PHARMACOTHERAPY NOT ONLY IN CHILDREN

Farmakoterapia u dzieci i nie tylko

Maria Droździk[1], Marek Droździk[2]

1. Medical University of Łódź
2. Chair of Pharmacology, Pomeranian Medical University in Szczecin

Abstract: The study presents the factors that can affect the response to drugs at various stages of a child's development, thus determining the effectiveness and safety of pharmacotherapy. Based on the presented developmental changes, methods of calculating doses were established to enable extrapolation of adult dosing to the paediatric population. Moreover, the article demonstrates other potential tools (therapeutic drug monitoring, pharmacogenetics) that may be used to optimise drug dosing in children.

Streszczenie: W pracy przedstawiono czynniki, które mogą wpływać na odpowiedź na leki w poszczególnych stadiach rozwoju organizmu, warunkując tym samym skuteczność i bezpieczeństwo farmakoterapii. W oparciu o przedstawione zmiany rozwojowe opracowano sposoby obliczania dawek, które umożliwiają ekstrapolację dawkowania u dorosłych na populację pediatryczną. Wskazano również inne potencjalne narzędzia (terapia monitorowana stężeniem leku, farmakogenetyka), które mogą służyć do optymalizacji dawkowania leków u dzieci.

Key words: medicine, dose, children, pharmacokinetics, pharmacodynamics.

Słowa kluczowe: lek, dawka, dzieci, farmakokinetyka, farmakodynamika.

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Corresponding author
Marek Droździk
Chair of Pharmacology,
Pomeranian Medical University in Szczecin
Telephone: 91 466 15 89
e-mail: drozdzik@pum.edu.pl

Introduction

Dosing medicines in children in most cases is based on the clinical data established in an adult patient population , thus unfortunately, as a result, a number of variables specific for the developmental age are disregarded. This thesis was formulated over 100 years ago by the father of American paediatrics, Dr Abraham Jacobi, who said: "Paediatricians do not deal with miniature women and men who need reduced doses of drugs for diseases occurring in a smaller organism, but (...) with patients who require a proper dosing regimen". Since then, a lot of factors that modify the response of a paediatric patient to treatment, especially those affecting the pharmacokinetic properties of drugs, have been identified. Unfortunately, the pharmacokinetics (including interactions) and effects (including adverse effects) of many medications used in daily clinical practice are not directly verified; therefore, their dosing, indications and adverse effects in the individual developmental periods of a child have not been established. It is associated with the need to use medications inconsistently with the recorded indications (off-label) or to administer medications in a way different than recommended by the manufacturer (unlicensed use). It is estimated that in the European Union approximately 50% and even up to 90% (depending on the source) of medications administered to children are used off-label [1, 2]. Therefore, the agencies regulating the marketing of drugs (e.g. European Medicines Agency [EMA] and Food and Drug Administration [FDA]) encourage manufacturers to conduct studies on medications that provide sufficiently high quality in the paediatric population, via initiatives such as the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) or by establishing advisory bodies, e.g. Paediatric Committee (PDCO) that specialise in the use of medications in children and adolescents. Hopefully, with a growing body of knowledge regarding developmental changes that determine the effectiveness and safety of pharmacotherapy, appropriate therapeutic guidelines, considering various stages in the development of the organism, will be established.

Pharmacokinetics

Development of the organism is associated with a number of functional changes that significantly affect the fate of medications in the body, i.e. pharmacokinetics, which include the following processes, represented by the acronym ADME: drug

absorption, distribution, metabolism i.e. biotransformation, and excretion. Optimisation of medicine dosing in children requires understanding and finding relationships between ontogenesis and the pharmacokinetic data.

