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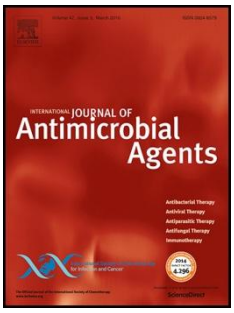

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Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis

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Highlights

- Interethnic differences in meropenem pharmacokinetics are absent.
- Creatinine clearance remains the strongest determinant of meropenem dosing.
- This study needs to be repeated for other antibiotics.

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.

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 2000–2005. 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 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.

3. Results

Six Indigenous and five Caucasian patients were included in the study, providing 216 plasma samples for analysis. The demographics and clinical information are presented in Table 1. In general, the Indigenous group was younger, had a lower CL_{Cr} and had more patients requiring vasopressor therapy, although not statistically significant. They also had significantly higher SOFA scores.

3.1. Population pharmacokinetic model building

A two-compartment model was found to describe the data adequately, with CL_{Cr} and patient's actual body weight being the only tested covariates that significantly improved the PK model. The final model is described as:

$$\mathrm{TVCL} = \mathrm{CL} \times \frac{\mathrm{CLCr}}{100}$$

$$\mathrm{TVVc} = \mathrm{Vc} \times \left(\frac{\mathrm{wt}}{80}\right)^{0.75}$$

where TVCL is the typical value of meropenem clearance in the population (includes Indigenous and non-Indigenous patients), CL is the population parameter estimate of meropenem clearance, TVVc is the

typical value of Vc, Vc is the population parameter estimate of the volume of the central compartment, and wt is total body weight. The goodness of fit for the individual- and population-predicted versus observed plots were acceptable (Fig. 1).

The combined and comparative population PK parameter estimates from the two-compartment model are also presented in Table 1. Clearance was significantly lower for the Indigenous patients compared with the Caucasian patients ($P = 0.004$). However, this difference in clearance was well described by CL_{Cr} but not by ethnicity, hence ethnicity was not included as a covariate in the final model.

3.2. Dosing simulations

Dosing recommendations for specific CL_{Cr} values against different MICs were performed using the results of PTA for various regimens (different doses, dosing intervals, and intermittent and continuous infusions) and are presented in Table 2. Continuous infusion of the same daily dose achieved higher PTA compared with 30-min infusion regimens, whereas an increase in CL_{Cr} resulted in a decline in PTA.

4. Discussion

To our knowledge, this is the first study to investigate the population pharmacokinetics of meropenem in Australian Indigenous patients with severe sepsis. These results suggest that meropenem pharmacokinetics were not significantly different in Australian Indigenous patients relative to Caucasian comparators.

The principal difference between the two groups related to drug clearance, which was adequately described by patient renal function defined as CL_{Cr}. This demonstrates that renal function remains the most important determinant of meropenem pharmacokinetics, and dosing regimens should be guided in accordance with the patient's CL_{Cr}. Although the median CL_{Cr} between the two groups was not significantly different, two of the Indigenous patients had a CL_{Cr} of 15–20 mL/min, which may have contributed to the significant difference in meropenem clearance observed between the two groups. The estimated meropenem clearance (median 11.0 L/h) in the Indigenous patients was also similar to results from previous studies in septic and critically ill patients with comparable CL_{Cr} (meropenem clearance 7.8–11.5 L/h [14–16]). Of note, the Indigenous group in the current study was 10–30 years younger compared with patients in the previous studies [14–16], although the level of renal function was similar. This observation supports previous data reporting the significantly higher prevalence of chronic kidney diseases and poorer renal function in the Australian Indigenous population compared with age-matched Caucasians [17].

The absence of interethnic differences in meropenem pharmacokinetics in this study aligns with previous observations demonstrating that interethnic PK differences are unlikely in antibiotics that are predominantly eliminated via glomerular filtration [8].

