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ORIGINAL RESEARCH

Recommendations of Gentamicin Dose Based on Different Pharmacokinetic/Pharmacodynamic Targets for Intensive Care Adult Patients: A Redefining Approach

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Background: In addition to the maximum plasma concentration (C_{max}) to the minimum inhibitory concentration (MIC) ratio, the 24-hour area under the concentration-time curve (AUC_{24h}) to MIC has recently been suggested as pharmacokinetic/pharmacodynamic (PK/PD) targets for efficacy and safety in once-daily dosing of gentamicin (ODDG) in critically ill patients.

Purpose: This study aimed to predict the optimal effective dose and risk of nephrotoxicity for gentamicin in critically ill patients for two different PK/PD targets within the first 3 days of infection.

Methods: The gathered pharmacokinetic and demographic data in critically ill patients from 21 previously published studies were used to build a one-compartment pharmacokinetic model. The Monte Carlo Simulation (MCS) method was conducted with the use of gentamicin once-daily dosing ranging from 5–10 mg/kg. The percentage target attainment (PTA) for efficacy, C_{max}/MIC ~8–10 and AUC_{24h}/MIC ≥110 targets, were studied. The AUC_{24h} >700 mg·h/L and C_{min} >2 mg/L were used to predict the risk of nephrotoxicity.

Results: Gentamicin 7 mg/kg/day could achieve both efficacy targets for more than 90% when the MIC was <0.5 mg/L. When the MIC increased to 1 mg/L, gentamicin 8 mg/kg/day could reach the PK/PD and safety targets. However, for pathogens with MIC ≥2 mg/L, no studied gentamicin doses were sufficient to reach the efficacy target. The risk of nephrotoxicity using AUC_{24h} >700 mg·h/L was small, but the risk was greater when applying a C_{min} target >2 mg/L.

Conclusion: Considering both targets of Cmax/MIC ~8–10 and AUC_{24h}/MIC ≥110, an initial gentamicin dose of 8 mg/kg/day should be recommended in critically ill patients for pathogens with MIC of ≤1 mg/L. Clinical validation of our results is essential.

Keywords: gentamicin, C_{max}/MIC, AUC_{24h}/MIC, nephrotoxicity, critically ill

Introduction

Gentamicin is an aminoglycoside antibiotic which effectively treats serious Gram-negative infections.[1] In addition, global Gram-negative resistance rates are increasing and there is limited availability of antibiotics to treat the emergence of resistance.[2] An appropriate empirical dose of gentamicin can be suggested based on local epidemiological data and susceptibility patterns. Critical illness and severe infection lead to altered pathophysiology and gentamicin pharmacokinetics. Increased volume of distribution (Vd) is frequently reported in critically ill patients.[2,3] Furthermore, augmented renal clearance of gentamicin in patients with sepsis, severe trauma, undergone major surgeries, or use of inotropic agents also plays a role in an alteration of gentamicin pharmacokinetics.[4] Therefore, appropriate dosing regimens of gentamicin in a timely manner, particularly during the acute phase of illness, are essential for successful therapeutic outcomes.

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