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Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens.

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Abstract

BACKGROUND:

Polymyxin B is a last-line therapy for multidrug-resistant gram-negative bacteria. There is a dearth of pharmacokinetic data to guide dosing in critically ill patients.

METHODS:

Twenty-four critically ill patients were enrolled and blood/urine samples were collected over a dosing interval at steady state. Polymyxin B concentrations were measured by liquid chromatography-tandem mass spectrometry. Population pharmacokinetic analysis and Monte Carlo simulations were conducted.

RESULTS:

Twenty-four patients aged 21-87 years received intravenous polymyxin B (0.45-3.38 mg/kg/day). Two patients were on continuous hemodialysis, and creatinine clearance in the other patients was 10-143 mL/min. Even with very diverse demographics, the total body clearance of polymyxin B when scaled by total body weight (population mean, 0.0276 L/hour/kg) showed remarkably low interindividual variability (32.4% coefficient of variation). Polymyxin B was predominantly nonrenally cleared with median urinary recovery of 4.04%. Polymyxin B total body clearance did not show any relationship with creatinine clearance (r(2) = 0.008), APACHE II score, or age. Median unbound fraction in plasma was 0.42. Monte Carlo simulations revealed the importance of initiating therapeutic regimens with a loading dose.

CONCLUSIONS:

Our study showed that doses of intravenous polymyxin B are best scaled by total body weight. Importantly, dosage selection of this drug should not be based on renal function.

KEYWORDS:

dose selection; pharmacokinetics; plasma protein binding; polymyxins; urinary recovery

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