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Review Article

Optimizing Gentamicin Dosing in Neonates Using PBPK and PKPD Modeling: A Comprehensive Review

Khalid A Alfaifi[1]*, Faisal K[2], Sama K[3] and Sajwa A[4]

[1]*Department of Pharmacy, Medical Services Directorate, Taif, KSA*

[2]*College of Pharmacy, Taif University, KSA*

[3]*College of Medicine, Taif University. KSA*

[4]*College of Pharmacy, King Khalid University, KSA*

***Corresponding Author:** Khalid A Alfaifi, Department of Pharmacy, Medical Services Directorate, Taif, KSA.

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Abstract

Gentamicin is a critical antibiotic used to treat neonatal infections, but its narrow therapeutic index presents significant challenges in optimizing dosing, especially in neonates with immature organ systems. The pharmacokinetics (PK) of gentamicin in neonates differs markedly from that in older children and adults due to developmental variations in body composition, renal function, and hepatic maturation. This review explores the application of Physiologically Based Pharmacokinetic (PBPK) and Pharmacokinetic/Pharmacodynamic (PK/PD) modeling to optimize gentamicin dosing in neonates, with a focus on improving therapeutic efficacy while minimizing the risk of toxicity, including nephrotoxicity and ototoxicity. PBPK modeling provides a detailed framework for simulating drug behavior by incorporating neonatal-specific physiological parameters such as total body water (TBW), extracellular fluid (ECF) volume, and organ function. These models can predict the volume of distribution (Vd), renal clearance, and half-life of gentamicin, facilitating the development of personalized dosing regimens. Neonates, particularly preterm infants, exhibit a high proportion of body water and reduced renal clearance, which alters the pharmacokinetics of hydrophilic drugs like gentamicin, potentially increasing the risk of toxicity. Furthermore, the maturation of renal and hepatic function over the neonatal period influences drug elimination and metabolism, further complicating dosing decisions.PK/PD modeling, which integrates drug concentration-time profiles with therapeutic response, can inform dosing schedules to optimize drug efficacy while minimizing adverse effects. This review highlights the importance of PBPK and PK/PD models in neonatal pharmacotherapy and underscores their role in enhancing the safety and efficacy of gentamicin therapy in this vulnerable population.

Keywords: *Gentamicin; Neonates; PBPK Modeling; PKPD Modeling; Dosing Optimization; Pharmacokinetics; Pharmacodynamics; Nephrotoxicity; Ototoxicity; Therapeutic Drug Monitoring*

Introduction

Gentamicin is a commonly prescribed aminoglycoside antibiotic for treating neonatal infections such as sepsis, meningitis, and pneumonia. Despite its broad efficacy, gentamicin's use in neonates is complicated by its narrow therapeutic window, and its pharmacokinetic profile is highly influenced by the developmental physiology of neonates. With the immature renal and hepatic function typical of neonates, it is essential to optimize dosing to avoid toxicity, particularly nephrotoxicity and ototoxicity, which are dose-dependent.

In this context, Physiologically Based Pharmacokinetic (PBPK) and Pharmacokinetic/Pharmacodynamic (PK/PD) modeling techniques have emerged as invaluable tools for precision medicine. These models simulate drug behavior within the human body based on

physiological parameters, making them ideal for optimizing drug dosing in vulnerable populations such as neonates. This review will discuss the application of PBPK and PKPD modeling in the neonatal population, focusing on how these approaches can improve the safety and efficacy of gentamicin therapy [4,5].

Pharmacokinetics of gentamicin in neonates

The pharmacokinetics (PK) of gentamicin in neonates is unique due to their immature organ systems and high total body water content. Understanding the pharmacokinetic profile of gentamicin in neonates is crucial for determining optimal dosing regimens.

