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Therapeutic Drug Monitoring in Neonates: Clinical Applications, Challenges and Emerging Strategies

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ABSTRACT

Neonates exhibit substantial variability in drug disposition because of ongoing maturation of physiological and biochemical processes, including renal function, hepatic metabolism, body composition, plasma protein binding, and gastrointestinal function. These developmental changes can result in unpredictable drug exposure and make conventional weight-based doing insufficient for achieving optimal therapeutic outcomes. Therapeutic drug monitoring (TDM) provides an individualized approach by integrating measured drug concentrations with pharmacokinetic principles, clinical characteristics, and therapeutic response. This review discussed the pharmacokinetic and pharmacodynamic factors influencing drug disposition in neonates and highlighted the role of therapeutic drug monitoring in optimizing pharmacotherapy in this vulnerable population. The clinical applications of TDM for commonly monitored drugs, including gentamicin, amikacin, vancomycin, phenobarbital, digoxin, and selected antifungal agents, were discussed. The review also examined challenges associated with blood sampling in neonates and emerging approaches such as capillary microsampling, dried blood spot sampling, volumetric absorptive microsampling, and advanced bioanalytical techniques. Variability in neonatal pharmacokinetics, limited neonatal-specific therapeutic ranges, restricted access to monitoring services, and the risk of iatrogenic blood loss remained important challenges. Emerging strategies including population pharmacokinetic modelling, Bayesian forecasting, model-informed precision dosing, pharmacogenomics, and clinical decision-support systems may further enhance individualized drug therapy. Overall, TDM represents an important component of precision pharmacotherapy in neonates and may improve therapeutic efficacy while reducing the risk of drug toxicity.

Keywords: Therapeutic drug monitoring, neonates, pharmacokinetics, pharmacodynamics, precision dosing, microsampling

INTRODUCTION

The neonatal period, defined as the first 28 days of life, is characterized by rapid physiological changes that significantly influence the pharmacology of medications. During this period, organ systems responsible for drug absorption, distribution, metabolism, and excretion are still undergoing maturation, resulting in

considerable variability in drug disposition among neonates, due to which standard weight-based dosing may not consistently achieve the desired therapeutic response and can increase the risk of treatment failure or drug toxicity.[1-3] Renal drug clearance is reduced during the early stages of life and is largely determined by glomerular filtration, which can be influenced by factors like age, concomitant use of non-selective cyclo-oxygenase inhibitors, growth restriction and peripartum asphyxia.[4,5] Phenotypic drug metabolism varies according to individual characteristics, including age, environmental factors like drug–drug interactions and feeding, and genetic variations such as polymorphisms.[6,7] Furthermore, developmental maturation of receptor expression, receptor function, cellular metabolism and enzyme activity occurs alongside growth. Consequently, tissue responsiveness to particular drugs may differ during early life, with some tissues exhibiting greater sensitivity despite similar drug concentrations or exposure levels.[8] Multiple medications such as antibiotics, anticonvulsants, cardiovascular drugs, and antifungal agents are frequently required by preterm infants and neonates admitted to neonatal intensive care units (NICUs). Majority of these medications have a narrow therapeutic index, where minute variations in drug concentration can lead to either subtherapeutic effects or serious adverse reactions.

Therapeutic drug monitoring (TDM) is the measurement and interpretation of drug concentrations in biological fluids to optimize individual patient therapy. Rather than relying solely on standard dosing regimens, TDM integrates measured drug concentrations with clinical assessment, pharmacokinetic principles, and patient-specific characteristics to guide dosage adjustments. It is particularly useful for drugs with a narrow therapeutic index, marked interpatient variability, and a well-established relationship between drug concentration and clinical response.[1,2] Over the past two decades, therapeutic drug monitoring has become an important component of neonatal pharmacotherapy. Routine monitoring of drugs such as gentamicin, amikacin, vancomycin, phenobarbital, and digoxin has contributed to improved therapeutic efficacy while minimizing drug-related toxicity.