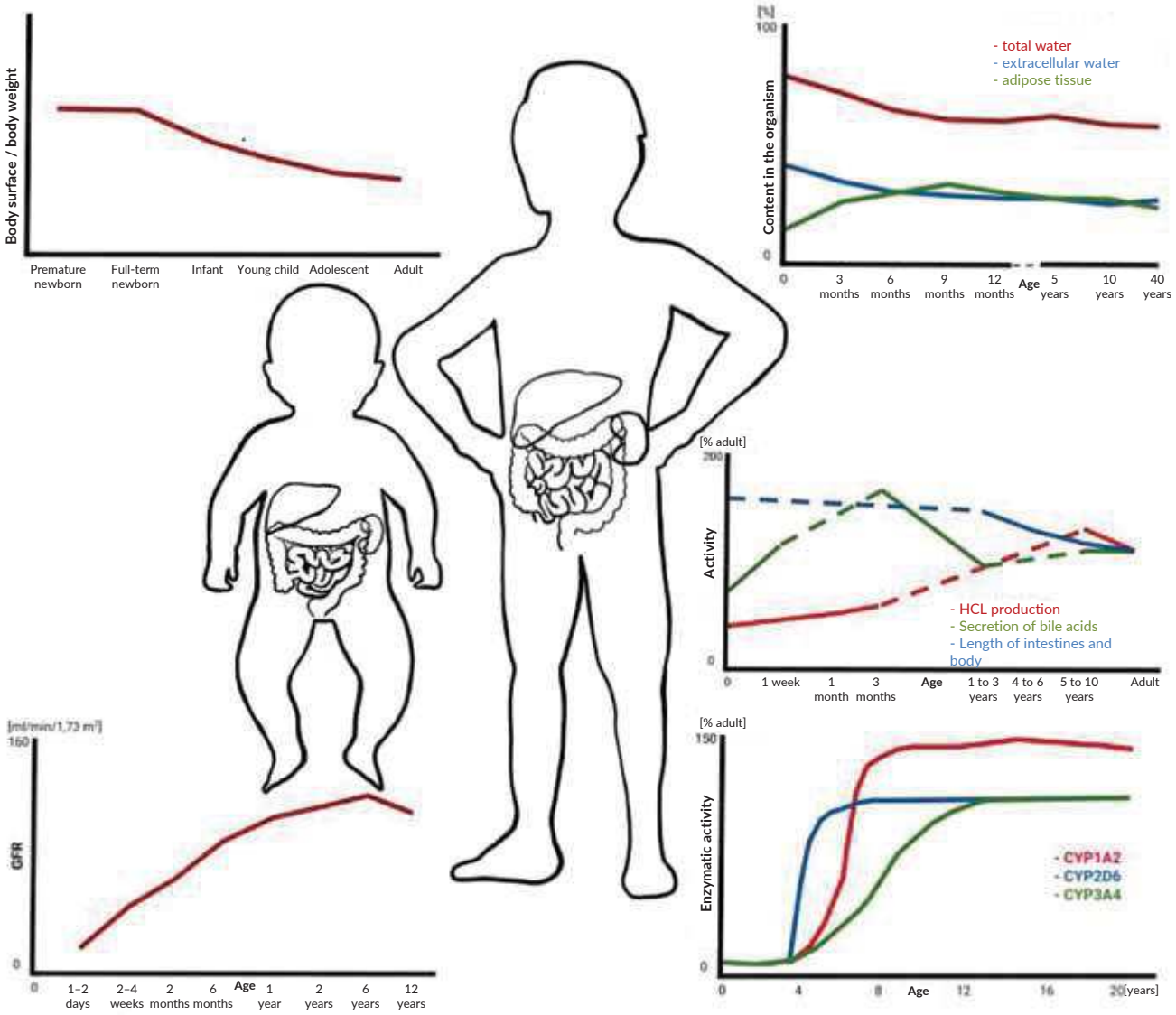
Drug absorption is affected by a number of mechanical, biological and physicochemical factors that determine substance penetration through biological barriers that have different characteristics in paediatric population. The first factor is pH, which changes in different parts of the digestive tract, affecting the level of drug ionisation and stability, as well as the function of drug transporters in the enterocyte membrane [3]. After birth, the pH in the neonate's stomach is higher than in adult, and is usually 4–6. This results in higher bioavailability of medications that degrade in an acidic environment (amoxicillin, erythromycin) in neonates compared with older children, as well as in a reduced absorption of weak acids (paracetamol, phenytoin, phenobarbital), whose ionisation increases in a more alkaline environment. Other differences include longer gastric emptying time, 6–8 hours (1–3 hours in an adult), which may lead to delayed drug absorption, e.g. the maximum concentration of paracetamol is delayed and is higher due to reduced drug clearance. The pharmacokinetics of the drug is also affected by the frequency, amplitude and duration of propulsive contractions that increase with age, as well as by a gradual maturation of the processes of passive and active drug absorption, which are fully active in the fourth month of life. Due to the above phenomena, the bioavailability of paracetamol in neonates and infants (up to two months of age) is 10 times lower than in older feverish children. Summing up, the absorption rate of most medications is lower in infants and younger children than in the older population, and the time to reach maximum concentration is longer [4].

