REVIEW

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Utility of Pharmacokinetic-Pharmacodynamic Modeling to Optimize Aminoglycoside Dosing in Neonates: A Mini-Review

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Abstract

Aminoglycosides (AG) remain essential in the management of severe neonatal infections, but their narrow therapeutic range demands precise dosing to maximize efficacy and minimize toxicity. This review evaluates the utility of pharmacokinetic/pharmacodynamic (PK/PD) models in optimizing AG dosing in neonates. An advanced literature search was conducted in PubMed using Boolean operators for accuracy and breadth. The search query combined ("AG" OR "gentamicin" OR "amikacin") AND "PK/PD modelling" AND ("neonates" OR "infants" OR "paediatrics"). The search focused on studies published between 2010 and 2024, emphasizing PK/PD modelling in neonatal and pediatric populations. Filters were applied to include only studies with free full-text availability, yielding eight relevant articles. The findings indicate that PK/PD models, combined with therapeutic drug monitoring, enhance dosing strategies by incorporating patient-specific variables such as gestational age, birth weight, postnatal age, and renal function (e.g., glomerular filtration rate). The predictive value of metrics like peak-to-minimal inhibitory concentration (MIC) and area under the curve-to-MIC ratios was evident for efficacy, while elevated trough levels were linked to nephrotoxicity. However, limitations of current approaches include insufficient consideration of disease-specific PK alterations (e.g., sepsis), reliance on invasive monitoring methods, and the absence of advanced PD indices, such as bacterial growth kinetics and immunological status. Future research should focus on developing less-invasive sampling techniques, such as dried blood spots and urine biomarkers for renal function while integrating advanced PD indices to refine neonatal dosing strategies further.

Keywords: Gentamicin, neonates, biosensors, artificial intelligence

INTRODUCTION

In neonatal intensive care units, antibiotics such as aminoglycosides (AG) are frequently prescribed, yet optimal dosing remains a common challenge. Optimizing antibiotic use is critical to ensuring effective treatment, minimizing toxicity, and mitigating the development of antibiotic resistance.[1] AG are essential for treating severe gram-negative infections. However, their use is associated with significant risks, including dose-dependent nephrotoxicity and ototoxicity,

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with higher risk in neonates due to their unique physiological vulnerabilities.[2]

Neonates, particularly preterm infants, present distinct pharmacokinetic (PK) and pharmacodynamic (PD) challenges. Factors such as immature renal function, high extracellular fluid volume, and variable body composition lead to complex PK of AG. For instance, the volume of distribution for gentamicin in neonates ranges from 0.40 to 0.45 L/kg, with even higher values observed in those with sepsis. Similarly, the half-life of AG can prolonged to 11.5 hours in extremely low birth weight neonates, compared to 8-9 hours in neonates with adequate weight.[3] These PK variations contribute to either suboptimal therapeutic levels or potential toxicity when using empirical dosing regimens.[4] Moreover, the rapidly developing yet unpredictable glomerular filtration rate (GFR) in neonates complicates AG clearance, while increased extracellular fluid volume affects drug distribution. Such factors necessitate dosing regimens with extended intervals to achieve optimal peak-to-minimal inhibitory concentration (MIC) OR area under the curve (AUC)-to-MIC ratios, which correlate with improved efficacy and reduced adaptive bacterial resistance.[5]

Figure 1 provides an overview of key PK and PD parameters related to the efficacy and toxicity of AGs. The figure highlights crucial parameters such as AUC, Cmax (peak concentration), Cmin (trough concentration), MIC and post-antibiotic effect (PAE), which is the continued suppression of bacterial growth after AG concentration falls below the MIC. For effective treatment of gram-negative infections, target ratios should be C_{max}/MIC ≥8-10 OR AUC/MIC ≥70-100. Additionally, maintaining Cmin levels <2 mg/L is associated with a reduced risk of nephrotoxicity.[6]

