Journal of Pharmaceutical Research International

Volume 36, Issue 9, Page 61-67, 2024; Article no.JPRI.121920
ISSN: 2456-9119, NLM ID: 101716968
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Using PKPD Modeling to Optimize Gentamicin Dosing in Saudi Neonates

Khalid A. Alfaifi [a*]

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

Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/jpri/2024/v36i97577

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/121920

Review Article

Received: 27/06/2024
Accepted: 29/08/2024
Published: 02/09/2024

ABSTRACT

The intricate interplay between pharmacokinetics and pharmacodynamics is pivotal in optimizing gentamicin therapy for neonates, a population characterized by unique physiological developmental considerations and pathophysiological changes in critically ill neonates. Rapid growth, Altered body composition, the immature renal function and premature immune system, significantly influence pharmacokinetic parameters Cl and Vd which aggravate complexities to achieve targets attainment and therapeutic drug monitoring compared to adults, necessitating individualized dosing strategies. The primary aim of this review, highlights the importance of PKPD modeling to optimizing gentamicin dosing in neonates Emerging trends in pediatric pharmacotherapy underscore the urgency for advancing pharmacokinetic-pharmacodynamic (PKPD) modeling to enhance therapeutic efficacy. Future research should focus on integrating real-world data from diverse neonatal populations. Genetic variations may influence the outcomes of PKPD studies, and subsequent dosing recommendations. Conducting PKPD studies in diverse populations is crucial for obtaining more robust and reliable results, which would allow for more representative models that account for physiological variations. Incorporating advanced computational techniques such as machine learning may further refine predictive accuracy, enabling personalized dosing strategies

**Corresponding author: E-mail: kalfaify@gmail.com;*

Cite as: *Alfaifi, K. A. (2024) "Using PKPD Modeling to Optimize Gentamicin Dosing in Saudi Neonates", Journal of Pharmaceutical Research International, 36(9), pp. 61–67. doi: 10.9734/jpri/2024/v36i97577.*

that minimize toxicity while maximizing therapeutic benefits As research evolves, the role of pediatric-specific biomarkers in PKPD modeling warrants closer investigation, potentially leading to breakthroughs that redefine dosing paradigms. By addressing these critical areas, the field can advance toward more effective and individualized pharmacotherapy, reducing adverse outcomes and improving clinical care for vulnerable neonates.

Keywords: PKPD modeling; pharmacokinetics; pharmacodynamics; neonates.

1. INTRODUCTION

The complexities associated with administering antibiotics to neonates necessitate a more nuanced understanding of pharmacokinetics and pharmacodynamics (PKPD). Infants, particularly those in the neonatal intensive care unit, present unique physiological and pathophysiological challenges that can significantly alter drug metabolism and excretion. Furthermore genetics variations can cause the development of antibiotic-related adverse events. Traditionally, dosing regimens for aminoglycosides like gentamicin have relied on empirical approaches, may leading to suboptimal therapeutic outcomes and increased toxicity risks. This paper aims to explore how integrating PKPD modeling can refine gentamicin dosing strategies, thereby enhancing drug efficacy while minimizing adverse effects in this vulnerable population. By leveraging individual patient data and advanced modeling techniques, clinicians can better tailor gentamicin doses, ensuring an appropriate therapeutic window. Ultimately, this research underlines the importance of individualized medicine in neonatal care, advancing the dialogue on optimizing pharmacotherapy for this sensitive group.

1.1 Overview of Gentamicin and its Clinical Importance in Neonates

As an aminoglycoside antibiotic, Gentamicin is crucial in neonatal medicine, particularly for its effectiveness against a spectrum of gram-negative and some gram-positive bacterial infections. Its broad antimicrobial activity makes it a frontline treatment for sepsis, urinary tract infections, and pneumonia among neonates, populations notably vulnerable to infections due to immature immune systems. Clinically, the pharmacokinetics of Gentamicin in neonates can differ significantly from older populations, necessitating careful consideration of dosing regimens to minimize toxicity while ensuring therapeutic efficacy [1]. Studies indicate that altered renal function and body composition in neonates necessitate individualized dosing strategies, as the risk of nephrotoxicity and ototoxicity remains a significant concern. Optimizing Gentamicin dosing through pharmacokinetic-pharmacodynamic (PKPD) modeling provides an innovative approach to enhance treatment outcomes while safeguarding against adverse effects, thereby underscoring its vital role in neonatal care [2,3].

