Pharmacokinetics and pharmacodynamics of a simplified fixed dose of polymyxin B in critically ill patients with extensive drug-resistant Gram-negative bacteria–induced nosocomial pneumonia

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Abstract

Background: The doses of polymyxin B (PMB) based on total body weight and adjusted body weight vary widely, especially for critically ill patients, whose pathophysiological and metabolic reactions change often. This study describes the pharmacokinetic (PK) and pharmacodynamic (PD) features and their influencing factors in severely infected patients treated with a simplified fixed dose of intravenous PMB.

Methods: This single-centre, prospective, observational study was conducted in the 40-bed mixed ICU of a 2000-bed teaching hospital in Beijing. For patients admitted to the ICU between September 2021 and December 2022 who received PMB (50 mg q12h after 100 mg loading dose) for the treatment of extensively drug-resistant Gram-negative-induced nosocomial pneumonia, series blood and/or bronchoalveolar lavage fluid (BALF) samples were collected to measure PMB concentrations, and clinical data were recorded. PK analysis was performed by using WinNonlin software.

Results: Plasma and BALF samples were collected from 27 patients, 5 had treatment failure, whilst the other 22 achieved the desired clinical response. Both noncompartmental and two-compartment models were used to describe the data. The parameter estimates for the plasma maximal drug concentration (C_{max}), clearance (Cl), volume of distribution, elimination half-life, area under the 0-12 h concentration–time curve ($AUC_{ss,0–12h}$) and plasma protein-binding ratio were 8.3 μg/mL, 1.55 L/h, 30.44 L, 19.56 L/h, 55.04 h·μg/mL and 85.53%, respectively. Receiver operating curve

(ROC) analysis suggested that $AUC_{ss,0-24h}$ (AUC_{ROC}=0.955) was superior to the $C_{ss,avg}$, C_{min}, and C_{max} for the prediction of clinical efficacy, with an optimal cut-off point of 77.27. The target AUC_{0-24h} of 50-100 $h \cdot \mu g \cdot mL^{-1}$ was reached by 48.15% of the patients, among whom 76.95% obtained the desired clinical response. Another 48.15% of the patients exceeded this target, among whom 92.31% obtained the desired clinical response. PMB exhibited low pulmonary penetration, with a median (IQR) epithelial lining fluid/plasma ratio (%) of 15.69 [16.86, 18.15]. TNF-α and IL-6/IL-10 ratio were correlated with PMB PK parameters.

Conclusions: Most critically ill patients achieved or exceeded recommended plasma PK targets and achieved the desired clinical response safely via intravenous administration of PMB at a simplified fixed dose, although there was wide interindividual variability. PMB could be good for treating lung infection in critically ill patients, although it did not reach a satisfactory pulmonary concentration, indicating it might act through alternative mechanisms. A more precise PK/PD modelling approach should be developed by comprehensively considering the inflammatory factors that contribute to PMB PK.

Key words: polymyxin B, pharmacokinetic and pharmacodynamics, bronchoalveolar lavage fluid, inflammatory factors