Traditional therapeutic drug monitoring (TDM), focused on measuring serum drug levels, often falls short in addressing the complexities of neonatal pharmacology. Factors such as gestational and postnatal age, organ immaturity, birth weight, and conditions like sepsis significantly influence drug PKs and PDs, necessitating advanced modeling techniques for precise dosing. These models refine dosing regimens by accounting for variables such as AG concentration-dependent killing, PAE, and accumulation in kidney and ear tissues among other variables.[6,7] Advanced PK/PD modelling techniques, including physiologically based PK/PD models (PBPK/PD), have further enhanced our ability to simulate neonatal drug PK and improve dosing accuracy.[8]

Figure 2 describes one of the sophisticated PK/PD models which integrates bacterial growth dynamics, adaptive resistance (AR), and PK of gentamicin. It consists of two key bacterial compartments: the susceptible (S) compartment, where drug-S bacteria proliferate, and the resting compartment, containing dormant, less drug-S bacteria. Transfer between these compartments occurs when the bacterial population exceeds a threshold, regulated by the rate constant (kSR). Both compartments experience natural bacterial death at a rate constant (kdeath), while the central system mediates drug-induced bacterial killing through the elimination rate constant (ke). The model also incorporates AR, where resistance develops at a rate constant (kon), stimulated by gentamicin, and reverses at a rate constant (koff). AR diminishes the maximum drug-induced bacterial killing effect (E_{max}).

The PK model is described as a three-compartment system (one central and two peripheral compartments PI and PII). The overall system effectively captures bacterial dynamics, and gentamicin PK offers a robust integration tool to predict gentamicin efficacy against specified infections.[9-11]

Objective

This review aims to evaluate the utility of PK/PD models in optimizing AG therapy for neonates, with a specific focus on addressing the unique challenges posed by both full-term and preterm neonates.

Methods

A comprehensive literature search was conducted in PubMed using Boolean operators. The search query included the terms (“AG” OR ”gentamicin” OR “amikacin”) AND ”PK/PD modelling” AND (“neonates” OR “infants” OR “paediatrics”). The search was restricted to studies published between 2010 and 2024, emphasizing PK/PD modeling specifically in neonatal and pediatric populations. Studies focusing on *in vitro* experiments or animal models were excluded to ensure relevance to human clinical contexts.

Pharmacokinetic Modeling of Aminoglycosides in Pediatric and Neonates

PK modelling of AG has demonstrated significant success in optimizing its clinical application in pediatric populations. For example, these models have played a crucial role in adjusting amikacin and tobramycin dosing for pediatric patients with cystic fibrosis, in whom altered PK necessitate individualized dosing regimens.[12-14] Additionally, PK modelling has highlighted important differences in AG disposition between oncology and non-oncology patients and supported tailoring dosing strategies for these distinct groups.[15,16]

However, PK modelling in neonates remains relatively underexplored. Only eight studies met the inclusion criteria, yet they provide valuable insights into optimizing AG therapy in this vulnerable population. These studies highlight the potential of PK modelling to inform dosing strategies, improve therapeutic outcomes, and minimize toxicity in neonates. Nonetheless, the limited number of studies underscores the need for further research to expand the evidence base and refine AG therapy for this age group. These studies are summarized below.

Mohamed et al. [11] developed a semi-physiological model to characterize the maturation of GFR across pediatric age groups. By analyzing data from 1,760 patients, they created a body weight-dependent exponent function for GFR maturation, which improved drug clearance predictions and supported safer dosing strategies for renally excreted drugs.

In a study by De Cock et al. [17], PBPK/PD was utilized to guide gentamicin dosing in preterm neonates. The validated model accounted for gestational age, showing that neonates with postmenstrual ages of 30-34 weeks or ≥35 weeks required higher doses with longer intervals (e.g., every 36 hours) to maintain optimal trough concentrations below 1 µg/mL.

Cristea et al.[18] highlighted that neonates with perinatal asphyxia exhibited a significant reduction in amikacin clearance, necessitating extended dosing intervals to reduce toxic trough levels while maintaining efficacy.

Cies et al.[19] analyzed gentamicin PK and PD in neonates with hypoxic-ischemic encephalopathy undergoing controlled hypothermia. A two-compartment model identified 5 mg/kg every 36 hours as the optimal regimen to achieve desired therapeutic targets.

