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REVIEW

Neonatal pharmacology and clinical implications

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Abstract

During the neonatal period, there is physiological immaturity of organs, systems and metabolic pathways that influences the pharmacokinetics and pharmacodynamics of administered drugs, the dosage of which should be constantly amended, considering the progressive increase in weight and the maturation of the elimination pathways. In this article, we analyse the main pharmacokinetic aspects (absorption, distribution, metabolism and excretion) that exist during the neonatal period, to offer a description of the physiological background for variability in pharmacological dosing.

Keywords: infant, newborn, pharmacology.

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Introduction

The correct dosage of drugs is crucial for newborns, whose disposition is significantly influenced by the route of administration, the metabolic capacity and the elimination pathways, which are significantly different in newborns compared with adults.[1,2]

The neonatal period, which includes the first 28 days of life from the moment of birth in term infants and a period up to 44 weeks of postmenstrual age in former preterms, is characterized by a physiological immaturity of organs and apparatuses. This affects the pharmacokinetics and pharmacodynamics of the administered drug, as well as the tolerance of the newborn to it.[3]

It should be considered that developmental and maturational changes are complex processes, and simplified methods of administering a drug may result in subtherapeutic doses and lack of effect, or adverse toxic events. For this reason, dosages must be constantly modified on the basis of progressive increase in weight and the maturation of the metabolic pathways.[4]

The rapid maturation in drug disposition in the neonatal period affects the safety and efficacy of drugs due to the various pharmacokinetic phases (absorption, distribution, metabolism and excretion); therefore, infants cannot be considered as "small adults."[5,6] Differences in pharmacokinetics and half-life of drugs (that depends on both the clearance and distribution volume) manifest themselves mostly in the first few months of life.[7] In newborns, the volume of distribution of hydrophilic drugs is greater with respect to adults: this is due to the presence of a greater relative volume of extracellular fluids and the total body water, as well as the lower relative amount of adipose tissue and muscular mass.

Changes in the composition and amount of circulating plasma proteins such as albumin and alpha 1-acid glycoprotein can also influence the distribution of highly bound drugs. A reduction in the quantity of total plasma proteins (including albumin), presence of foetal albumin (which has reduced binding affinity for weak acids) and an increase in endogenous substances (e.g. bilirubin and free fatty acids) that are able to displace a drug from albumin binding sites during the neonatal period may also contribute to the higher free fractions of highly protein-bound drugs in neonates.[1]

Highly lipophilic drugs such as propofol have a lower distribution volume in newborns, potentially resulting in higher concentrations in the effect compartment because of more limited distribution.[3,8,9]

Metabolic clearance relates to regional blood flow, liver size, compound-specific extraction rate and intrinsic isoenzyme specific capacity. A consistent observation in clinical studies of drugs metabolized in the liver is an age-dependent increase in plasma clearance in children less than 10 years of age, as

compared with adults, which necessitates relatively higher weight-based dose requirements.[1]

The final destiny of most drugs and their metabolites is elimination via the renal route. Consequently, it is important to understand its maturation. Maturation of renal elimination capacity is a continuous process that starts during foetal organogenesis and is completed only at the end of childhood. In neonates, glomerular filtration rate (GFR) is mainly based on the weight at birth and on the postnatal age with a two- to fourfold increase in GFR in the first 4 weeks of postnatal age. However, renal elimination covers both GFR and renal tubular transport activity (both excretion and absorption). Collectively, developmental changes in renal function may dramatically alter the plasma clearance of compounds, with extensive renal elimination and that constitutes a major determinant of the age-appropriate selection of a dose regimen.[10,11]

In general, it is known that the excretion mechanism of drugs is reduced in all infants; however, these processes cannot be generalised and the response to each drug, as well as the elimination pathway involved, must be analysed on a case-by-case basis.[12]

The investigation and understanding of the response mechanisms of the neonatal organism to administered drugs is extremely useful to determine the correct dosage.[13] However, many of the drugs for neonatal use remain poorly studied, and their dosage is often based on information that is extrapolated from their use in adults or in older children. This is because conducting clinical trials during the neonatal period is problematic for ethical and logistical reasons.[14–16]

Little information exists about the effect of human ontogeny on interactions between drugs and receptors and the consequence of these interactions (i.e. the pharmacodynamics).

