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Review Article

Extended-Interval Dosing (EID) vs. Traditional Dosing (TDD) of Gentamicin in Premature and Term Neonates: Role of Pharmacokinetics and Pharmacodynamics

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Abstract

Gentamicin, an aminoglycoside antibiotic, is widely used in neonatal intensive care units (NICUs) for its efficacy against Gram-negative pathogens. However, its pharmacokinetics (PK) and pharmacodynamics (PD) are influenced by neonatal physiology, necessitating tailored dosing strategies. This review examines the comparative efficacy and safety of extended-interval dosing (EID) versus traditional dosing (TDD) in premature and term neonates. It also evaluates the role of PK/PD principles, particularly therapeutic drug monitoring (TDM) and the area under the curve to minimum inhibitory concentration (AUC/MIC) ratio, in optimizing gentamicin therapy. EID demonstrates superior efficacy and safety by achieving optimal Cmax/MIC ratios and reducing nephrotoxicity and ototoxicity risks, making it the preferred regimen in most neonatal scenarios. Future integration of advanced pharmacometric models and biomarkers promises further improvement in individualizing gentamicin dosing.

Keywords: *Extended-Interval Dosing; Traditional Dosing; Gentamicin; Neonates; Dosing Optimization; Pharmacokinetics; Pharmacodynamics; Nephrotoxicity; Ototoxicity; Therapeutic Drug Monitoring*

Introduction

Gentamicin is an essential antibiotic in neonatal medicine due to its potent activity against Gram-negative organisms, such as *Escherichia coli* and *Klebsiella pneumoniae*. However, neonates' physiological immaturity, particularly in renal function, complicates gentamicin's pharmacokinetics, necessitating careful dosing. Traditional dosing (TDD) involves multiple daily doses to maintain therapeutic serum levels, but it increases the risk of toxicity due to drug accumulation. Extended-interval dosing (EID), which involves a single daily dose, optimizes concentration-dependent killing while minimizing toxicity risks. This article compares EID and TDD in premature and term neonates, emphasizing the role of PK/PD principles in therapeutic optimization.

Gentamicin pharmacokinetics and pharmacodynamics in neonates

Pharmacokinetics (PK)

Gentamicin's PK profile in neonates is distinct due to their unique physiology:

- **Volume of distribution (Vd):** Neonates have a higher Vd owing to greater total body water content, diluting gentamicin concentrations. Premature neonates exhibit even higher Vd values compared to term neonates [1].
- **Clearance (Cl):** Gentamicin is primarily eliminated via glomerular filtration, which is immature at birth. Premature neonates exhibit significantly reduced clearance, leading to a prolonged half-life compared to term neonates [2].
- **Half-Life (t½):** The half-life of gentamicin in premature neonates averages 12 hours or more, compared to 4-8 hours in term neonates, necessitating tailored dosing regimens [3].

Pharmacodynamics (PD)

Gentamicin exhibits concentration-dependent killing, with efficacy best predicted by the peak-to-MIC (Cmax/MIC) ratio. The prolonged post-antibiotic effect (PAE) further supports EID by allowing longer drug-free intervals without loss of efficacy. Emerging evidence underscores the importance of the AUC/MIC ratio as a predictor of clinical success and reduced toxicity [5].

Efficacy of extended-interval dosing vs. traditional dosing

Premature neonates

Premature neonates benefit from EID with close monitoring due to its ability to accommodate their immature renal function:

- **Peak concentrations:** EID achieves higher Cmax values, which are critical for bactericidal activity, compared to TDD. In a study comparing regimens, EID achieved a mean Cmax of 9.8 µg/mL versus 6.5 µg/mL with TDD, correlating with improved clinical outcomes [6].
- **Trough levels:** Lower trough levels with EID (<2 µg/mL) reduce nephrotoxicity risk, a significant concern in this population [7].
- **Clinical outcomes:** A systematic review of neonatal sepsis management found that EID was associated with a 15% reduction in mortality compared to TDD [8].

Term neonates

For term neonates, EID is also advantageous, as their relatively mature renal function allows for efficient drug clearance:

- **Safety profile:** EID significantly reduces the incidence of nephrotoxicity and ototoxicity compared to TDD. In a cohort study, nephrotoxicity occurred in 2% of neonates on EID versus 8% on TDD [9].
- **Convenience:** The once-daily dosing regimen simplifies administration and reduces the burden on NICU staff.

Safety considerations

Nephrotoxicity

Nephrotoxicity is dose-dependent and more common in neonates with impaired renal function. Strategies to minimize risk include:

- Using EID to reduce trough levels.
- Monitoring renal function regularly (serum creatinine, urine output) [10].

Ototoxicity

Although less common, ototoxicity is irreversible. Avoiding prolonged exposure and cumulative doses can mitigate this risk [11].

Role of PK/PD in optimizing gentamicin therapy

- **Therapeutic drug monitoring (TDM):** TDM is essential for tailoring dosing regimens to individual neonates. Peak levels should be maintained between 8 - 12 µg/mL, and trough levels should be < 2 µg/mL to minimize toxicity [12].
- **AUC/MIC ratio:** Recent studies advocate for AUC-guided dosing to improve therapeutic outcomes. An AUC/MIC is associated with optimal efficacy and reduced toxicity risks in neonates [13].
- **Pharmacometric models:** Advances in pharmacometric modeling, including population-based and Bayesian approaches, enable real-time AUC estimation and individualized dose adjustments. These tools can integrate patient-specific data such as renal function and infection severity.

Artificial intelligence and machine learning

AI and machine learning have the potential to predict optimal dosing regimens based on large datasets, improving precision and reducing reliance on empirical methods.

Challenges

- **PK variability:** Interpatient variability complicates dosing, particularly in premature neonates.
- **Resource limitations:** Access to TDM and pharmacometric tools is limited in many settings.

Future directions

- Development of biomarker-based toxicity monitoring.
- Integration of Bayesian software for AUC estimation in NICUs [15].

Conclusion

EID offers significant advantages over TDD in both premature and term neonates, optimizing bactericidal activity while minimizing toxicity risks. Incorporating PK/PD principles, particularly AUC/MIC and TDM, increase its importance in premature neonates, ensures individualized dosing tailored to neonatal physiology. While challenges persist, advancements in pharmacometrics and biomarker research promise to further refine gentamicin therapy, ensuring safe and effective treatment for this vulnerable population.

Authors Contribution

Authors actively participated in this research. Author KA design, interpreted, writing, prepared the manuscript, Author NA, reviewed neonatal pathophysiological issue. Author FK, reviewed The Pharmacokinetic of Gentamicin in neonates, Author SK reviewed Physiological immaturity issue, SA reviewed Pharmacodynamics of Gentamicin in neonates. YK reviewed Artificial Intelligence and Machine Learning in TDM. FB, reviewed neonatal physiology issue.

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