METHODOLOGY

A literature search was conducted using Google Scholar to identify relevant published literature on therapeutic drug monitoring in neonates. The search was performed using combinations of keywords including “therapeutic drug monitoring”, “neonates”, “pharmacokinetics”, “pharmacodynamics”, “precision dosing”, “microsampling”, “vancomycin”, “gentamicin”, “amikacin”, “phenobarbital”, “digoxin”,and “antifungal agents”. Relevant articles addressing neonatal pharmacokinetics and pharmacodynamics, therapeutic drug monitoring, commonly monitored drugs, sampling techniques, analytical methods, challenges, and emerging approaches were considered for inclusion. The identified literature was reviewed and synthesized narratively to provide an overview of the current evidence and clinical applications of therapeutic drug monitoring in neonates.

REVIEW OF LITERATURE

Therapeutic drug monitoring (TDM) has been studied to a large extent as an essential element of individualized pharmacotherapy in neonates. Conventional dosing regimens often fail to achieve predictable therapeutic concentrations due to continuous maturation of physiological processes in neonatal stage. Over the years, several researchers have emphasized the necessity of merging pharmacokinetic principles, clinical assessment, and serum drug concentration measurements to refine drug therapy in this vulnerable population. Selected studies relevant to neonatal TDM are summarized in Table 1.

Table 1. Summary of selected literature on therapeutic drug monitoring in neonates

Authors	Year	Study	Major findings
Salman FS *et al.*	2026	Precision dosing in neonates: AI as a pharmacological tool	Reviewed the emerging role of AI, machine learning, Bayesian dosing, and model-informed precision dosing in neonates, highlighting their potential to improve dose prediction and individualized therapy, particularly for antibiotics and analgesics.
De Rose DU *et al.*	2020	Therapeutic drug monitoring is a feasible tool to personalize drug administration in neonates using new techniques: An overview on the pharmacokinetics and pharmacodynamics in neonatal age.	Discussed advances in micro sampling, pharmacokinetic modelling, and precision dosing to improve individualized therapy.
Mian P *et al.*	2017	Therapeutic Drug Monitoring in Neonates: What Makes Them Unique?	Explained neonatal pharmacokinetic variability and highlighted the challenges associated with establishing neonatal-specific therapeutic targets.
Pauwels S, Allegaert K	2016	Therapeutic Drug Monitoring in Neonates	Reviewed the current clinical applications of TDM and identified aminoglycosides, vancomycin, phenobarbital, and digoxin as the drugs most frequently monitored in neonatal practice.
Koren G.	1997	Therapeutic Drug Monitoring Principles in the Neonates	Described the fundamental principles of neonatal TDM and emphasized developmental changes affecting drug therapy.
Gal P.	1988	Therapeutic Drug Monitoring in Neonates	Highlighted the importance of individualized interpretation of serum drug concentrations in neonates due to developmental pharmacokinetic variability.

The available literature consistently shows how a simple measurement of serum drug concentrations had advanced to an extensive clinical tool for individualized drug therapy. Unlike earlier studies that mainly engaged in the principles of pharmacokinetics and dose optimization, recent publications have highlighted the role of population pharmacokinetic modelling, advanced analytical techniques, and precision medicine in neonatal practice. Despite these developments, the literature continues to identify important challenges, like finite neonatal-specific therapeutic ranges, challenges associated with repeated blood sampling, and the demand for new evidence supporting TDM for a broader range of medications.

PHARMACOKINETICS AND PHARMACODYNAMIC CONSIDERATIONS IN NEONATES

Drug disposition in neonates exhibits considerable variability, which is influenced by both developmental maturation and non-pharmacokinetic factors, such as accuracy of dose preparation and administration.11 Formulation-related challenges, such as the use of highly concentrated preparations, small doses, low infusion rates, and dead-space volume, can further contribute to this variability.[9] Also, maturational changes in pharmacokinetics combined with non-pharmacokinetic factors may result in poor predictability of drug concentrations from the administered dose in neonates. Two major pharmacokinetic parameters, volume of distribution (Vd) and clearance (Cl), are used to characterize the disposition of a drug. Volume of distribution represents the theoretical volume required to account for the observed plasma drug concentration, whereas clearance refers to the volume of plasma from which a drug is completely eliminated per unit time.[10] Elimination pathways undergo maturation at different rates and follow pathway-specific developmental patterns. For example,

maturation may differ between glomerular filtration and renal tubular excretion, as well as among individual metabolic enzymes such as CYP2D6 and CYP3A4/5.[6,7,11,12] Therefore, understanding the developmental changes associated with individual elimination pathways is essential for predicting drug-specific pharmacokinetic behavior in neonates.