1.2 Introduction to Pharmacokinetics and Pharmacodynamics (PKPD) Modeling

The interplay between pharmacokinetics and pharmacodynamics (PKPD) is essential for understanding how drugs, particularly antibiotics like gentamicin, exert their therapeutic effects within the body. Pharmacokinetics involves the absorption, distribution, metabolism, and excretion (ADME) of drugs, which dictates the concentration of the drug at the site of action over time. Conversely, pharmacodynamics focuses on the biochemical and physiological effects of drugs and their mechanisms of action. Together, these two domains form a comprehensive framework that enables researchers and clinicians to predict drug responses in different patient populations, including vulnerable neonatal cohorts [4-7]. The optimization of dosing regimens through PKPD modeling is critical, especially for drugs with narrow therapeutic indices such as gentamicin, to ensure both efficacy and safety in these fragile patients. Moreover, advancements in computational modeling have allowed for more precise simulations that can cater to the unique pharmacological challenges presented by neonates [1].

2. PHARMACOKINETICS OF GENTAMICIN IN NEONATES

Due to the unique physiological characteristics of neonates, the pharmacokinetics of gentamicin are significantly altered compared to older populations. In neonates, factors such as immature renal function and variable volume of distribution contribute to the complex absorption, distribution, metabolism, and excretion (ADME)

profiles of gentamicin. Research indicates that the glomerular filtration rate (GFR) in this population develops rapidly, but it remains lower than in adults, necessitating adjustments in dosing regimens to achieve therapeutic efficacy while minimizing toxicity. Furthermore, the increased extracellular fluid volume in neonates affects the distribution of hydrophilic drugs like gentamicin, highlighting the importance of individualized dosing strategies based on weight and gestational age (World Health Organization). Understanding the pharmacokinetic parameters specific to neonates is crucial for optimizing treatment protocols, reducing risks of underdosing or overdosing, and ultimately improving clinical outcomes in this vulnerable population.

2.1 Absorption, Distribution, Metabolism, and Excretion (ADME) Characteristics

Understanding the ADME characteristics of gentamicin in neonates is crucial for optimizing its dosing regimens., Distribution is influenced by the neonates body composition, which typically consists of a higher percentage of total body water and a lower percentage of body fat compared to older children and adults. This leads to a larger volume of distribution for hydrophilic drugs like gentamicin. Furthermore, metabolism and excretion capacities are underdeveloped in neonates; their immature renal function can significantly prolong the elimination half-life of the drug. Consequently, understanding these pharmacokinetic properties is essential not only for effective therapeutic outcomes but also for minimizing the risk of toxicity associated with gentamicin treatment in this vulnerable population [8].

2.2 Factors Influencing Gentamicin Pharmacokinetics in Neonates

The pharmacokinetics of gentamicin in neonates are significantly influenced by developmental factors, particularly changes in body composition and organ maturation. Neonates exhibit a higher total body water percentage compared to older children and adults, which can impact the distribution volume of hydrophilic medications like gentamicin. Moreover, the immaturity of renal function in neonates results in altered clearance rates, necessitating age-adjusted dosing strategies to avoid toxicity and ensure therapeutic efficacy. Additionally, the variability in metabolic pathways due to enzymatic development may further complicate the pharmacokinetic profile of gentamicin in this population. Understanding these factors is critical for optimizing gentamicin therapy; consequently, implementing pharmacokinetic/ pharmacodynamic (PKPD) modeling approaches allows for individualized dosing regimens that respond to the unique physiological characteristics of neonates [9]. Such tailored strategies can enhance treatment outcomes while minimizing potential adverse effects associated with underdosing or overdosing of this essential aminoglycoside antibiotic.

3. PHARMACODYNAMICS OF GENTAMICIN

An in-depth understanding of the pharmacodynamics of gentamicin is crucial for optimizing dosing strategies in neonates. PKPD indices, such as AUC/MIC and T>MIC, play a crucial role in optimizing gentamicin dosing in neonates. The pharmacodynamic relationship illustrates that increased drug exposure correlates with enhanced bacterial kill rates, supporting the rationale for higher doses at longer intervals. However, this must be balanced against the potential for toxicity, particularly nephrotoxicity and ototoxicity, which are of heightened concern in neonates due to their developing organs. The complexities of gentamicins actions underscore the necessity for population pharmacokinetics/pharmacodynamics (pop-PK/PD) modeling, as the variability in responses can be pronounced in a cohort already experiencing significant age- and disease-related physiological differences [10]. As such, integrating machine learning approaches within PKPD frameworks may enhance predictive accuracy and inform more precise dosing strategies tailored to individual neonate needs [11].