Renal function and gentamicin elimination

Gentamicin is primarily excreted by the kidneys, and its elimination is heavily dependent on glomerular filtration rate (GFR). In neonates, particularly preterm infants, the kidneys are not fully developed at birth, leading to a lower GFR and reduced renal clearance of gentamicin. The half-life of gentamicin in neonates is significantly prolonged compared to older children and adults due to this reduced renal elimination. Therefore, gentamicin's therapeutic concentration can be maintained longer, increasing the risk of toxicity if dosing is not appropriately adjusted [6].

Body composition and volume of distribution

Neonates have a high percentage of body water (approximately 70 - 80% of body weight), especially in preterm infants, which alters the volume of distribution (Vd) of hydrophilic drugs such as gentamicin. The high extracellular fluid (ECF) volume in neonates results in an increased Vd for gentamicin, requiring adjustments in dosing to achieve therapeutic serum concentrations. Conversely, the lower fat content in neonates may lead to lower Vd for lipophilic drugs, but gentamicin's hydrophilic nature means that the primary concern is its distribution in ECF [8].

Effect of water type during milk feeding in neonates on body composition, PBPK, and PK/PD during gentamicin therapy

The type of water used in formula feeding-whether hard or soft water-can influence various physiological parameters in neonates, such as hydration, electrolyte balance, and body composition. These changes can have downstream effects on physiologically-based pharmacokinetic (PBPK) modeling and, consequently, on pharmacokinetics (PK) and pharmacodynamics (PD) of medications, including gentamicin [9].

Effect of water type on body composition in neonates

Hard water

- **Higher mineral content:** Hard water contains higher levels of minerals such as calcium and magnesium. These minerals are essential for bone development, muscle function, and electrolyte balance. However, excessive intake could contribute to fluid retention due to the body's need to balance mineral concentrations.
- **Impact on fluid balance:** If hard water is consumed in excess, it could slightly increase extracellular fluid (ECF), which is primarily composed of plasma and interstitial fluid. This could potentially alter body weight due to fluid retention rather than actual changes in fat or muscle mass [1,25].
- **Electrolyte imbalance:** Excessive calcium or magnesium could also affect the neonatal kidney, which is still maturing. In rare cases, kidney dysfunction from mineral overload could affect the excretion of drugs (like gentamicin), potentially altering the drug's pharmacokinetics.

Soft water

- **Lower mineral content:** Soft water contains lower levels of calcium and magnesium, which might impair mineral absorption in neonates, especially if formula feeding lacks sufficient mineral supplementation.
- **Impact on hydration and fluid balance:** Dehydration is a potential risk with soft water if the infant is not receiving adequate minerals to support hydration and electrolyte balance. Dehydration could lead to fluid loss, decreased plasma volume, and a temporary reduction in body weight due to the loss of water, but not fat or muscle mass.
- **Electrolyte balance:** Low mineral content in water could exacerbate hypocalcemia (low calcium levels) or hypomagnesemia (low magnesium levels) in neonates, potentially affecting overall hydration status and renal function.

Body composition and PBPK modeling

PBPK modeling involves understanding how drugs distribute in the body, metabolize, and exert effects based on physiological characteristics, including body composition. In neonates, these characteristics can vary significantly, and fluid balance (which is influenced by the type of water used in formula feeding) is a key factor.

Total body water (TBW): Neonates have a higher proportion of total body water (approximately 70 - 80% of body weight) compared to adults. This includes both intracellular fluid (ICF) and extracellular fluid (ECF). Because hydration status is closely tied to body water content, water type (hard vs. soft) can indirectly impact drug distribution.

Hard water: The increased fluid retention from higher calcium and magnesium levels could increase extracellular fluid and potentially influence the volume of distribution (Vd) of hydrophilic drugs like gentamicin (which is water-soluble). Gentamicin may have a larger Vd in neonates, meaning more of the drug will be distributed in the body's water compartments, possibly requiring adjustments in dosing [1,25].

Soft water: Dehydration resulting from low mineral content in soft water could reduce plasma volume and decrease Vd for hydrophilic drugs like gentamicin. This could lead to higher drug concentrations in the bloodstream and potential toxicity unless the dose is adjusted to account for the decreased fluid volume.