Absorption

Gastrointestinal drug absorption in neonates is primarily influenced by gastric acidity and gastric emptying time, both of which differ considerably from those observed in adults. At birth, gastric pH is relatively high, generally ranging from 6 to 8, due to the presence of alkaline amniotic fluid. Within the first day of life, pH gradually decreases to approximately 1-3; however, gastric acidity remains poorly maintained in neonatal period. Gastric emptying is also slower in infants younger than 6 months compared with older children and adults. In adults, gastric emptying occurs in a biphasic pattern, with an initial rapid phase followed by a slower phase, whereas preterm infants generally exhibit slower and more linear gastric emptying. Prolonged gastric emptying in small infants, typically lasting about 6–8 hours, may increase the absorption of certain drugs, such as penicillins (ampicillin and nafcillin), while reducing the absorption of acidic drugs such as nalidixic acid.[2] For drug administered through non-intravenous routes, absorption is influenced by several patient-specific factors associated with the functional maturation of different organs and physiological systems. Following oral administration, drug absorption is affected by gastric emptying, gastric pH, intestinal motility, intestinal first-pass metabolism and gastrointestinal permeability.[7] Furthermore, the type and composition of milk, including formula, hydrolyzed preparations, and human milk, may affect gastric emptying, which is generally slower in neonates than in older children.[13] Absorption of lipid-soluble medications may be markedly impaired because of decreased bile salt production. The thin epidermis and immature skin barrier in preterm infants make percutaneous absorption also high, increasing the risk of systemic toxicity from topical medications.[1,3]

Distribution

Neonates, particularly preterm infants, have a higher proportion of total body water and lower body fat stores than older children and adults. [14,15] These differences in body composition can substantially influence the volume of distribution of both lipophilic and hydrophilic drugs. Lipophilic drugs, such as diazepam and propofol, generally have a lower volume of distribution, whereas hydrophilic drugs, including aminoglycosides and paracetamol, tend to have a higher volume of distribution in neonates. In addition, plasma protein binding contributes to drug distribution and may differ during the neonatal period.[10] Several factors affecting the distribution of antimicrobial drugs, including plasma protein binding and the compartmentalization of body water, undergo continuous changes during the first years of life, leading to corresponding changes in drug distribution. In neonates, plasma protein binding is generally lower than in older children and adults, which may be attributed to lower albumin concentrations, reduced drug-binding affinity of foetal albumin, and competition for binding sites from endogenous substances such as bilirubin. Drugs reported to exhibit reduced protein binding in neonates include phenytoin, salicylates, ampicillin, nafcillin, sulfisoxazole, and sulfamethoxypyrazine.[16-18]

Body water also differs considerably between neonates and adults. In newborns, water accounts for approximately 70-75% of body weight, compared with about 50–55% in adults. The extracellular water component also represents a greater proportion of body weight in neonates. In addition, neonates have relatively less adipose tissue and a different proportion of muscle mass compared with adults. These differences in

body composition influence the volume of distribution of drugs, particularly those that are primarily distributed in body water and, to a lesser extent, lipophilic drugs. Gentamicin and amikacin, for example, have been reported to show greater distribution in neonates, which gradually decreases during childhood.[19]

Metabolism

Hepatic enzyme systems, including cytochrome P450 enzymes and conjugating enzymes, are under development during the neonatal period unlike that of adults. This makes hepatic drug metabolism immature, resulting in prolonged elimination half-lives, requiring adjustments in dosage or dosing intervals of drugs. The extent of metabolic capacity varies according to gestational age, postnatal age, and clinical condition.[2,10]