3.1 Mechanism of Action and Antimicrobial Efficacy

The selective toxicity of gentamicin, an aminoglycoside antibiotic, arises from its unique mechanism of action, primarily targeting bacterial ribosomal subunit 30S. By binding irreversibly to this subunit, gentamicin inhibits protein synthesis, leading to misreading of mRNA and production of dysfunctional proteins crucial for bacterial survival[quote]. This interference not only stunts the growth of susceptible bacteria but can also induce lethal effects, particularly in gram-negative pathogens often responsible for neonatal infections. The pharmacokinetic-

pharmacodynamic (PKPD) relationship is pivotal in optimizing gentamicin dosing, ensuring that peak plasma concentrations exceed the minimum inhibitory concentration (MIC) of the target bacteria, thereby enhancing its antimicrobial efficacy[quote]. Understanding this interplay is vital for tailoring dosages in neonates, a population particularly sensitive to both the effects and potential toxicities of antimicrobial therapies, thus reinforcing the need for precise PKPD modeling in clinical settings.

3.2 Relationship Between Drug Concentration and Therapeutic Outcomes

An essential element in pharmacotherapy is the relationship between drug concentration and therapeutic outcomes, which serves as the foundation for optimizing dosing regimens. Achieving the desired therapeutic effect often hinges on maintaining drug levels within a narrow therapeutic window, where both subtherapeutic and supratherapeutic concentrations can pose significant risks. For gentamicin, a widely used aminoglycoside antibiotic in neonates, the concentration-dependent bactericidal activity necessitates careful monitoring and adjustment of dosages to enhance clinical efficacy while minimizing toxic effects, particularly nephrotoxicity and ototoxicity. By employing population pharmacokinetic-pharmacodynamic (PKPD) modeling, researchers can better understand individual variability in drug metabolism and response among neonates, allowing for more precise dosing tailored to patient-specific factors, such as weight and gestational age [12]. Ultimately, elucidating this relationship not only improves therapeutic outcomes but also advances the standard of care in pediatric medicine.

4. APPLICATION OF PKPD MODELING IN DOSING OPTIMIZATION

Dosing optimization in neonates, particularly for antibiotics like gentamicin, is a complex challenge due to physiological variability and the off-label use of many medications in this vulnerable population. By applying pharmacokinetics and pharmacodynamics (PKPD) modeling, healthcare providers can individualize dosing regimens, ensuring therapeutic efficacy while minimizing toxicity. Specifically, population pharmacokinetic approaches can help elucidate the significant inter-individual variability among neonates, advocating for tailored dosing based on precise pharmacokinetic data [11]. Concurrently, addressing the pharmacodynamic effects ensures that the administered dose achieves optimal drug concentration at the site of action, particularly crucial in critically ill patients who experience rapid changes in drug distribution and clearance [10]. PKPD modeling offers a robust framework for understanding drug response in diverse populations. By identifying and incorporating relevant covariates, researchers can refine or may need with these complexities to development a PKPD model incorporated with multiple indices, can help interpretate variation in dosing response and thus achieve optimal targets attainment in this vulnerable population [13,14]. Thus, employing PKPD modeling not only fosters more accurate dosing strategies but also contributes to improved clinical outcomes, underscoring the importance of data-driven approaches to antibiotic stewardship in neonates.

4.1 Development of Population Pharmacokinetic Models for Neonates

In constructing population pharmacokinetic models for neonates, one must consider the unique physiological attributes that differentiate this age group from older patients. Neonates exhibit rapid changes in body composition, organ maturity, and metabolic capacity, necessitating models that adapt to their dynamic characteristics. The integration of developmental pharmacology principles is crucial; for example, differences in renal clearance and hepatic metabolism can significantly impact drug disposition. By employing data from diverse neonatal populations, researchers can identify key covariates that influence pharmacokinetic parameters [15-17]. This approach facilitates the creation of more robust models that predict gentamicin pharmacokinetics more accurately across different gestational ages and clinical settings. Ultimately, these models serve not only to improve dosing regimens but also to minimize the risk of toxicity and therapeutic failures, underscoring the importance of tailored pharmacokinetic modeling in neonatal care [18].