Importantly, in this study we have found a large interindividual variability in meropenem pharmacokinetics in the studied patients. Significant fluctuations in drug clearance and V_d are common in critically ill patients [18] and have been reported in other studies investigating meropenem pharmacokinetics [14,16]. These studies generally conclude that this profound variability in pharmacokinetics increases the likelihood of subtherapeutic concentrations or drug accumulation and associated toxicities.

The dosing simulations aiming for the 40%$fT_{>MIC}$ target revealed that a regimen of 500 mg twice daily gives an acceptable PTA for pathogens with an MIC of 2 mg/L (clinical breakpoint for most non-resistant Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Haemophilus influenzae* and *Moraxella catarrhalis*) in patients with CL_{Cr} of 21–50 mL/min. However, 1 g three times daily is needed in patients with CL_{Cr} of 100 mL/min; 1 g four times daily is likely required in a patient with CL_{Cr} of 130 mL/min.

Continuous infusion, however, consistently achieved better PK/PD target attainment, as has been shown in previous studies [19]. As expected, with increasing CL_{Cr}, higher daily doses or use of continuous infusion is required to achieve PK/PD targets. We would note that a standard dose of 1 g three times daily would be insufficient for patients with CL_{Cr} > 100 mL/min for pathogens with a MIC of ≥2 mg/L.

This study has some limitations. Specifically, the small sample size limited the power to detect other potential covariates affecting meropenem pharmacokinetics and also to determine whether failure to achieve PK/PD targets was associated with an altered clinical outcome. Second, samples were collected on two dosing intervals and so may not have been able to describe all of the perturbations in pharmacokinetics that occurred over the duration of treatment. Finally, samples were not collected from the site of infection (e.g. epithelial lining fluid in pneumonia) and therefore the dosing recommendations relate to achievement of target exposures in blood only.

5. Conclusions

This study has highlighted that CL_{Cr} remains the strongest determinant of meropenem pharmacokinetics in patients with severe sepsis. Although no interethnic differences in meropenem pharmacokinetics between Indigenous and Caucasian Australians were demonstrated in this study, this may be, at least in part, due to the low number of patients recruited and high interindividual PK variability.

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Competing interests: None declared.

Ethical approval: Ethical approval was obtained from local (Central Australian Human Research Ethics Committee, approval code HREC-13-149) and university (The University of Queensland Human Research Ethics Committee, approval code 2013000904) ethics committees.

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Fig. 1. Diagnostic plots for the final covariate model. Observed versus population-predicted concentrations (left) and individual-predicted concentrations (right) in plasma. Data are presented in mg/L.