Elimination

Drug elimination in neonates occurs primarily through hepatic and renal pathways, both of which undergo significant developmental changes. In preterm infants, nephrogenesis may continue after birth, particularly in those born before approximately 36 weeks of gestation.[20] Glomerular filtration rate (GFR) is low at birth but increases progressively during early life. GFR values of approximately 30 mL/min/1.73m^2 may be reached after two weeks, while levels comparable to those typically observed in adults (approximately 120 mL/min/1.73 m^2) are generally achieved by around two years of age.[21] Serum creatinine concentrations are relatively high at birth (approximately 60–70 µmol/L), largely reflecting maternal concentrations, while GFR and tubular reabsorption remain low. Furthermore, serum creatinine clearance (CrCl) increases with advancing gestational age, particularly among extremely low birth weight (ELBW) infants.[22]

Pharmacodynamics

Table 2. Physiological characteristics of neonates influencing therapeutic drug monitoring

Physiological characteristic	Effect on drug disposition	Implication for TDM
High gastric pH	Variable oral absorption	Unpredictable bioavailability
Delayed gastric emptying	Delayed absorption	Altered onset of action
High total body water	Increased distribution of hydrophilic drugs	Higher loading doses may be required
Low plasma protein binding	Increased free drug concentration	Greater risk of toxicity
Immature hepatic enzymes	Reduced drug metabolism	Prolonged half-life
Reduced glomerular filtration rate	Delayed drug elimination	Increased need for dose adjustment
Immature blood-brain barrier	Increased CNS drug penetration	Higher susceptibility to neurotoxicity

The physiological characteristics in Table 2 explain why standard dosing regimens may not achieve optimal therapeutic outcomes in neonates. Therapeutic drug monitoring plays a vital role in overcoming this variability by enabling individualized dose adjustments based on measured drug concentrations and clinical response.

PRINCIPLES OF THERAPEUTIC DRUG MONITORING IN NEONATES

Therapeutic drug monitoring is a clinical pharmacology approach that involves the measurement and interpretation of drug concentrations in biological samples to optimize individual drug therapy. It is particularly valuable for medications with narrow therapeutic index, substantial interindividual pharmacokinetic variability, or a defined relationship between drug concentration and therapeutic or toxic effects. In neonates, these characteristics are further influenced by developmental changes in organ function, body composition, protein binding, drug-metabolizing enzyme activity.[1,2] The decision to perform therapeutic drug monitoring should be based on the characteristics of the drug and the

clinical condition of the patent rather than on drug concentration measurement alone. The interpretation of drug concentrations should therefore be integrated with gestational age, postnatal ages, body weight, renal and hepatic function. Disease status, concomitant medications, dosing history, and clinical response.[1-3]

The timing of sample collection is an important determinant of the clinical usefulness of TDM. Drug concentrations should be interpreted according to the time elapsed since the previous dose, the duration and rate of drug administration, and the expected pharmacokinetic phase represented by the sample. Peak and trough concentrations have traditionally been used for selected drugs; however, exposure-based approaches such as the area under the concentration-time curve are increasingly being applied for certain medications.[2,3] TDM should not be considered as an isolated laboratory measurement. The measured concentration should be interpreted in relation to the prescribed dose, dosing interval, sampling time, pharmacokinetic characteristics of the drug, and therapeutic target. When appropriate, concentration measurements can be incorporated into pharmacokinetic models to estimate individual drug clearance and volume of distribution and to guide subsequent dosing.[2,5]

In neonates, population pharmacokinetic modelling and Bayesian approaches provide additional opportunities for individualized dose optimization. These approaches can combine previously established population pharmacokinetic information with individual patient characteristics and measured drug concentrations to estimate patient-specific pharmacokinetic parameters. Such approaches may be particularly useful when only a small number of samples can be obtained because of the limited circulating blood volumes in neonates.[5]

Thus, effective TDM in neonates requires appropriate patient selection, accurate dose and sampling information, reliable analytical measurement, pharmacokinetic interpretation, and timely adjustment of therapy. The overall objective is to achieve adequate drug exposure while minimizing the risk of toxicity.[1-3,5]