Another important factor affecting the bioavailability of a medication is the varying activity of the intestinal enzymes participating in drug metabolism, which may determine the absorbed quantity of the medicine. Previous studies demonstrated that the activity of cytochrome P4501A1 increases and the activity of glutathione S-transferase decreases with age. Changes in bile secretion, affecting the bioavailability of lipophilic medicines through modification of their solubility, also appear to be significant.

Absorption of medicines administered via routes other than oral may also differ between children and adults. In neonates and younger children, after rectal administration, the bioavailability of drugs metabolised in the liver may be significantly higher, primarily due to the immaturity of the enzymatic systems. In prematurely born children, full-term newborns and younger children, transdermal absorption is increased, probably due to a thinner epidermal corneal layer, higher water content and increased blood flow through the skin (compared to the adult population). Therefore, the amount of medicines absorbed through the skin (glucocorticosteroids, antihistamines, disinfectants) may exceed the desired therapeutic values and result in adverse effects. Studies demonstrated that local treatment of nappy rash for approximately two weeks may lead to dysregulation of the hypothalamic-pituitary-adrenal axis, resulting in iatrogenic Cushing's syndrome. In clinical practice, the use of steroids should be limited exclusively to cases where it is necessary, with a possibly short time of treatment (products characterised by a low transdermal penetration should be chosen).

Drug distribution describes the location of medicines in the organism. It is illustrated by distribution volume (the hypothetical volume of body fluids in which the medicine, following a balanced distribution in the organism, would reach the same concentration as in the blood). Having reached systemic circulation, the medicine is distributed in the blood, tissues and organs. This process is determined by a number of patient-specific factors, i.e. the level of blood supply, permeability of membranes and pH differences between tissues and blood plasma, as well as drug-dependent factors, i.e. the degree of binding with plasma proteins and tissues, molecule size and its physicochemical properties. Drugs with large distribution volume (lipophilic, non-polar) are characterised by a low capacity to bind with plasma proteins, they bind strongly to peripheral tissues and have low molecular weight. The higher total water content in organisms of newborns (compared to adults) results in lower plasma concentrations of hydrophilic medicines dosed per body weight unit. In addition, a higher water-to-lipids ratio in the adipose tissue of newborns contributes to this situation. An important factor affecting the distribution, but also metabolism and activity of medicines, is the degree of their binding to plasma proteins, as only the unbound fraction of the drug may penetrate to tissues. Therefore, changes in the quantity or composition of plasma proteins (especially of albumin and acidic α1-glycoprotein) may affect the distribution volume of medicines characterised by high binding. Newborns have foetal albumin and higher concentrations of endogenous substances that can displace medicines from protein-bound molecules (including bilirubin and free fatty acids), and that contribute to the increase of the biologically active free drug fraction with high affinity to albumin (a clinically significant degree of binding: 90–95%). Factors other than age, important for neonatologists and paediatricians, may also affect the degree of drug binding to plasma proteins: pathological conditions that increase the unbound drug fraction, i.e. hypoalbuminemia in cystic fibrosis, malnutrition, kidney or liver diseases or conditions increasing the concentration of acidic α1-glycoprotein, i.e. injuries, postoperative condition, burns, inflammatory processes and neoplastic diseases, contribute to a higher degree of binding of alkaline medicines (lidocaine, propranolol).

Figure 1. Developmental changes affecting pharmacokinetics.



Another group of pharmacokinetic processes characterised by age-dependent variability depends on the activity of the enzymes that metabolise drugs. Metabolism/biotransformation of medicines typically occurs in two phases. Phase I reactions include oxidation, reduction and hydrolysis, while phase II reactions include conjugation with glucuronic acid, sulphuric acid, glutathione or amino acids and acetylation and methylation of drugs or their metabolites resulting from phase I reactions.

