[95] HIV-infected patients may develop HIV-associated nephropathy.

Drugs can influence metabolism by interactions, influence on maturation (e.g. corticosteroids lower the maturation of the nephrons), toxicity (busulfan may cause hepatic veno-occlusive disease, gentamicin may cause nephrotoxicity), etc.[96-98]

Genetic polymorphism of target receptors may influence the effect of the drug in the infant. Polymorphism of metabolising enzymes, carrier mechanisms and drug transporters may affect the absorption and excretion of drugs.

Pharmacokinetic processes in male and female children under the age of 12 years, normalised for body size, are generally similar. However, the puberty-associated hormonal changes occurring with the onset of gender differentiation are a potentially important source of pharmacokinetic variability in adolescents.[1,49]

Because there is an increase in childhood obesity in the Western world, one may question whether the literature data regarding the relationship between age and physiological processes are still valid for present-day children.[47] More research is needed on the development of the physiology in obese children; for example, whether dosages should be based on lean bodyweight or actual bodyweight (or BSA) in these children.

Data from adults may assist predictions about the effect of specific disease states, metabolism-based drug interactions and the effects of obesity or genetic polymorphisms on drug disposition in children.

9. Discussion and Conclusion

The paediatric patient population exhibits unique differences in pharmacokinetic parameters as opposed to adults and, consequently, requires specialised dosage considerations. While the paucity of pharmacokinetic and physiological data make it difficult to precisely determine drug dosages in children, knowledge of the effects of maturation and growth will allow tentative recommendations to be made.

To date several approaches for paediatric dose selection have been published. The four current methods to approximate the initial dose for an infant are: (i) age-based categories; (ii) normalisation to body mass; (iii) normalisation to BSA; and (iv) using an allometric method. All these have some physiological basis. By unravelling the effect of the developmental physiology in the child on the four most important pharmacokinetic processes, it was possible to correlate the developmental pharmacology of the child to these and other approaches for paediatric dose selection. None of the four processes could be studied on its own. Integration of the guidelines based on the four processes into one general guideline has been clarified in this article and is shown in figure 6. With this method, a much more refined dosing regimen could be designed. A drug dosage should be based on the characteristics of the drug and the age of the child.

One reason to be careful when using the guideline to design a dosing regimen for a child is the high interindividual variability in the pharmacokinetic data.[39] The variability is often 3- to 6-fold. The variability is much greater in children than in adult patients, since all parameters that have been mentioned influence each other and processes change rapidly and individually. The most extensive variability is observed in the first 3 days of life. With increasing postnatal age, both elimination half-life and the degree of interindividual variability decrease.[39] Therefore, after the initial dose regimen has been set and given, the subsequent doses must be individualised for patients, based on careful observation of response or adverse effects. TDM of plasma concentrations should be considered. TDM

is of use when the concentration-effect relationship has been proven for the indication in which the drug is used, and there must be a reliable method for the analysis of the drug.[99] TDM is a well known strategy to individualise dosing in children and routine plasma drug monitoring of drugs, such as antibacterials, antiepileptics, immunosuppressants and antineoplastics. TDM of these drugs are performed in paediatric patients in clinical routine. When TDM is used in monitoring drugs in children, all developmental pharmacokinetic parameters that have been mentioned in this article should be considered.

With the results of TDM, studies should be performed based on these data. A population pharmacokinetic approach is attractive to study the pharmacokinetic parameters of a single drug in children. In this approach small numbers of measurements are taken at random times from a large heterogeneous group of subjects. Less blood samples are needed than in the classical approach, and blood sampling times are flexible.[100] This is a large advantage in children, since drawing blood is difficult especially in very young infants. Further optimisation of paediatric dosing can be obtained by pharmacokinetic/pharmacodynamic approaches. This approach correlates plasma concentrations, measurement of clinical effectiveness and the concentrations needed to obtain that pharmacodynamic effect in children.[101] An example of pharmacokinetic/pharmacodynamic modelling in children is a study with sotalol.[102] In this study the QT interval prolongation and the antiarrhythmic effect of sotalol were studied in connection with the sotalol plasma concentrations of patients of different ages. Another approach is paediatric physiologically based pharmacokinetic (PBPK) modeling. PBPK models combine the developmental physiological processes of the child with adult pharmacokinetic data. Some PBPK modeling has been performed to date, including modeling of theophylline, midazolam and caffeine.[103,104] Pharmacokinetic studies will determine much more accurately the most appropriate doses for neonates, infants, children and adolescents and these data are critical from the moment that a new drug is introduced for clinical practice. The pharmaceutical industry should synchronise the development of drugs in adults with these studies in children.

Much more research is needed to fully comprehend the influence of age on the disposition of a drug. As shown, studies with substrates as markers for hepatic metabolic activity or renal function and *in vitro* data are very useful for a better understanding of this influence. Adult data are a good starting point for the prediction of the effect of drugs in infants and children. Absorption of drugs is currently the most difficult parameter to predict in children. More research is needed on the metabolic capacity of gastrointestinal tract, and on carrier mechanisms and drug transporters in the gastrointestinal tract, for example on P-glycoprotein and CYP activity. The first-pass metabolism should be studied in more detail. In order to understand the effect of the protein binding capacity of a drug in children, further studies should be performed with drugs that are extensively protein bound. The pharmacological effect of the drug in the child should be studied with pharmacokinetic/pharmacodynamic modelling. To further increase our knowledge of the development physiology and pharmacokinetics of the child, the guidelines described in this article can be considered as a starting point for more research on drugs in children.

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