SAMPLING STRATEGIES, ALTERNATIVE BIOLOGICAL MATRICES AND ANALYTICAL METHODS

Therapeutic Drug Monitoring in neonates presents important ethical and clinical challenges because venipuncture can cause pain and distress in this vulnerable population. Repeated or extensive blood sampling should be minimized because neonates have a limited circulating blood volume and are particularly susceptible to iatrogenic anemia and blood transfusions. Therefore, alternative sampling strategies have been developed to reduce blood loss, while minimally invasive methods and reliable biological matrices are increasingly being considered for pharmacokinetic studies and TDM.[10]

As far as neonates are considered, circulating blood volume is limited, which makes blood sampling a major challenge. Frequent blood collection may contribute to iatrogenic anemia, especially in preterm and low birth weight infants. Capillary micro-sampling (CMS) enables the collection of very small blood volumes using specialized micro-sampling devices. This approach is currently being investigated in preclinical studies.[23] CMS can also be combined with dried blood spot (DBS) sampling to reduce variability associated with blood collection volume. In addition, capillary-based devices represent a promising approach for TDM in neonates. Studies have demonstrated that these techniques can provide reliable measurements of drug concentrations for several medications used in neonatal care.[24]

A volumetric absorptive micro-sampling (VAMS) device consists of a plastic handle fitted with a hydrophilic tip that absorbs liquid biological matrices, including blood, saliva, urine, sweat and tears. Following collection, the sample is dried, stored in a protective container, transported to the

laboratory, and subsequently recovered using an appropriate extraction solvent. Although VAMS is a promising micro-sampling technique, its routine application in neonates remains limited. It can be used to collect blood from a single finger or heel prick, allowing accurate sample volumes to be obtained while minimizing the influence of hematocrit.

An important factor of therapeutic drug monitoring is the selection of an appropriate bioanalytical technique for determining drug concentrations in plasma or other biological fluids. The principal analytical approaches used for this purpose include immunoassays and mass spectrometry (MS) coupled with liquid chromatography (LC) or gas chromatography (GC).[10]

Advances in laboratory technology have considerably enhanced the precision of therapeutic drug monitoring. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) has emerged as one of the most sensitive and specific methods for measuring drug concentrations. Compared with conventional immunoassays, LC–MS/MS offers greater analytical accuracy, improved specificity, and the ability to simultaneously quantify multiple drugs using very small sample volumes. These advantages are particularly valuable in neonatal intensive care settings, where minimizing blood loss is the major motto.[25]

Advances in instrumentation and computational approaches have enabled pharmacodynamic (PD) TDM based on biomarkers. Technologies such as mass spectrometry, computational biology, pharmacology and bioinformatics can facilitate the quantitative assessment of biochemical processes and provide information on drug-target interactions. Integrating these approaches with pharmacokinetic (PK) and pharmacodynamic (PD) monitoring may provide a more comprehensive understanding of drug exposure, response, and clinical outcomes.[10]

DRUGS COMMONLY REQUIRING THERAPEUTIC DRUG MONITORING IN NEONATES

Therapeutic drug monitoring is not routinely indicated for all medications used in neonatal practice. In neonatal intensive care units (NICUs), TDM is most commonly performed for aminoglycosides, vancomycin, phenobarbital, digoxin, and selected antifungal agents to maximize therapeutic efficacy while minimizing toxicity.[2]

Aminoglycosides

Gentamicin

Gentamicin is one of the most frequently prescribed antibiotics in neonatal intensive care units and is commonly used as empirical therapy for neonatal sepsis caused by Gram-negative organisms. It exhibits concentration-dependent bactericidal activity and possesses a narrow therapeutic index. Since gentamicin is almost exclusively eliminated through glomerular filtration, immature renal function in neonates may result in drug accumulation, increasing the risk of nephrotoxicity and irreversible ototoxicity.[1-3] Therapeutic drug monitoring is therefore recommended to ensure adequate peak concentrations for effective bacterial killing while maintaining low trough concentrations to minimize toxicity. Dosage adjustment is based on serum drug concentrations together with gestational age, postnatal age, body weight, renal function, and clinical response. Extended-interval dosing has become increasingly preferred because it improves bacterial killing and reduces toxicity.

