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Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis

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ABSTRACT

Currently there are no pharmacokinetic (PK) data to guide antibiotic dosing in critically ill Australian Indigenous patients with severe sepsis. This study aimed to determine whether the population pharmacokinetics of meropenem were different between critically ill Australian Indigenous and critically ill Caucasian patients. Serial plasma and urine samples as well as clinical and demographic data were collected over two dosing intervals from critically ill Australian Indigenous patients. Plasma meropenem concentrations were assayed by validated chromatography. Concentration–time data were analysed with data from a previous PK study in critically ill Caucasian patients using Pmetrics. The population PK model was subsequently used for Monte Carlo dosing simulations to describe optimal doses for these patients. Six Indigenous and five Caucasian subjects were included. A two-compartment model described the data adequately, with meropenem clearance and volume of distribution of the central compartment described by creatinine clearance (CL_{Cr}) and patient weight, respectively. Patient ethnicity was not supported as a covariate in the final model. Significant differences were observed for meropenem clearance between the Indigenous and Caucasian groups [median 11.0 (range 3.0–14.1) L/h vs. 17.4 (4.3–30.3) L/h, respectively; $P < 0.01$]. Standard dosing regimens (1 g intravenous every 8 h as a 30-min infusion) consistently achieved target exposures at the minimum inhibitory concentration breakpoint in the absence of augmented renal clearance. No significant interethnic differences in meropenem pharmacokinetics between the Indigenous and Caucasian groups were detected and CL_{Cr} was found to be the strongest determinant of appropriate dosing regimens.
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1. Introduction

Sepsis has been a major health issue in the Australian Indigenous population and is associated with high morbidity and mortality rates [1–3]. It remains one of the greatest health concerns; ca. 60% of deaths in the Indigenous patient population of the largest Central Australian remote hospital were related to infection in comparison with 25% in the non-Indigenous patient population from 2000 to 2005. Fifty-six per cent of the infection-related deaths were attributed to bacterial sepsis [4].

Meropenem is a broad-spectrum antibiotic commonly used in the intensive care unit (ICU) [5]. Its pharmacokinetic/pharmacodynamic (PK/PD) properties show a time-dependent bacterial kill characteristic with a target of maintaining the free drug concentration above the minimum inhibitory concentration (MIC) for ≥40% of the dosing interval (>40%$fT_{>MIC}$) [6]. However, significant changes in the volume of distribution (V_d) and drug clearance observed in critically ill patients can alter the possibility of achieving this target [7]. These PK changes are difficult to predict, especially in the absence of therapeutic drug monitoring.

Conventional dosing guidelines are usually followed in critically ill Indigenous patients; however, a recent systematic review suggested PK differences between ethnicities for some antibiotics [8]. Indeed, young, healthy Indigenous adults are reported to have 30% less nephrons than non-Indigenous comparators as well as having a mean kidney volume that is 27% greater [9]. From an

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anthropometric perspective, the Australian Indigenous have a lower body mass, higher central fat and slimmer limbs [10]. Furthermore, they were shown to have a similar allele frequency to South Asians for some cytochrome P450 enzymes [11]. Whether these physiological differences affect meropenem pharmacokinetics in the acute setting is unknown. Currently there are no available data on the antibiotic pharmacokinetics of critically ill Indigenous patients in Australia.

This study aimed to compare the population pharmacokinetics of meropenem in Australian Indigenous patients with severe sepsis and critically ill Caucasian patients with sepsis.

2. Materials and methods

2.1. Institution where the work was carried out

This work was carried out at the Department of Intensive Care Medicine of Alice Springs Hospital (Alice Springs, Northern Territory, Australia).

2.2. Setting

This was a prospective, observational cohort study investigating the pharmacokinetics of meropenem. Ethical approval was obtained from local (Central Australian Human Research Ethics Committee) and university (The University of Queensland Human Research Ethics Committee) ethics committees.

2.3. Study population

The inclusion criteria were: (i) Australian Indigenous; (ii) ≥18 years of age; (iii) confirmed or suspected severe sepsis within the previous 48 h; (iv) prescribed meropenem; and (v) an arterial line in situ. The exclusion criteria were: (i) creatinine clearance (CL_{Cr}) <15 mL/min; (ii) requiring haemodialysis or continuous renal replacement therapy; and (iii) pregnancy.