The main goal of the processes above is biotransformation of lipophilic compounds into hydrophilic compounds, which demonstrate a considerably lower ability to penetrate through biological membranes and can be eliminated with urine. The principal site of drug metabolism is the liver. The enzymatic system found in its microsomal fractions (cytochrome P450 isoenzymes) catalyses over 90% of the drug oxidation reactions. The most important isoenzymes in the fraction include: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CY-P3A4. At birth, especially in premature newborns, the activity of certain metabolic pathways is reduced. After the birth, the activity of CYP2E1 and CYP2D6 increases significantly, while the activity of CYP3A7 decreases (it is present in foetuses and neonates, providing a protective role through the metabolism of dehydroepiandrosterone sulfate and the teratogenic derivatives of retinoic acid), to be replaced by CYP3A4. In the first week of life, the activity of CYP2C9 and CYP2C19 can be observed, and CYP1A2 occurs from first to third month. The most important (considering drug biotransformation) isoenzyme of P450 cytochrome is CYP3A4. Its expression is reduced in neonates and infants, which affects pharmacokinetics, including the medicines used in the early period of postnatal life. As a result of this lower activity, the substrates of CYP3A4 (cisapride, macrolide antibiotics, amiodarone, glucocorticosteroids) are slowly metabolised and

eliminated from the organism, which may result in frequent adverse effects in young children. Among the most serious ones is *torsade de pointes*, polymorphic ventricular tachycardia following the use of cisapride. In older children and adolescents, the activity of CYP3A4 is higher than in adults, so medicines are metabolised and eliminated faster, e.g. the increased clearance of carbamazepine is observed. In medical practice, it is recommended to increase the dosing of these medicines in order to obtain therapeutic concentrations. The immaturity of CYP2C9 and CYP2C19 (to a lesser degree) results in an extended half-life of drugs, e.g. phenytoin: in preterm newborns it is approximately 75 hours, in full-term neonates it is approximately 20 hours. The rate of phenytoin metabolism decreases with age: in the neonate period it is approximately 14 mg/kg/day and at puberty it is 8 mg/kg/day. The activity of CYP2D6 increases considerably after birth, reaching 20% of the adult values in 28-day-old infants. Clinical studies demonstrate that these correlations must be considered and neonates and infants need to be treated as slow metabolisers. It is assumed that in children aged approximately 10 years old the activity of CYP2D6 is comparable to that in adults. The metabolic activity of CYP1A2, of which theophylline is a substrate, increases gradually after birth and in 6-month-old children it can exceed the values observed in adults. The adult levels of activity are achieved in puberty. In clinical practice, higher doses of theophylline should be used in children.

The ontogenesis of the enzymatic systems catalysing the reactions in phase II of drug metabolism is much less known. It appears that the activity of phase II enzymes is also lower at birth than in adults. Therefore, medicines that require glucuronidation will have a longer half-life, and may undergo modifications via different metabolic pathways than in adults. In neonates and younger children, a reduced paracetamol glucuronidation capacity is observed, due to the lower activity of the UDP-glucuronosyltransferase (UGT) isoforms: UGT1A6 and UGT1A9 (to a lesser extent). The activity of UGT2B7 (morphine glucuronidation) is found in premature neonates as young as 24 weeks of gestation, and it increases gradually until 28–40 weeks of gestation. Therefore, newborns and infants cannot synthesise sufficient amounts of an active morphine metabolite (morphine-6-glucuronide), so they require higher doses of the drug. Reduced activity of the enzymes that catalyse glucuronidation causes hyperbilirubinaemia in neonates. Using phenobarbital as a UGT inducer increases the efficiency of bilirubin conjugation and its further elimination. Contrary to the glucuronidation reactions, in neonates, infants and young children a considerably higher efficiency of conjugation with sulphuric acid is observed, which enables partial conjugation of paracetamol with sulphuric acid (which in adults undergoes only glucuronidation), thus improving the medicine's safety [4, 5].

Drugs are eliminated from the organism in an unchanged form or as metabolites produced as a result of the transformations presented above. Most medicines are eliminated with urine through the kidneys, but some may also be eliminated with bile through the liver, with faeces through the digestive tract, with saliva through the salivary glands, with sweat through the sweat glands, with the air exhaled through the lungs and with milk through the mammary glands.