Amikacin

Amikacin is another aminoglycoside commonly administered for severe neonatal Gram-negative infections, especially when resistance to gentamicin is suspected. Similar to gentamicin, amikacin demonstrates considerable pharmacokinetic variability during the neonatal period due to differences in renal maturation and body water composition. Therapeutic drug monitoring

helps achieve adequate bactericidal concentrations while preventing nephrotoxicity and ototoxicity. Dose adjustments should always consider serum drug concentrations in addition to renal function and gestational age.[3,8]

Vancomycin

Vancomycin is widely used for the treatment of serious Gram-positive infections, especially those caused by methicillin-resistant Staphylococcus aureus (MRSA) and coagulase-negative staphylococci in NICUs. Vancomycin clearance varies considerably among neonates because renal function matures rapidly after birth, emphasizing the need for routine therapeutic drug monitoring to optimize treatment and minimize nephrotoxicity. Traditionally, trough serum concentrations have been used to guide therapy. More recently, area under the concentration-time curve (AUC)-guided monitoring has been recommended because it better correlates with treatment efficacy while reducing toxicity. However, trough-based monitoring remains the most widely practiced approach in many neonatal centers because of its simplicity and availability.[2,25]

Phenobarbital

Phenobarbital remains the first-line anticonvulsant for neonatal seizures in many hospitals worldwide. Although effective, its pharmacokinetics vary considerably because hepatic enzyme activity and protein binding are immature during the neonatal period. Therapeutic drug monitoring is useful for ensuring adequate seizure control while avoiding adverse effects such as excessive sedation, respiratory depression, and hypotension. Monitoring is must in neonates receiving prolonged anticonvulsant therapy or those with persistent seizures despite treatment.[2,10]

Digoxin

Digoxin is occasionally prescribed in neonates with heart failure, supraventricular tachycardia, and selected congenital heart diseases. Even small increases in serum concentration may result in significant toxicity, including cardiac arrhythmias, vomiting, feeding intolerance, and neurological manifestations owing to its narrow therapeutic index. Dose adjustments should consider renal function, electrolyte status, body weight, as well as clinical response in addition to serum digoxin concentrations.[1,2]

Antifungal agents

Invasive fungal infections remain an important cause of morbidity and mortality among critically ill and extremely preterm neonates. Fluconazole is widely used for both prophylaxis and treatment of neonatal candidiasis, whereas voriconazole is reserved for selected invasive fungal infections. Routine therapeutic drug monitoring is generally unnecessary for fluconazole because of its relatively predictable pharmacokinetics, but not in the case of voriconazole, owing to its marked pharmacokinetic variability and nonlinear metabolism. TDM helps optimize antifungal efficacy while reducing hepatotoxicity (ranging from mild and asymptomatic increased serum transaminases to hepatic failure) and neurotoxicity.[3,6]

Table 3. Commonly monitored drugs in neonates and their therapeutic drug monitoring considerations

Drug	Major neonatal indication	Rationale for TDM	Monitoring approach	Major concerns
Gentamicin	Neonatal bacterial infection/sepsis	Variable renal clearance and narrow therapeutic index	Serum concentration monitoring with consideration if dosing interval ad renal function	Nephrotoxicity and ototoxicity
Amikacin	Serious Gram-negative infections	Developmental changes in renal	Serum concentration monitoring with	Nephrotoxicity and ototoxicity

		clearance and variable exposure	individualized dose adjustment	
Vancomycin	Serious Gram-positive infections	Variable clearance and exposure-response relationship	Exposure-based monitoring or concentration-based monitoring according to clinical setting	Nephrotoxicity
Phenobarbital	Neonatal seizures	Variable pharmacokinetics and narrow therapeutic index	Serum concentration monitoring with clinical response	Sedation, respiratory depression and hypotension
Digoxin	Selected neonatal cardiac conditions	Narrow therapeutic index and variable disposition	Serum concentration monitoring with clinical and laboratory parameters	Cardiac arrhythmias and other toxic effects
Selected antifungal agents	Invasive fungal infections	Drug-specific pharmacokinetic variability	Drug-specific concentration monitoring when clinically indicated	Hepatotoxicity and other drug-specific toxicities