Impact on PK/PD of gentamicin in neonates

Gentamicin is an aminoglycoside antibiotic that is water-soluble and primarily distributed in the extracellular fluid. Its pharmacokinetics (PK) can be influenced by changes in body composition, particularly the volume of distribution and renal clearance [7,18].

Volume of distribution (Vd)

Hard water: Higher mineral content could increase extracellular fluid volume, which may increase Vd for gentamicin. As a result, a higher dose of gentamicin might be required to achieve therapeutic drug concentrations in the body.

Soft water: Dehydration could reduce plasma volume and Vd, potentially causing higher plasma concentrations of gentamicin for a given dose. This could increase the risk of toxicity (e.g. nephrotoxicity and ototoxicity), which is a well-known side effect of gentamicin [12].

Renal clearance

Hard water: Excessive mineral intake (particularly calcium and magnesium) could impact renal function in neonates, who have immature kidneys. If the kidneys struggle to filter out excess minerals, it might also affect drug clearance, leading to prolonged half-life and potential toxicity if gentamicin is not cleared effectively.

Soft water: In the case of dehydration, soft water could lead to reduced renal perfusion, potentially slowing the clearance of gentamicin from the body. This could increase drug concentrations and prolong the drug's effect, raising the risk of nephrotoxicity.

Pharmacodynamics (PD)

Gentamicin's pharmacodynamics in neonates are influenced by the drug's concentration-time curve (Cmax) and the area under the curve (AUC). If the Vd is altered by water type (as in hard or soft water), it could affect the Cmax and AUC, which are critical for its efficacy and safety.

Hard water could lead to lower peak concentrations due to increased Vd, which might affect the drug's effectiveness against infections.

Soft water could cause higher peak concentrations if dehydration leads to a reduced Vd, increasing the risk of toxicity.

Practical implications for gentamicin therapy in neonates

Dosing adjustments: Based on the water type used for formula feeding, it may be necessary to adjust gentamicin dosing in neonates:

- **Hard water:** If an infant is consuming hard water, the increased extracellular fluid may warrant a higher dose of gentamicin to achieve the desired therapeutic concentration.
- **Soft water**: If an infant is dehydrated due to soft water, gentamicin toxicity could be a risk, and dosing should be carefully monitored, possibly requiring lower doses or closer monitoring of drug levels to avoid nephrotoxicity.

Monitoring: Close monitoring of hydration status, renal function, and drug levels (gentamicin serum concentrations) is essential, especially in neonates, who are vulnerable to the effects of both dehydration and fluid overload.

The type of water used during formula feeding in neonates (hard vs. soft water) can significantly influence body composition and fluid balance, which in turn affects PBPK modeling and PK/PD of drugs like gentamicin. Adjustments to dosing may be required to account for altered fluid distribution, electrolyte imbalances, and renal function. Gentamicin therapy in neonates, in particular, must be tailored to the individual's hydration status and fluid balance, with careful monitoring to prevent toxicity or ineffective dosing.

Maturation of drug metabolism

The liver plays a critical role in drug metabolism, but in neonates, hepatic enzymes are immature. This affects the metabolism of gentamicin and other drugs. While gentamicin does not undergo extensive hepatic metabolism, its renal elimination can still be impacted by protein binding, which changes as neonates age and develop. Thus, pharmacokinetic models must account for these developmental changes to accurately predict gentamicin concentration-time profiles [20].

Impact of the type of water on body weight

The type of water used during milk feeding in neonates-whether hard or soft-can influence their body weight indirectly through its impact on hydration, fluid balance, and electrolyte levels. While water type does not directly alter neonatal body weight, it can affect factors that contribute to weight fluctuations, such as:

Hydration status and fluid balance

- Hard water: Hard water contains higher concentrations of calcium and magnesium. These minerals may contribute to fluid retention in the body, which could potentially increase body weight temporarily due to an increase in extracellular fluid (ECF) volume. However, this effect is likely subtle and might not result in significant long-term weight gain, as the body typically regulates fluid balance through mechanisms like kidney function and sweating.