In this article, we analyse the main aspects of pharmacokinetics (absorption, distribution, metabolism and excretion) that are typical of the neonatal period.

Drug absorption

The absorption of drugs is different in children up to 2 years and is affected by the maturation process of the various organs.[17]

At gastric level, there is a variation in pH, which is neutral at birth. In the first 24 hours after birth, it is 1–3 and returns to neutral around the eighth day, and subsequently it decreases to match the values of an adult around the second to third year of life. If the pH of the stomach is high, drugs that are weak acids are absorbed slower than drugs that are weak bases. For this reason, in newborns there is good gastric absorption of acid-labile drugs, such as benzylpenicillin, ampicillin, amoxicillin and erythromycin.

The rate of gastric emptying appears to be directly influenced by gestational and postnatal age as well as the type of feeding. Infants have a delayed gastric emptying (6–8 hours) that determines a delay in the absorption of drugs and in reaching the concentration peak, with a reduced concentration peak. Gastric emptying is also conditioned by the composition of the meal and is faster in neonates after they are fed an extensively hydrolysed formula than an intact protein or partially hydrolysed formula. In contrast, slower gastric emptying times have been reported with increasing caloric density and medium-chain triglycerides in premature infants. Gastric emptying time appears to approach adult values within the first 6–8 months of life.[18–20]

Together with the reduced synthesis of bile acids and the delayed gastrointestinal transit, all these conditions cause a reduction in the absorption of orally administered drugs in the neonatal period.[21] The gastrointestinal absorption of the drugs is then completed around the fourth month of life, when both passive and passive transport processes reach maturation.[3,9] Conversely, in newborns and young children up to 2 years there is an increased absorption of transdermally administered drugs, due to the lesser thickness of the epidermis and the stratum corneum. Other factors contribute to the acceleration in the absorption of transdermally administered drugs in this age period such as increased skin perfusion due to the immaturity of vasomotor system, the increase in the water content and the high ratio between body surface and weight.[22] In fact, the ratio of the total body water to body weight is higher in newborns compared with that in older children and adults (the total body water decreases from 80% of body weight at birth to 60% at 1 year). The total body water gradually decreases with age and reaches adult value by the age of 12 years.[6]

The intramuscular absorption of drugs in newborns is negatively influenced by the reduced mass, perfusion and muscle contractility. However, it is also influenced by the physicochemical characteristics of the drugs such as the pH, molecular weight, solubility and dissolution rate. In fact, water-soluble drugs show an increased intramuscular absorption in newborns who have a high intramuscular water content and a large amount of capillaries in the skeletal muscles.[10,23]

The rectal absorption of drugs is generally increased in newborns; however, the variability in the depth of administration or in the retention of drugs can vary their absorption, similarly to adults. In fact, drugs administered at deep rectal level reach the hepatic level directly through the superior rectal veins, whereas drugs administered at distal rectal level reach the systemic circulation via the medium and inferior rectal veins.[24,25]

Drug distribution

After absorption, drugs are distributed in the various body compartments depending on their physicochemical properties such as molecular weight, ionization constant and solubility in water and in lipids. The distribution of the drug varies depending on the age of the individual and also on

Table 1. Developmental aspects of fluid compartment sizes.

	Patient age					
Body fluid	**3 month foetus**	**Term gestation**	**4–6 months**	**12 months**	**Puberty**	**Adult**
% of total body water[a]	92	75	60	–	~60	50–60
% of extracellular fluid[a]	65	35–44	23	26–30	20	20
% of intracellular fluid[a]	25	33	37	–	40	40

[a] Values are expressed as percentages of total body weight.
Modified from Tayman and colleagues.[18]

the permeability of the cell membrane, on the extent of its binding to proteins, the binding capacity of individual tissues and on the change in the volume of the extracellular fluids in proportion to the total quantity of water in the body.[3,26]

Finally, drug transporters such as the ABC efflux pump P-glycoprotein (MDR1/ABCB1), which show an ontogenic profile not only in the small intestine but also in the lung, can influence drug distribution because these transporters can markedly influence the extent to which drugs cross membranes in the body and whether drugs can penetrate or are secreted from the target sites (e.g. cerebrospinal fluid).[22]