The elimination process is typically described using clearance (i.e. the volume of plasma that was cleared from the drug in a unit of time) and half-life (i.e. the time in which drug concentration in blood is reduced by half compared to the initial value). Drug clearance is largely determined by the function of the kidneys and liver, so physiological developmental changes in these organs, as well as any pathological conditions, will be reflected in the pharmacokinetic parameters. The glomerular filtration rate in full-term neonates is approximately 2–4 ml/min/m^2 of body surface area (0.6–0.8 ml/min/m^2 in premature neonates) and it increases gradually, until 8–12 months of age, when it approaches adult levels (90 ml/min/1.73 m^2). In this time, the permeability of the filtration membrane and renal blood flow increase, which improves glomerular filtration. Similarly develops tubular transport, reaching maturity in the first 12 months of age. However, due to the uneven rate of renal development (filtration and tubular transport), significant caution should be exercised when administering drugs eliminated through the kidneys to children, especially in the 1–2 week of age. A considerable extension of the aminoglycoside half-life in children up to 6 months of age (due to reduced glomerular filtration) was observed clinically. The immaturity of the tubular transport until at least 7 months of age may impair the elimination of drugs dependent on its activity: cephalosporins, digoxin, thiazide diuretics and furosemide [6–9].

Pharmacodynamics

Unfortunately, little is known about the effect of developmental changes in the organism on pharmacodynamics, i.e. the response to medications associated with their effect in the target sites (e.g. receptors, enzymes). Therefore, children are sometimes referred to as "pharmacodynamic orphans". For instance, a relationship was found between age and the effect of famotidine, i.e. a more pronounced inhibition of hydrochloric acid production in children. Other studies demonstrated different pharmacodynamic responses to medicines based on their effect on receptors (ciclosporin) or the relation between their blood concentration and the clinical effect (midazolam as a sedative), an increased frequency of paradoxical responses to diphenhydramine, an increased frequency of obesity during treatment with antipsychotics and increased hepatotoxicity of the valproic acid (decreasing with age) [9, 11].

Table 1. Examples of different half-lives (hours) according to age (adapted from [10]).

Isoenzyme	Drug	Neonate	Infant	Child	Adult
CYP1A2	Theophylline	24–36	7	3	3–9
CYP 2C9	Phenytoin	30–60	2–7	2–20	20–30
CYP2C19	Phenobarbital	70–500	20–70	20–80	60–160
	Diazepam	22–46	10–12	15–21	24–48
CYP3A	Carbamazepine	8–28	–	14–19	16–36

Pharmacotherapy

The above pharmacokinetic and pharmacodynamic dissimilarities occurring in the developmental age and absence of direct studies in the paediatric population make selecting a proper dose (or even a medicine) difficult in daily clinical practice. Due to the above differences between adults and children at various developmental stages, a direct extrapolation of the clinical use of a drug used in adult patients is not always appropriate and which was many times the cause of numerous adverse effects in children (e.g. thalidomide – teratogenic effect; chloramphenicol – grey baby syndrome; tetracyclines – teeth discolouration).

Due to an incomplete knowledge of the factors affecting drug pharmacokinetics and pharmacodynamics, the developed dosing regimens, especially in children under 8 years old, are imperfect. Doses are usually estimated based on a child's body weight, which is the easiest, but not necessarily the most accurate method. It is accepted that in children up to 10 years old, dosing based on body surface area is more appropriate. In 6-month-old infants, a dose based on body weight is underestimated by approximately 56%, whereas when the dose is established based on body surface area, it is underestimated by approximately 22%. Dose underestimation is primarily due to the relatively higher renal clearance per kilogram of body weight in children, which may lead to ineffectiveness of treatment. However, it should be mentioned that the therapeutic index of most medicines exceeds 50%, which minimised the clinical manifestation of dose underestimation. The above difficulties related to appropriate dosing result from an assumption that the relationship between body weight and surface area is linear. However, the processes of growth and maturation are not always linear, due to age-dependent variations in body composition and development of the organs that change dynamically, especially in the first decade of life.

Body surface area is commonly included as the parameter to calculate drug dose, but – as mentioned above – it is not free from flaws. To calculate body surface area, a range of nomograms are used (also taking into account other variables), which have certain disadvantages. The original nomogram for determination of body surface area, developed by DuBois and Du Bois uses a standard surface area of 1.9 m^2. Therefore, the resulting clearance values are appropriate only for children whose body weight is over 7 kg. Using 1.73 m^2 as a standard body surface area (in the above model), typically results in clearance overestimation by approximately 10% (this is associated with the varying development of the area of the skin, intestines, pulmonary alveoli and filtration membrane). The presented two models are most frequently used in daily clinical practice, but they are not perfect. Their limitations are most visible in neonates, infants and young children (e.g. using body surface area to calculate a dose results in its underestimation by approximately 22% in 6-month-old infants, whereas dose calculation using body weight is associated with underestimation by 56%).