- Soft water: Soft water, being low in calcium and magnesium, may reduce the likelihood of fluid retention. In neonates, particularly if hydration is insufficient or the neonate experiences dehydration (which may be more common in the case of inadequate feeding with soft water), there may be a decrease in body weight due to reduced fluid intake or loss of body water. Dehydration can lead to a loss of weight due to reduced extracellular and intracellular fluid volumes.

Electrolyte balance and fluid distribution

- Hard water: The higher levels of calcium and magnesium in hard water could contribute to changes in electrolyte balance, which in turn might affect fluid distribution. However, this effect is usually small and doesn't result in large fluctuations in body weight unless there is a significant disruption in the neonate's hydration or electrolyte balance.
- Soft water: Soft water may lead to an imbalance in electrolytes if the neonate's hydration is not properly managed. This could potentially lead to issues like dehydration, which might reduce body weight. Additionally, imbalances in sodium, calcium, and magnesium levels could affect the body's ability to retain and distribute fluid, potentially affecting weight [10].

Impact of dehydration on weight

Neonates, particularly preterm or low-birth-weight infants, are highly sensitive to dehydration. Inadequate hydration, which can be exacerbated by soft water (due to lower electrolyte content), could result in reduced body weight. Dehydration is one of the most common causes of weight loss in neonates, particularly in the first few days of life. If a neonate is not receiving adequate fluid intake or has an electrolyte imbalance, it may show weight loss until proper hydration and feeding are restored.

While the water type does not directly influence neonatal body weight in a large, direct manner, it can affect factors like hydration, fluid retention, and electrolyte balance, which may cause minor weight fluctuations. Dehydration caused by soft water (low in minerals) could lead to weight loss, while hard water might contribute to slight fluid retention and potentially a small increase in body weight. The most significant effects on body weight are likely to be related to overall fluid intake, hydration status, and nutrition, rather than the type of water used in feeding itself.

To design optimal PBPK model for gentamicin therapy in neonates

The development of a Physiologically-Based Pharmacokinetic (PBPK) model for gentamicin therapy in neonates involves a structured approach, with careful consideration of the unique physiological characteristics of neonates, including differences between term and premature infants. The following steps outline the process for designing an optimal PBPK model and subsequently a Pharmacokinetic/Pharmacodynamic (PK/PD) model for gentamicin therapy.

Step 1: Define the objective and model scope

- Objective: Define the purpose of the model, whether it's for individualizing dosing, predicting drug exposure, or optimizing therapeutic strategies for gentamicin.
- Scope: Determine if the model will cover term neonates, preterm neonates, or both, and decide the specific therapeutic goals (e.g., minimizing nephrotoxicity, maximizing efficacy).

Step 2: Collect physiological data for neonates

- Neonatal physiology: Gather data on the physiological parameters of neonates, including body weight, total body water (TBW), extracellular fluid (ECF), organ volumes, and tissue composition. This is particularly important for developing accurate PBPK models that simulate drug distribution in neonates, as these parameters change significantly between term and premature infants.

- Age-specific differences: Include developmental aspects such as renal and hepatic maturation, which significantly affect drug metabolism and clearance in neonates.

Step 3: Drug-specific data

Gentamicin pharmacokinetics: Collect data on gentamicin's absorption, distribution, metabolism, and elimination. For neonates, focus n:

- Absorption: Consider how gentamicin is administered (e.g., IV vs. IM).
- Distribution: Include data on protein binding, which is low in neonates, and body water composition (high ECF in neonates).
- Elimination: Gentamicin is primarily excreted unchanged by the kidneys, so neonatal renal function is crucial. Determine glomerular filtration rate (GFR) and renal clearance in neonates, which are significantly different [22].