Newborns, compared with children and adults, have a relatively higher volume of extracellular fluid and body water content, with a relatively reduced concentration of adipose tissue and reduced muscle mass. In particular, premature babies have a relatively reduced body fat content, increased membrane permeability and water content that is even greater compared with that of full-term babies.[27]

The body water content is greater in newborns, where it represents 80–90% of the body weight with respect to a low fat content, which is equivalent to approximately 10–15% (Table 1).[28] In newborns, this condition determines the high volume of distribution of water-soluble drugs, which reduces their bodily distribution during growth as a result of the reduction of the concentration of water in the body. Therefore, in newborns and children the high volume of distribution of hydrophilic drugs involves the need of larger doses of the drug by body weight to reach therapeutic concentrations.[3]

In addition to this, changes in the composition and the amount of circulating plasma proteins, such as albumin and alpha 1-acid glycoprotein, can alter the distribution of drugs: the affinity of albumin for acidic drugs increases from birth to early infancy.

The binding of drugs with plasma proteins (generally acidic drugs bind to albumin and basic drugs to globulins, alpha 1-acid glycoprotein and lipoproteins) is reduced in infants and children up to 2 years due to a lower concentration of plasma proteins in children than in adults (59 g/L against 72 g/L in adults) and due to their reduced ability to bind to the drugs. It is also important to bear in mind that in newborns, both physiologically and as a result of pathologies, there may be an increase in the plasma concentrations of bilirubin and free fatty acids, which compete with the binding of the drugs to albumin.[29]

With regard to drug distribution in the central nervous system (CNS), in newborns the intracranial concentration of the drug is greater with respect to that in children and adults due to the reduction of binding proteins, the greater encephalic weight, the high ratio between encephalic blood flow and systemic blood flow as well as the high volume of cerebrospinal fluid, brain and spinal cord with respect to the body surface area.[30]

Another factor that contributes to this process is the increased vascular permeability from the encephalic interstitial fluid and from the cerebrospinal fluid through the blood–brain barrier (formed by the endothelium in the brain) and the blood–cerebrospinal fluid barrier (including the endothelium of the choroid plexuses), which are believed to be more immature and therefore more permeable to drugs in newborns, with increased risk of overdose and toxicity.[31,32]

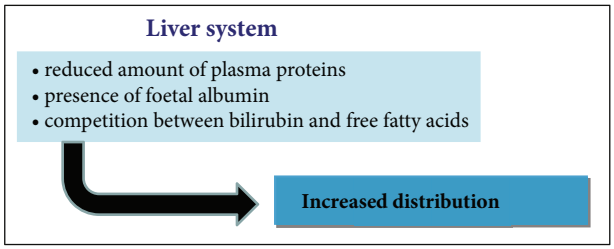
Drug metabolism

Liver metabolism

In general, the rate of drug elimination by biotransformation in neonates and infants is slower than that in adults. During the first week of life, there are rapid physiological postnatal changes in the liver blood flow, including increasing portal vein blood flow, and gradual closure of the ductus venosus shunt. In addition, the loss of the umbilical blood supply causes changes in hepatic oxygenation. These relevant changes may affect the capacity of not only hepatic drug metabolism but oral bioavailability in neonates.[18]

In addition to this, the low concentration of plasma proteins, presence of a qualitatively different albumin, high serum concentration of substances such as bilirubin and fatty acids and low blood pH determine a reduced binding of the drug to plasma proteins, with consequent increase of the free fraction of the drug (Figure 1).[33] In addition to this, the reduction of the metabolism of bile acids due to the immaturity of the liver may determine an increase in the clearance of the drug, which is normally excreted in the bile, with a consequent increased risk of toxicity.[34]

Figure 1. Characteristics of the neonatal liver system and drug metabolism.



Phase I and II reactions

Paediatric patients, especially neonates, exhibit distinct hepatic drug metabolism activity from adults due to differences in P450 expression during development. Mechanisms regulating paediatric gene expression and induction may also differ from those of adults. Drug metabolism occurs through phase I and phase II reactions, which, in newborns and children, are not entirely developed processes.[35]

With regard to phase I reactions, it is important to analyse the CYP system, the different forms of which mature at different times.

For the metabolism of non-CYP or UGT-dependent drugs, the influence of age is less known.