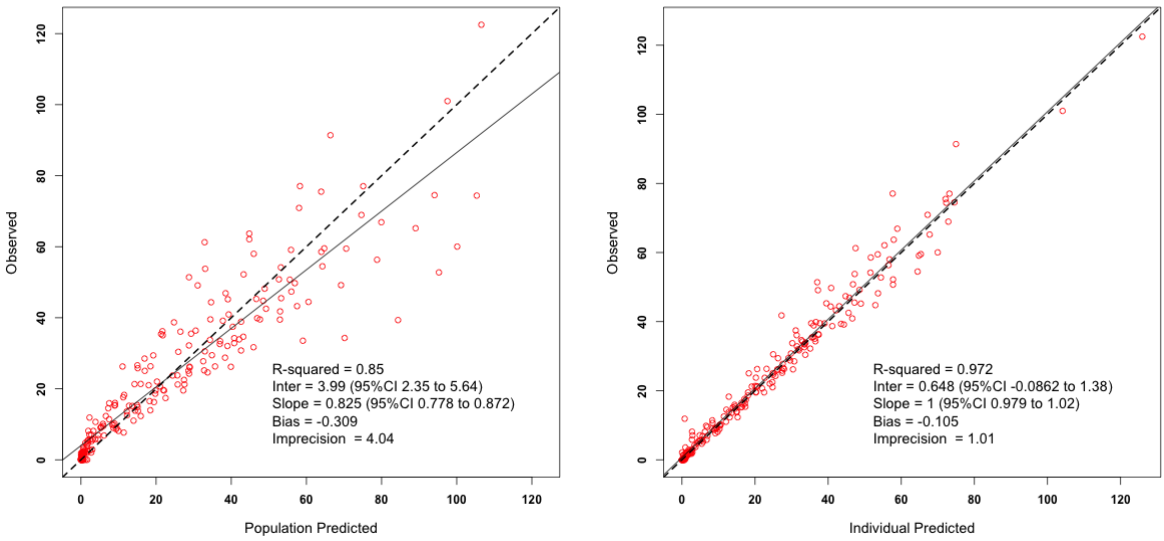

Table 1

Demographics, clinical data and pharmacokinetic parameter estimates from two-compartment model [a]

	Total (*n* = 11)	Indigenous (*n* = 6)	Caucasian (*n* = 5)	*P*-value [b]
Age (years)	48 (22–76)	45 (22–76)	55 (29–69)	0.329
Female sex	6 (55)	4 (67)	2 (40)	0.782 [c]
Weight (kg)	80 (60–110)	73 (60–104)	80.0 (60–110)	0.519
Height (cm)	170 (157–185)	167.5 (157–176)	170 (165–185)	0.231
BMI (kg/m^2)	26.6 (23.7–34.1)	26.4 (23.7–34.1)	26.6 (20.8–30.3)	1.000
SCr (μmol/L)	73 (37–301)	76 (37–301)	73 (43–109)	1.000
CL_{Cr} (mL/min)	105.7 (15.5–164.0)	98.2 (15.5–164.0)	105.7 (19.6–144.3)	0.662
Albumin (g/L)	32 (20–39)	32 (26–39)	28 (18–37)	0.782
Vasopressors	8 (73)	6 (100)	2 (40)	0.122 [c]
SOFA score	10 (2–15)	11 (10–15)	3 (2–11)	**0.007** [d]
Vc (L)	13.6 (9.7–18.4)	11.0 (9.8–17.0)	15.3 (9.7–18.4)	0.082
CL (L/h)	14.1 (3.0–30.3)	11.0 (3.0–14.1)	17.4 (4.3–30.3)	**0.004** [d]
K_{cp} (h^{-1})	1.49 (0.57–5.32)	1.25 (0.57–1.73)	1.91 (0.69–5.32)	0.247
K_{pc} (h^{-1})	2.38 (0.77–16.6)	1.41 (1.07–2.37)	5.89 (0.77–16.6)	**0.017** [d]

BMI, body mass index; SCr, serum creatinine; CL_{Cr}, creatinine clearance; SOFA, Sequential Organ Failure Assessment; Vc, central volume of distribution; CL, meropenem clearance; K_{cp}, distribution rate constant from central to peripheral compartment; K_{pc}, distribution rate constant from peripheral to central compartment.

[a] Data are presented as the median (range) or *n* (%).

[b] The *P*-value was obtained by Mann–Whitney *U*-test unless otherwise specified.

[c] The *P*-value was obtained by Pearson's χ^2 test.

[d] Figures in bold are statistically significant ($P < 0.05$).

Table 2

Dose recommendations for critically ill patients

CL_{Cr} (mL/min)	MIC ≤ 0.25 mg/L	MIC = 2 mg/L
≤20	0.5 g q24h	0.5 g q24h
21–50	0.5 g q12h	0.5 g q12h
51–100	0.5 g q8h	1 g q8h
101–130	1 g q8h	1 g q6h or 3 g CI
131–170	1 g q8h	1 g q6h or 3 g CI

CL_{Cr}, creatinine clearance; MIC, minimum inhibitory concentration; q24h, every 24 h; q12h, every 12 h; q8h, every 8 h; q6h, every 6 h; CI, continuous infusion.