CHALLENGES AND LIMITATIONS

Despite its well-established clinical value, several challenges continue to limit the routine implementation of therapeutic drug monitoring in neonates. One of the major limitations is the small circulating blood volume in newborns, which restricts repeated blood sampling and may contribute to iatrogenic anemia. Although micro sampling techniques have reduced this concern, their availability remains limited in many healthcare settings.[2,25]

Another challenge is the considerable variability in drug pharmacokinetics among neonates. Differences in gestational age, postnatal age, body weight, organ maturation, disease severity, and concomitant medications make it difficult to establish universal dosing recommendations and therapeutic targets. Consequently, drug concentrations must always be interpreted alongside clinical findings rather than in isolation.[1,3] Access to therapeutic drug monitoring services also varies considerably across institutions. Many hospitals, particularly in resource-limited settings, lack specialized laboratory facilities, advanced analytical instruments, and trained personnel required for accurate drug concentration analysis. Furthermore, neonatal-specific therapeutic ranges remain unavailable for several medications, highlighting the need for additional pharmacokinetic and pharmacodynamic research.[25]

EMERGING APPROACHES AND FUTURE PERSPECTIVES

Population PK and model-informed precision dosing

Recent advances in pharmacokinetic modelling, bioanalytical technologies, and computational methods have created opportunities to move TDM from conventional concentration-based dose adjustment toward individualized precision dosing. Population pharmacokinetic models can characterize variability in drug disposition across neonatal populations and identify patient characteristics that contribute to differences in drug exposure.[5,25]

Bayesian forecasting

Model-informed precision dosing represents a promising approach in which pharmacokinetic models are combined with individual patient characteristics and measured drug concentrations to optimize dosing. Bayesian forecasting can further facilitate individualized dose estimation by integrating prior population pharmacokinetic information with patient-specific concentration measurements. These approaches may be particularly advantageous in neonates bcaiuse obtaining

multiple blood samples is often impractical.[5,25]

Microsampling

Minimally invasive sampling techniques are another important area of development. Capillary microsampling, dried blood spot sampling, and volumetric absorptive microsampling may reduce the blood volume required for pharmacokinetic assessment and TDM. Further analytical validation and clinical implementation are required before these techniques can be routinely incorporated into neonatal practice.[26,27]

Pharmacogenomics

Pharmacogenomics may also contribute to individualized drug therapy by identifying genetic factors that influence drug metabolism, transport, or pharmacodynamic response. However, the clinical utility of pharmacogenomic approaches in neonates remains limited for many medications and requires further investigation.[8,25]

Electronic decision support/AI

The integration of TDM with electronic health records, Bayesian forecasting, clinical-decision support systems, and automated dosing tools may eventually allow timelier and more individualized dose optimization. Further research should therefore focus on validating these approaches in diverse neonatal populations, establishing clinically meaningful neonatal-specific therapeutic targets, and determining whether their implementation leads to improved clinical outcomes and reduced drug-related toxicity.[5,25,28]

CONCLUSION

TDM represents an important component of individualized pharmacotherapy in neonates, a population characterized by substantial developmental variability in pharmacokinetics and pharmacodynamics. Changes in renal and hepatic function, body composition, plasma protein binding, and other physiological processes can result in unpredictable drug exposure and make conventional dosing approaches insufficient for some medications. TDM can assist in optimizing drug exposure when concentration measurements are approximately obtained and interpreted in conjunction with patient-specific clinical and pharmacokinetic factors.

The clinical application of TDM is particularly relevant for drugs with narrow therapeutic indices or considerable pharmacokinetic variability. At the same time, limitations related to blood sampling, analytical availability, neonatal-specific therapeutic targets, and interindividual variability continue to restrict its implementation.

Emerging approaches like microsampling, population pharmacokinetic modelling, Bayesian forecasting, model-informed precision dosing, and advanced analytical techniques provide opportunities to improve individualized drug therapy. Further clinical research and standardization of neonatal therapeutic targets are required to determine the optimal integration of these approaches in routine neonatal practice. A coordinated approach combining accurate drug concentration measurement, pharmacokinetic interpretation, clinical assessment, and individualized dose adjustment may ultimately improve therapeutic efficacy while minimizing drug-related toxicity in neonates.

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