Phase I reactions

The CYP-dependent metabolism at birth is 50–70% of that in adults. Between 2 and 3 years of age, CYP enzymatic activity is higher in children than in adults in respect of CYP1A2, CYP2C9 and CYP3A4 isoforms, whereas the portion of drug metabolised by CYP2C19, CYP2D6, NAT2 and UGT is similar to that in adults.[36]

CYP1A2 is hardly visible in the microsomes of newborns: it increases at around 1–3 months and reaches 50% of the concentration present in adults at 1 year of age. Two methylxanthines (caffeine and theophylline), utilized for treatment of apnoea, have been utilized extensively to evaluate CYP1A2 in vivo in young children.

At birth, caffeine-3-demethylation, a measure of CYP1A2 activity, is very low. Consequently, Erenberg and colleagues published that the efficacious dose of caffeine is 10 mg/kg every day.[37]

The half-life of caffeine is 72–96 hours in infants compared with approximately 5 hours in older children and adults. Similarly, 8-hydroxylation of theophylline is reduced at birth. Nevertheless, longitudinal data indicate a rapid maturation process for CYP1A2, as it appears to reach adult levels within the first year of life, often within the first 6 months of life. Finally, it is important to note that caffeine activity is highly inducible by drugs, diet and exogenous toxins such as cigarette smoke. In adults, variability in CYP1A2 activity of up to hundredfold has been reported.[22]

Moreover, Blake and colleagues reported that caffeine elimination half-life in neonates who are breast-fed is longer than that of formula-fed infants.[38] This information suggests that the composition of infant diet (i.e. an environmental factor) can influence the pattern of ontogenic expression of a drug-metabolizing enzyme.

The CYP3A subfamily consists of CYP3A4, CYP3A5, CYP3A7 and CYP3A43. CYP3A43 is not known to play a significant role in hepatic metabolism. It has been established that CYP3A4 is the predominant CYP3A enzyme in adults, whereas CYP3A7 is the predominant CYP3A enzyme in foetus and infants. Moreover, CYP3A5 is expressed more in children and adolescents than in adults. Furthermore, there is a great deal of overlap of specificity of ability for CYP3A4 and CYP3A7 to metabolize therapeutic agents.

In 2003, Stevens and colleagues published the results of examining the largest collection of foetal and paediatric 212 liver samples and demonstrated that CYP3A7 has a high expression between 94 and 168 postconceptional days on a pmol/mg basis of total hepatic protein. The level at birth is less than half that of the high prenatal value, but it remains higher than adult CYP3A4 levels.

CYP3A7 content remains higher than CYP3A4 content until at least 6 months of age. CYP3A4 protein level increased very gradually during the first 6 months of age, and levels for the 5- to 15-year age group were lower compared with adults.[39]

Proteins in the CYP2C family develop early during the neonatal period. The ontogeny of CYP2C9 is much better understood than CYP2C19. Indeed, hepatic liver samples have shown that CYP2C9 activity is functionally very low just prior to birth. However, much like CYP2D6, this activity increases quickly in the first year of life.[22]

Phenytoin is an example of the effects of this very low level of CYP2C9 activity at birth.[40] For this reason, the recommended daily dose for newborns is 5 mg/kg/day, but by 6 months to 3 years of age this increases to 8–10 mg/kg/day, consequent to increased CYP2C9 activity.

Benzodiazepines and proton pump inhibitors are the two major pharmaceutical classes of drugs that are metabolized by CYP2C19 and are used in the literature to indirectly determine the ontogeny of CYP2C19 activity.[41] Hydroxylation of diazepam is a classic example of the effects of the maturation process of CYP2C19.[42] In neonates, the half-life of diazepam is reported to be 50–90 hours. It decreases in the first year of life (diazepam half-life 40–50 hours) and becomes much closer to the adult value, which is reported to be 20–50 hours.[43]

All proton pump inhibitors other than rabeprazole are metabolized by CYP2C19. The biotransformation of pantoprazole is predominantly dependent on CYP2C19 activity. When the weight-normalized apparent oral clearance

of pantoprazole is examined in paediatric patients from 1 month to 16 years of age, a developmental profile for the acquisition of CYP2C19 activity is evident. As expected, exposures of the CYP2C19 metabolism-dependent proton pump inhibitors are universally increased in the youngest infants, when genetic polymorphisms of CYP2C19 are fully accounted for.[44]