Step 4: Develop the PBPK model

- Model structure: Create a physiological structure of the body, dividing it into compartments representing different tissues (e.g. blood, liver, kidney, muscle, adipose) and consider the volumes of distribution for gentamicin, which is hydrophilic and primarily distributed in extracellular fluids.
- Mathematical modeling: Use a system of differential equations to represent the movement of gentamicin between compartments, including equations for drug absorption, distribution, metabolism (if applicable), and elimination.
- Maturation effects: Incorporate age- and weight-specific scaling laws to account for changes in body composition, renal clearance, and enzyme activity as the neonate matures, with take into account the type of water of milk feeding.
- Validation: Validate the model using available clinical data, adjusting for differences between preterm and term neonates.

Step 5: Calibration and sensitivity analysis

- Calibration: Calibrate the PBPK model with experimental or clinical data, such as plasma concentration-time profiles of gentamicin in neonates.
- Sensitivity analysis: Perform sensitivity analysis to assess how changes in key parameters (e.g., renal clearance, body water composition) affect gentamicin concentrations. This will help identify critical factors influencing the pharmacokinetics of gentamicin in neonates [23].

Step 6: Design the PK/PD model for gentamicin therapy in neonates

Once the PBPK model is established, the next step is to design the PK/PD model for gentamicin, which links the pharmacokinetics of the drug (concentrations over time) with its pharmacodynamics (efficacy and toxicity).

Step 6.1: Define the PK/PD parameters for gentamicin

- Concentration-dependent killing: Since gentamicin is concentration-dependent, focus on maximizing peak concentrations (Cmax) relative to the Minimum Inhibitory Concentration (MIC) of the pathogen.
- Toxicity thresholds: Include pharmacodynamic endpoints such as nephrotoxicity (kidney damage) and ototoxicity (hearing loss). Define Toxicity Indices based cumulative exposure (AUC).

Step 6.2: Select the appropriate PK/PD index

For gentamicin, the most commonly used PK/PD index is AUC/MIC because it effectively captures the relationship between the dose, drug exposure, and bacterial killing while accounting for toxicity risk.

Other potential indices include Cmax/MIC and T>MIC, but AUC/MIC is often preferred for gentamicin due to its strong correlation with clinical outcomes.

Step 6.3: Simulate drug exposure and efficacy

Use the PBPK model to simulate the AUC, Cmax, and other pharmacokinetic parameters for different dosing regimens in neonates, ensuring that the gentamicin concentration remains within a therapeutic window.

Incorporate age- and weight-specific adjustments to optimize drug exposure for term and premature neonates.

Step 6.4: Model calibration and validation

- Calibration: Calibrate the PK/PD model using clinical data from neonates treated with gentamicin (plasma concentrations, therapeutic outcomes, adverse effects).
- Validation: Validate the model by comparing predicted outcomes (e.g., therapeutic efficacy, toxicity) with real-world clinical observations to ensure the model accurately reflects drug behavior in neonates.

Step 6.5: Model-informed precision dosing (MIPD)

Once the PBPK and PK/PD models are developed and validated, they can be used for model-informed precision dosing (MIPD), where individualized gentamicin doses are calculated based on a neonate's physiological characteristics (age, weight, renal function, hydration status).

MIPD can be implemented to fine-tune dosing regimens in real-time to minimize toxicity while ensuring therapeutic efficacy.

This process integrates the critical steps needed to design an optimal PBPK model and a PK/PD model, followed by the application of model-informed precision dosing (MIPD) for optimizing gentamicin therapy in neonates. These models allow for individualized dosing regimens that maximize therapeutic outcomes while minimizing risks associated with toxicity, particularly in the vulnerable neonatal population.

Therapeutic drug monitoring (TDM)

Given the variability in drug metabolism and elimination in neonates, Therapeutic Drug Monitoring (TDM) is often employed to guide gentamicin dosing. TDM involves measuring serum drug concentrations and adjusting doses to maintain them within the target therapeutic range. PKPD models can aid in predicting optimal dosing intervals and adjustments based on TDM data.