Other calculation methods that enable adult dose extrapolation are not free from flaws either. They use age, body weight or surface area and the adult dose as the basis for calculations (Table 2).

Table 2. Paediatric dose calculation methods.

Method	Paediatric dose
Fried's equation (for children under 2 years of age)	age (months) / 150 x adult dose
Young's equation (from 2 to 12 years of age)	age (years) / age (years) + 12 x adult dose
Clark's equation	body weight (pounds) / 150 pounds x adult dose
Formula based on modified body weight	body weight (kg) / 50 kg x adult dose
Formula based on body surface area	Body surface area (m^2) / 1.73 m^2 x adult dose
Gowling's equation (over 12 years of age)	adult dose x age (years) / 24

The above formulas do not take into consideration developmental changes, which makes them imperfect. They are not equally appropriate for children in individual age groups. Summing up, the formulas based on body surface area are the most appropriate for children up to 2 years of age. They become less suitable for patients as they grow older. The formulas based on modified body weight (i.e. assuming that adult body weight is 50 kg) appear to be the best available methods of dose calculation in children over 10 years. The above formula appears to be more appropriate than the one

that uses 68 kg (150 pounds) as the adult body weight (Clark's equation). The last formula uses a body weight that is closer to the real mean body weight adapted when establishing adult doses (i.e. 70 kg). However, dosing based on the actual body weight of adult patients results in administration of too low doses in children, due to the increased drug clearance (per kilogram of body weight) in paediatric patients. Therefore, when calculating paediatric doses, using 50 kg as a referential body weight is appropriate. The above methods of dose calculation seem to be adequate at the beginning of pharmacotherapy, but may appear to be inadequate for long-term medication, when age-specific differences, especially regarding pharmacokinetics, should be considered. To optimise drug dosing in children, ontogenesis must be considered with relation to the parameters that describe the fate of medications in the organism and their effects. The most appropriate method consists in using the dosing range established in clinical studies involving children of the relevant age, but the availability of such data is limited. In older children and adolescents, no significant differences are found in the functioning of the organism compared to young adults (except the age-dependent differences in bioavailability) [12, 13].

Options for optimising pharmacotherapy

Therapeutic drug monitoring – in the case of certain medicines, particularly those with a narrow therapeutic index (i.e. drugs characterised by a small difference between the therapeutic dose range and a potentially toxic concentration), it is possible to adjust the dosing based on measurement of the drug concentration in the blood plasma/serum/full blood. For the measurement, a blood sample is usually collected in steady-state concentration, i.e. the state of dynamic equilibrium between the processes of absorption and elimination, established after approximately 5 half-lives of a given medication. Such management of pharmacotherapy makes it possible to adjust the dosing regimen to obtain therapeutic concentrations of the drug. The need for individualised therapy occurs more frequently in children than in adults, due to the differences in pharmacokinetics and uneven functional development of various organs. Recommendations for paediatric clinical practice include monitoring of blood concentrations of aminoglycoside antibiotics (amikacin, gentamicin), vancomycin, theophylline, digoxin, methotrexate and antiepileptics (carbamazepine, valproic acid, phenytoin) [14, 15].

Pharmacogenetics is another option for treatment optimisation. It makes it possible to select a medicine or its dose based on the patient's genetic profile. Multiple genetic variants have been described in the literature, especially regarding drug-metabolising enzymes, and the information regarding the effect of genetic factors on the response to medications is presented in Summaries of Product Characteristics for approximately 80 medicinal products. Regarding medications used in the paediatric population, it is recommended (but not required) to determine the polymorphism of the thiopurine methyltransferase gene (TPMT) to calculate doses of drugs that are substrates of this enzyme, i.e. azathioprine (AZA), 6-mercaptopurine (6-MP) and 6-thioguanine, in order to prevent a myelotoxic effect in slow metabolisers. Based on the genetic data, the initial dose of 6-MP or AZA in slow metabolisers can be established at 5–15%, and in patients with intermediate metabolism at 70% of the standard therapeutic dose. Determination of the polymorphism of the CYP2D6-coding gene also has clinical implications, as the enzyme catalyses the conversion of codeine and tramadol to active metabolites, morphine and M1, respectively; genetic information may help to prevent respiratory depression (in ultrafast metabolisers) or the lack of an analgesic effect (in slow metabolisers) [16, 17].

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