Sridharan et al.[9] employed a semi-mechanistic model to describe gentamicin's bactericidal activity and AR in preterm neonates. Despite lower peak concentrations in preterm neonates, the drug's extended half-life enhanced bacterial killing, supporting extended dosing intervals of 36-48 hours to balance efficacy and toxicity.

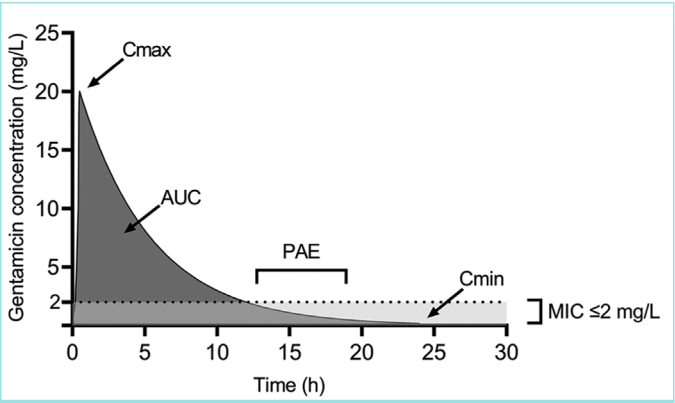

Figure 1. Overview of PK/PD parameters related to the efficacy and toxicity of AG.[6]

AUC: Area under the curve, C_{max}: Peak concentration, C_{min}:Trough concentration, MIC: Minimal inhibitory concentration, PAE: Post-antibiotic effect, defined as the continued suppression of bacterial growth after the gentamicin concentration falls below the MIC For effective treatment of gram-negative infections, target ratios include Cmax/MIC ≥8-10 and AUC/MIC ≥ 70-100. A C_{min} <2 mg/L is linked to a decreased risk of nephrotoxicity.

Neeli et al.[20] used Bayesian PK modelling and Monte Carlo simulations to evaluate gentamicin dosing in critically ill neonates. They found that increasing the dose from 4 to 5-6 mg/kg/day enhanced the likelihood of achieving both peak (C_{max}) and (AUC0-24) targets, underscoring the need for individualized dosing in this population.

Similarly, Gastine et al.[21] used PK/PD modelling to evaluate gentamicin in neonatal sepsis. The study revealed that standard dosing regimens were inadequate for *Enterobacteriaceae*, prompting a need for alternative therapies to ensure effective empirical coverage.[21]

Matcha et al.[22] validated a two-compartment PK model for amikacin in term-neonates, identifying creatinine clearance and body weight as critical covariates. This model enabled the development of dosing nomograms for neonates with varying renal function, ensuring safe and effective therapy.

Pharmacokinetic Software in Therapeutic Drug Monitoring

PK software has become indispensable in TDM, particularly within the framework of model-informed precision dosing (MIPD). A recent review identified 28 MIPD software tools, of which 18 are actively used. These tools, predominantly based on Bayesian methods, offer population models to guide dosing decisions. However, the evidence supporting their clinical utility remains limited, underscoring the need for further standardization and validation, especially in neonates. Of the 19 selected MIPD tools, 13 are web-based, with several (e.g., Autokinetics, MwPharm, PrecisePK, and RxStudio) also available as desktop versions. Tools such as DoseMeRx, MwPharm, and RxStudio offer mobile