Advantages and limitations of PBPK and PKPD modeling for gentamicin in neonates

Advantages of PBPK and PKPD modeling

- Personalized medicine: PBPK and PKPD models enable individualized dosing regimens by considering the unique physiology of each neonate, including gestational age, body composition, and renal function
- Minimizing toxicity: By simulating the pharmacokinetics and pharmacodynamics, these models help identify dosing strategies that minimize the risk of nephrotoxicity and ototoxicity while ensuring therapeutic efficacy.
- Reducing the need for clinical trials: PBPK models can simulate various dosing scenarios in silico, reducing the need for large-scale clinical trials, especially in neonates, where ethical and practical considerations limit trial designs.

Limitations and challenges

- Data gaps: Despite advances in PBPK modeling, data on neonatal-specific parameters (e.g. renal maturation, enzyme development) are still limited, which can affect the accuracy of these models.
- Model validation: Ongoing efforts are needed to validate these models in neonatal populations with diverse characteristics, such as gestational age and birth weight, to ensure their clinical applicability.
- Complexity and computational resources: While PBPK and PKPD models are powerful, they are computationally intensive and require significant data inputs. Implementing these models in real-time clinical settings can be challenging due to the need for specialized software and expertise in pharmacometrics.
- Individual variability: Neonates, particularly preterm infants, exhibit wide variations in their physiological parameters. This variability can make it difficult to create universally applicable models for all neonates. Despite this, advances in machine learning and artificial intelligence hold promise in personalizing models further to account for this individual variability.

Clinical implementation and future directions

Model-informed precision dosing (MIPD) in neonatal care

One of the key advancements in drug dosing for neonates is the shift toward Model-Informed Precision Dosing (MIPD). By combining PBPK, PKPD, and therapeutic drug monitoring (TDM), MIPD offers a data-driven approach to optimizing gentamicin therapy. Through these models, dosing decisions can be based on real-time pharmacokinetic data and predicted responses, improving clinical outcomes and reducing adverse effects.

Implementing MIPD in neonatal intensive care units (NICUs) could lead to better individualized care, ensuring that each neonate receives the most appropriate dose based on their specific physiological profile and current clinical state. This would also minimize the potential for antibiotic resistance, as more accurate dosing could help achieve adequate drug concentrations without unnecessary overexposure.

Advancing neonatal PBPK models

Advancing PBPK models specific to neonates requires overcoming several challenges. The development of age-specific anatomical and physiological datasets will be key in improving the accuracy of neonatal PBPK models. Incorporating more data on renal function, hepatic enzyme maturation, and the evolving immune system in neonates will further enhance the predictive power of these models.

Moreover, integrating population pharmacokinetic (PopPK) data with PBPK models could allow for better prediction of interindividual variability in gentamicin pharmacokinetics. This is particularly important in neonates, as factors such as birth weight, gestational age, and the presence of concomitant diseases can influence drug behavior.

Personalized neonatal gentamicin dosing using AI and big data

With the increasing availability of big data in neonatal intensive care units, artificial intelligence (AI) and machine learning algorithms could be integrated with PBPK and PKPD models to create highly personalized gentamicin dosing recommendations. AI can help analyze large datasets, including clinical records, laboratory results, and genetic information, to make real-time dosing adjustments for individual neonates. This approach would allow clinicians to provide more precise treatment tailored to the neonate's physiological condition, improving safety and efficacy.

Conclusion

Gentamicin is a life-saving antibiotic in neonatal care, but its administration requires careful management due to its narrow therapeutic index and the immature physiology of neonates. PBPK and PKPD modeling represent a powerful approach to optimizing gentamicin dosing in neonates by integrating physiological, anatomical, and drug-specific parameters. These models provide personalized dosing strategies, minimize the risk of toxicity, and improve clinical outcomes.

While the use of Model-Informed Precision Dosing (MIPD) in neonates holds great promise, challenges remain, including the need for more neonatal-specific data, improved model validation, and overcoming computational barriers.

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