2.4. Study protocol

The dose of meropenem (DBL Meropenem; Hospira Australia, Melbourne, VIC, Australia) was determined by the treating clinicians and was made up in 100 mL of sodium chloride 0.9% and infused intravenously over 30 min. Ten blood samples were collected in 2 mL lithium heparin tubes from the existing arterial line over one dosing interval at 0, 15, 30, 45, 60, 90, 120, 180, 360 and 480 min from initiation of infusion. A second set of samples following the same regimen was obtained the next day. Demographics, clinical information and routine laboratory test results performed on the study days were also collected.

2.5. Sample handling and storage

Blood samples were placed in a drug refrigerator at 2–8 °C immediately after sampling. Samples were then centrifuged at 5000 rpm for 6 min within 8 h of collection. Both plasma and urine samples were aspirated into cryovials and were stored in a freezer at –70 °C. Samples were packed with dry ice and were freighted to the Burns Trauma & Critical Care Research Centre, The University of Queensland (Brisbane, QLD, Australia) for drug assay.

2.6. Drug assay

Plasma concentrations of meropenem were determined by validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV) on a Shimadzu Prominence instrument. Sample analysis was conducted in batches with calibration standards and quality controls in which batch acceptance criteria were applied. Before the chromatographic analysis was performed, acetonitrile was added to 100 µL aliquots of plasma combined with internal standard (cefotaxime) to precipitate proteins. Following centrifugation, the supernatant was isolated and was washed with dichloromethane to remove acetonitrile and lipophilic components. Following centrifugation, the upper layer was isolated for chromatographic analysis.

For the chromatography, the stationary phase was a Waters XBridge C18 2.1 × 50 mm column. The mobile phase was 4% acetonitrile/96% 50 mM phosphate buffer at pH 2.5 delivered isocratically. The eluent was monitored at 304 nm. For sample validation, the calibration curve was linear with a weighting of $1/x^2$ over the range 0.2–100 mg/L. The precision and accuracy at the lower limit of quantification were ≤5.9%. The assay was validated against matrix effects (precision and accuracy within 4% at high and low concentrations). The assay's precision and accuracy was determined both within-day and between-day and was within 6.5% at all three concentrations tested.

2.7. Population pharmacokinetic modelling

Data collected from six Indigenous patients' plasma samples were combined with five critically ill Caucasian patients from a previously published study with a similar study protocol including concentration–time data that were available to us in order that ethnicity of the patient group could be tested regarding whether it significantly influences meropenem pharmacokinetics as a covariate [12]. A two-compartment model was developed with Nonparametric Adaptive Grid (NPAG) algorithm using the Pmetrics software package [13] for R v.3.2.2. Demographic and clinical data [age, ethnicity, sex, weight, CL_{Cr}, Sequential Organ Failure Assessment (SOFA) score, serum albumin, serum creatinine and vasopressor therapy requirement] that may influence meropenem pharmacokinetics were tested for inclusion in the model as covariates. If the covariate inclusion resulted in an improvement in the log likelihood ($P < 0.05$) and/or improved the goodness-of-fit plots, they were included in the model.

2.8. Model diagnostics

Model evaluation was assessed by visual assessment of the goodness of fit of the observed–predicted plots and the coefficient of determination of the linear regression of the observed–predicted values (r^2 close to 1, intercept close to 0) from each run. The predictive performance was assessed on mean prediction error (bias) and the mean biased-adjusted squared prediction error (imprecision) of the population and individual posterior predictions.

2.9. Dosing simulations

The probability of target attainment (PTA) was obtained from Monte Carlo simulation ($n = 1000$) in Pmetrics. This assesses the likelihood of achieving 40%$fT_{>MIC}$ (considering 2% protein binding) over the first 24 h for various dosing regimens and levels of CL_{Cr} for MICs between 0.125 mg/L and 32 mg/L. Results were then used to make dosing recommendations based on the lowest dosing regimen that still achieved 90% PTA.

2.10. Statistical analysis

Continuous data were presented as the median (range) and categorical data were presented as counts (%). Statistical differences were assessed for demographic data and pharmacokinetic parameters between the Indigenous and Caucasian population using Pearson's χ^2 and Mann–Whitney U-tests in R. A P-value of <0.05 was considered statistically significant.

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