CYP2D6 increases during the first postnatal week and, at 5 years of age the level reaches two thirds of that in adults. Finally, CYP2E increases after birth, reaching 40% of the value present in adults during the first year of life and finally concluding this value within the tenth year of life.[32]

Phase II reactions

The phase II reactions include acetylation, methylation (between enzymes that promote the methylation there are the thio-methyltransferase, whose activity increases with increasing age both at hepatic and at renal levels), glucuronidation (which does not reach the levels present in adults before the first 3–6 months of life) and sulphation (which reaches maturity already at birth).

Neonatal glucuronidation of acetaminophen (a substrate for UGT1A6 and UGT1A9) and morphine (a UGT2B7 substrate) is decreased in newborns and young children compared with that in adolescents and adults. The activity reaches adult values between 2 and 6 months for morphine.[1,45]

Paracetamol is either sulphated or glucuronidated and thus provides us a drug substrate to simultaneously assess ontogeny of sulphation and glucuronidation in neonates and young infants.[12,46]

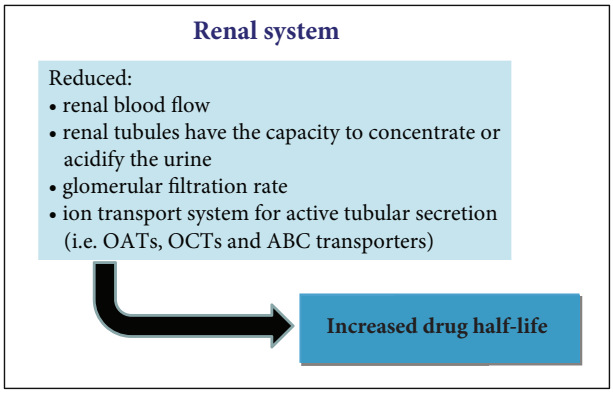
Kidney excretion

Neonatal renal function is lower than expected on the basis of the body weight or body surface area, due to the reduced renal blood flow, lower capacity of the renal tubules to concentrate or acidify the urine, slower GFR and reduced transport system of organic ions for the active tubular secretion.[47]

The decreased GFR prolongs half-lives of drugs, delaying clearance. The GFR is directly dependent on gestational age and this effect is more pronounced in preterm neonates.[22] Consequently, in newborns and small children, drugs that require a renal excretion are eliminated much slower, with an increase in the plasma concentration and their potential toxicity (Figure 2).[5,11,36,37] Many commonly used drugs, such as aminoglycosides, have clearances strongly correlated with glomerular function. The renal clearance of the drug increases with the increase in gestational age, postnatal age and body weight, which affects the mechanisms involved in the renal excretion, such as the GFR, active tubular excretion and tubular reabsorption.[35]

With regard to the development of the renal excretion system, renal filtration increases rapidly during the first 2 weeks of life and reaches the same levels as in adults between the eighth and twelfth month of life, whereas tubular secretion is immature at birth and reaches the same levels as in adults during the first year of life.[38]

Figure 2. Characteristics of the neonatal renal system and drug metabolism.



Absorption mechanisms along the tubule mature faster than tubular secretion. So, proximal tubule is rapidly able to reabsorb xenobiotics not retained by the glomerulus. For example, aminoglycosides undergo tubular reabsorption and may accumulate in the body.

Tubular secretion is particularly altered in neonates as a result of poor peritubular blood flow, shorter tubular length, reduced urine concentrating ability, lower urinary pH values and decreased energy for transporters as well as decreased transporters' expression. This particularly affects the excretion of penicillin and furosemide, the elimination of which depends on GFR.