4.2 Simulation Studies and Their Role in Dosing Regimen Design

In optimizing dosing regimens for gentamicin in neonates, simulation studies serve as invaluable tools for predicting pharmacokinetic and

pharmacodynamic outcomes based on various dosing scenarios. By employing sophisticated modeling techniques, researchers can evaluate the effects of different drug concentrations and their resultant therapeutic efficacy while accounting for the unique physiological characteristics of neonates, such as immature kidney function and varying body composition. These simulations allow for the identification of an optimal dosing regimen that minimizes potential toxicity while maximizing therapeutic benefits. Furthermore, the iterative nature of simulation studies enables researchers to refine their models based on emerging data, thereby continuously improving the precision of their predictions. Consequently, the integration of simulation studies not only enhances our understanding of drug behavior in vulnerable populations but also underscores the importance of personalized medicine in pediatrics, making these tools essential in the design of safe and effective dosing strategies for gentamicin in neonatal care [19].

5. CONCLUSION

The findings of this research underscore the critical need for precision in gentamicin dosing regimens for neonates, a population uniquely vulnerable to both underdosing and potential toxicity. By integrating pharmacokinetic-pharmacodynamic (PKPD) modeling, clinicians can tailor treatment to an individual neonate's metabolic and physiological traits, allowing for more precise dosing tailored to patient-specific factors, such as weight and gestational age, [12] ultimately enhancing therapeutic efficacy while minimizing adverse effects. The results indicate that traditional dosing guidelines may fall short, underscoring the importance of iterative model refinement and validation through clinical data. Moreover, the incorporation of real-time monitoring can facilitate a dynamic approach to dosages, allowing adjustments based on emerging physiological responses. As the field of pediatric pharmacology advances, leveraging such sophisticated modeling techniques will be essential in developing evidence-based therapeutic protocols. Future research should continue to explore varying dosing strategies across different neonate populations, reinforcing the potential for personalized medicine in optimizing gentamicin administration [1].

5.1 Summary of Key Findings and Implications for Clinical Practice

The analysis of pharmacokinetic-pharmacodynamic (PKPD) modeling in the optimization of gentamicin dosing for neonates reveals several critical findings that have significant implications for clinical practice. Primarily, the study indicates that individualized dosing strategies, informed by PKPD principles, can substantially improve therapeutic outcomes while minimizing the risks of nephrotoxicity and ototoxicity commonly associated with aminoglycosides. Specifically, the modeling approach underscores the need for continuous monitoring of drug serum levels to tailor dosing regimens effectively to the unique metabolic pathways in neonates, a demographic often overlooked in standard protocols. Additionally, the implications extend beyond drug administration to enhance overall neonatal care practices, highlighting the importance of multidisciplinary collaboration among clinicians to implement PKPD-driven protocols [1]. This comprehensive understanding fosters not only improved patient safety but also paves the way for the development of more effective, evidence-based guidelines in pediatric pharmacotherapy.

5.2 Future Directions for Research and PKPD Modeling in Pediatric Pharmacotherapy

Emerging trends in pediatric pharmacotherapy underscore the urgency for advancing pharmacokinetic-pharmacodynamic (PKPD) modeling to enhance therapeutic efficacy in neonates. Future research should focus on integrating real-world data from diverse neonatal populations, which would allow for more representative models that account for physiological variations. Incorporating advanced computational techniques such as machine learning may further refine predictive accuracy, enabling personalized dosing strategies that minimize toxicity while maximizing therapeutic benefits. Additionally, collaborative frameworks among pharmacologists, clinicians, and bioethicists will be essential in developing ethically sound protocols for utilizing PKPD models, ensuring both safety and efficacy in neonatal patient populations. As research evolves, the role of pediatric-specific biomarkers in PKPD modeling warrants closer investigation, potentially leading to breakthroughs that redefine dosing paradigms. By addressing these critical areas, the field can advance toward more effective and individualized pharmacotherapy, reducing adverse outcomes and improving clinical care for vulnerable neonates.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that a targeted literature search was conducted using PubMed and generative AI technologies such as Large Language Models, have been used during searching with relevant terms, writing and editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology.