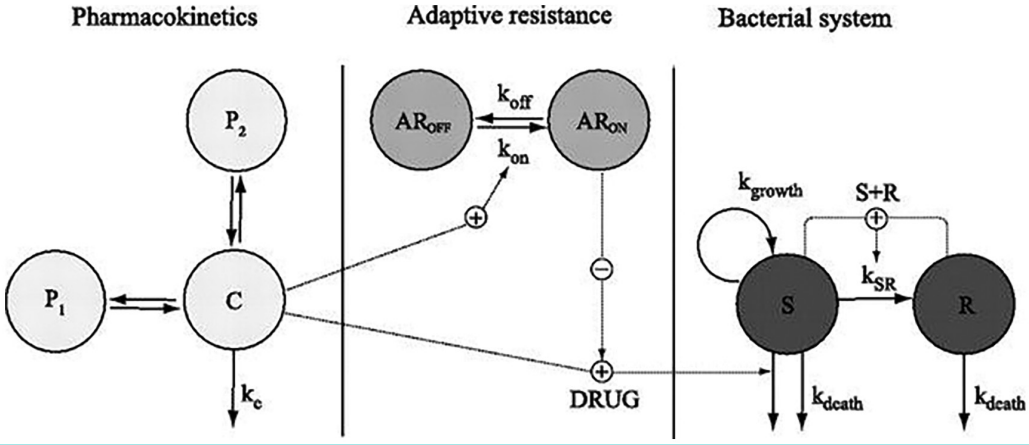

Figure 2. Schematic Illustration of the final PK/PD model the final PK/PD model comprises the following components.[11]

Bacterial compartments: susceptible compartment (S), contains proliferating and drug-susceptible bacteria, with growth occurring at a first-order rate constant. Resting compartment (R): it contains resting and drug-insusceptible bacteria. The transfer from S to R is stimulated by the total bacterial content when it exceeds a certain threshold, with a transfer rate constant (kSR).

Bacterial dynamics: both compartments experience natural bacterial death at a first-order rate constant (kdeath). The central compartment is responsible for bacterial killing, driven by a first-order elimination rate constant (ke).

Pharmacodynamic (PD) model: adaptive resistance (AR): includes a binding model with a development rate constant (kon) for AR, stimulated by gentamicin concentration, and a return rate constant (koff) for restoring susceptibility. AR reduces the maximum bacterial killing effect of gentamicin (E_{max}).

Model structure: *in vitro* experiments: utilized a two-compartment model with one peripheral compartment (P1). Predictions: applied a three-compartment model with two peripheral compartments (P1, P2).

This model captures the dynamics of bacterial growth, resistance development, and the effects of gentamicin, providing a framework for optimizing dosing strategies.

PK: Pharmacokinetic

compatibility, enhancing their usability in diverse clinical settings. These advancements highlight the growing importance of integrating MIPD tools into routine neonatal care to optimize antibiotic therapy and improve clinical outcomes.[23]

CONCLUSION

PK/PD modelling has improved AG dosing in neonates, but gaps remain, especially in complex conditions like neonatal sepsis and preterm birth. Current models often rely on extrapolated adult data, overlooking neonatal-specific physiological differences like immature renal function and variable body composition. Traditional PK-PD indices, such as C_{max}/MIC, AUC/MIC, and T% > MIC, oversimplify the relationship between drug exposure and bacterial response, highlighting the need for more tailored approaches.

Despite advances in research, neonates, particularly preterm infants, are underrepresented in research. New PBPK-PD models show promise but still rely on adult data and simplified indices that don't capture neonatal complexity. The integration of biosensors, artificial intelligence, and less invasive sampling methods, such as dried blood spots, may revolutionize dosing strategies and improve therapeutic outcomes. However, challenges in data accuracy and clinical integration remain.

MAIN POINTS

- Pharmacokinetic/pharmacodynamic models: These help adjust aminoglycoside doses in neonates, optimizing effectiveness and minimizing toxicity.
- Drug level monitoring: Regular monitoring reduces the risk of renal and ototoxicity by keeping drug levels within a safe range.
- Model limitations: Current models don't fully account for factors like infection, gestational age, and weight, which affect drug metabolism.
- Less invasive monitoring: Urine tests or spot samples could simplify monitoring for neonates, reducing discomfort.
- AI and biosensors: AI and biosensors could enable personalized, real-time treatment adjustments, improving safety and efficacy.

Footnotes

Authorship Contributions

Concept: A.S.A., K.A.Y.A., A.A.S., F.K.A., S.A.A., A.S.M., Literature Search: A.S.A., K.A.Y.A., A.A.S., F.K.A., S.A.A., A.S.M., Writing: A.S.A., K.A.Y.A., A.A.S., F.K.A., S.A.A., A.S.M.

DISCLOSURES

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