Many mechanisms are involved in renal elimination, such as transport across the basolateral membrane, intracellular transport and secretion across the apical (brush border) membrane to the lumen. Drug transporters play a pivotal role in drug excretion in the proximal tubules and in the determination of the speed of drug elimination. Organic anion transporters (OATs), organic cation transporters (OCTs) and ABC transporters (e.g. P glycoprotein and MRPs) are the main renal transporters. Many drugs, such as ACE inhibitors, angiotensin receptor blockers, beta-lactam antibiotics or nonsteroidal anti-inflammatory drugs (NSAIDs), are transported by OATs. It is well established that organic anion secretion is low at birth and increases over the first few weeks of the neonatal period through specific maturation rather than growth and development of the kidney itself. In rats, the expression level of OAT1, OAT2 and OAT3 increases from birth to 45 days postpartum. Human newborn kidneys are only able to excrete p-aminohippurate (PAH; a substrate for the OATs) at 20–30% of adults levels, reaching adult excretion levels only by 7–8 months of age. Moreover, in mice, the maturation of the organic cation system seems to develop gradually. So, it seems that the OATs system functions mature more quickly than the

OCTs. P-glycoprotein and multidrug resistance-related proteins 1 and 2 seem to also have specific age-dependent expression throughout kidney development. The maturational effect on transporter expression may facilitate drug interactions in newborns, but further studies are required for understanding tubular alterations in neonates.

Little is known about renal drug receptors (beta-adrenergic, RAS or dopaminergic receptors), their expression and pharmacogenomics in the neonatal immature kidney.[48]

Renal flow increases with age because cardiac output increases and the peripheral vascular resistances decrease. Kidneys in newborns receive only 5% of the cardiac output compared with 25% in adults. In addition, the renal flow seems to increase with the development of the renal tubules, reaching the same level as in adults at around 5 months.[47]

The GFR normalized for the body surface in newborns is reduced (equivalent to approximately 40 ml/min/1.73 m^2, and reduced even more in premature babies) and reaches the adult rate between 6 and 12 months of age. Therefore, renally excreted drugs in newborns are eliminated more slowly, with a reduced plasma clearance and increased risk of adverse events.[49–51]

A reduction in renal blood flow or renal damage may result in a reduction of the GFR. Various perinatal problems (i.e. perinatal asphyxia, respiratory distress syndrome and jaundice) can cause renal stress and hypoperfusion and may impair renal glomerular and tubular functions, accelerating or delaying the maturation of drug disposition pathways. Moreover, in such conditions, neonates are often exposed to nephrotoxic medications, such as indomethacin or ibuprofen (NSAIDs), or drugs that interfere with the renin–angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors or AT-I type-angiotensin II blockers. Indeed, in neonates, a low GFR is maintained by a delicate balance between vasoconstrictor and vasodilator renal forces. NSAIDs can cause renal hypoperfusion through inhibition of the vasodilatory effect of prostaglandins on afferent arteries. ACE inhibitors and AT-I blockers interfere with the vasoconstricting effect of angiotensin II on the efferent arteriole, thus reducing glomerular filtration pressure. Studies have shown that coadministration with ibuprofen may prolong the median serum half-life of amikacin and reduce the clearance of amikacin in very extremely preterm neonates (less than 31 weeks gestation). Moreover, NSAIDs can disrupt excretion of weak organic acids, potentiating toxicity of such xenobiotics. However, maternally administered drugs can also positively affect the neonatal kidney. For example, betamethasone is often prescribed to pregnant women to accelerate foetal lung maturation. Prenatal administration of glucocorticoids induces a positive maturational effect on both GFR and tubular functions. Animal studies suggest a vasodilatory action of glucocorticoids on the glomerular microvessels, leading to an improvement in renal blood flow and GFR. Moreover, betamethasone directly affects tubular function through an increase in the NA/K ATPase activity and increased expression and activity of tubular ionic transporters.[48]

Conclusions

Paediatric and adult populations show significant differences with regard to the absorption, distribution, metabolism and excretion of various drugs. Newborns are neither small adults nor small children. In various paediatric age bands, it is possible to encounter different pharmacokinetic behaviours that are strongly influenced not only by age but also by body weight. Neonatal drug therapy should be based on a critical interpretation of available data and an understanding of foetal development and maturation processes and how diseases can affect the bio-arrangement of the drug in this specific population. Although there is a significant amount of literature that describes the ontogenesis and maturation aspects of pharmacokinetics in the foetus, a greater degree of clarity about the ontogenesis of the isozymes and the influence of pharmacogenomics in newborns is required. The understanding of the differences with respect to adulthood is fundamental to determine the correct dosage of drugs, to achieve the desired therapeutic effect to maximize therapy effectiveness and limit the toxic effects.

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