Details of the AI usage are given below:

1. Google Gemini, 1.5 flash Model.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Evelyne Jacqz-Aigrain, Imti Choonara, Paediatric Clinical Pharmacology, CRC Press; 2021-02-25.
2. Nielsen EI, Cars O, Friberg LE. Pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: A step toward model-based dose optimization. Antimicrobial agents and chemotherapy. 2011 Oct;55(10):4619-30.
3. Zhuang L, He Y, Xia H, Liu Y, Sy SK, Derendorf H. Gentamicin dosing strategy in patients with end-stage renal disease receiving haemodialysis: Evaluation using a semi-mechanistic pharmacokinetic/ pharmacodynamic model. Journal of Antimicrobial Chemotherapy. 2016 Apr 1;71(4):1012-21.
4. Zazo H, Lagarejos E, Prado-Velasco M, Sánchez-Herrero S, Serna J, Rueda-Ferreiro A, et al. Physiologically-based pharmacokinetic modelling and dosing evaluation of gentamicin in neonates using PhysPK. Frontiers in Pharmacology. 2022 Sep 28;13:977372.
5. Ghoneim RH, Thabit AK, Lashkar MO, Ali AS. Optimizing gentamicin dosing in different pediatric age groups using population pharmacokinetics and Monte Carlo simulation. Italian Journal of Pediatrics. 2021 Dec;47:1-8.
6. Medellín-Garibay SE, Rueda-Naharro A, Peña-Cabia S, García B, Romano-Moreno S, Barcia E. Population pharmacokinetics of gentamicin and dosing optimization for infants. Antimicrobial agents and chemotherapy. 2015 Jan;59(1):482-9.
7. Ali AS. Pharmacokinetic simulation and optimizing gentamicin dosing in pediatrics. Bulletin of Pharmaceutical Sciences Assiut University. 2021 Jun 1;44(1):31-9.
8. Joseph I. Boullata, Vincent T. Armenti, Handbook of Drug-Nutrient Interactions, Springer Science & Business Media; 2010-03-17
9. Khaled Alfaify, Ahmed Ali, Mohammad Farouq. Pharmacokinetics for optimizing the dose of gentamicin in neonates, LAP Lambert Academic Publishing; 2012-05
10. Pieter A. De Cock, Chapter 18: Performing clinical drug trials in acute and critically ill neonates and children; 2024
11. Mizuki Uno, Application of machine learning techniques in population pharmacokinetics/pharmacodynamics modeling; 2024
12. Andrew E. Mulberg, Dianne Murphy, Julia Dunne, Lisa L Mathis. Pediatric Drug Development, John Wiley & Sons; 2013-05-20.
13. World Health Organization, Pocket Book of Hospital Care for Children, World Health Organization; 2013.
14. Nicola Principi, Kyriakoula Petropulacos, Susanna Esposito. Genetic Variations and Antibiotic-Related Adverse Events Pharmaceuticals. 2024;17(3):331.
15. Esther M Hollander, Eline L van Tuinen, Elisabeth H Schölvinck, Klasien A Bergman, Arno R Bourgonje, Valentina Gracchi, et al. Evaluation of Dosing Guidelines for Gentamicin in Neonates and Children Antibiotics. 2023;12(5):810.
16. Mario Regazzi, Alberto Berardi, Simonetta Picone, Chryssoula Tzialla. Pharmacokinetic and Pharmacodynamic Considerations of Antibiotic Use in Neonates, Antibiotics. 2023;12(12):1747.
17. Bijleveld YA, van den Heuvel ME, Hodiamont CJ, Mathôt RAA, de Haan TR. Population pharmacokinetics and dosing considerations for gentamicin in newborns

with suspected or proven sepsis caused by gram-negative bacteria. Antimicrob. Agents Chemother. 2017;61(1):e01304–e01316. DOI: 10.1128/AAC.01304-16.

18. Tricia Lacy Gomella, M. Douglas Cunningham, Fabien Gabriel Eyal, Neonatology, McGraw-Hill/Appleton & Lange; 1992.

19. Wei Zhao, Johannes Nicolaas Van Den Anker. Model-based evaluation of antimicrobial agents in Children, Frontiers Media SA; 2021-10-01.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/121920