O253
1-hour Oral Session
PK/PD-based optimized broad-spectrum beta-lactam therapy

Optimizing meropenem dosing in severely septic Australian indigenous patients

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Background: Severe sepsis is a common condition seen in Australian Indigenous patients and often requires admission to an intensive care unit (ICU). The associated mortality rate is high. Meropenem is commonly used in the clinical scenario. Unfortunately, there are no pharmacokinetic data to guide dosing in this population which is problematic given that young and healthy Australian Indigenous adults are reported to have 30% less nephrons compared with the non-Indigenous comparators. This study aims to describe the pharmacokinetics of meropenem in severely septic Australian Indigenous patients.

Material/methods: An observational prospective pharmacokinetic study was conducted in the ICU of a remote teaching hospital. Ethics approval was obtained and included patients provided written informed consent. The inclusion criteria were Australian Indigenous patients ≥18 years of age, no end stage renal failure, severe sepsis and clinical indication for meropenem. Series of plasma urine samples were collected over two dosing intervals and assayed by validated chromatography. Concentration-time data were combined with data from a previous study which included critically ill Caucasian patients. Population pharmacokinetic modelling was performed with Pmetrics® (version 1.4.1). Statistical tests were performed using R® (version 3.2.2). Various demographic, clinical and physiological data were also collected.

Results: Six Indigenous subjects were recruited and data from 5 critically ill Caucasian subjects were extracted from a published study. The combined mean (SD) of age, weight, sequential organ failure assessment (SOFA) score and creatinine clearance (CrCL) were 48.2 (16.3) years, 78.7 (15.6) kg, 7.9 (4.3) and 97.6 (44.2) mL/min respectively (Table 1). A two compartment model was found to describe the data adequately with SOFA scores describing volume of distribution of the central compartment (Vc) and CrCL describing meropenem clearance. Clearance and Vc of the Indigenous and Caucasian groups are 9.6 (0.44) vs 20.3 (5.8) L/h, $p< 0.01$, and 12.0 (2.7) vs 15.3 (2.9) L, $p=0.08$, respectively (Table 1). The rate constant from central to peripheral compartment (Kcp) and from the central to

peripheral compartment (Kpc) for the Indigenous and Caucasian groups were 1.2 (0.4) vs 2.6 (1.7), *p*=0.25, and 1.6 (0.6) vs 6.9 (5.2), *p*=0.02, respectively (Table 1).

Conclusions: In this study, the Indigenous group had a mean 50% lower drug clearance and a slightly greater Vc when compared with the Caucasian group, with these findings best described by the greater disease severity (SOFA) score and a lower CrCL.

Table 1. Patient demographics, clinical data and pharmacokinetic parameters*

	Total (n=11)	Indigenous (n=6)	Caucasian (n=5)	*p* value#
Age (y)	48.2 ± 16.3	44.7 ± 17.5	52.4 ± 13.6	0.329
Weight (kg)	78.7 ± 15.6	76.0 ± 14.5	82.0 ± 16.3	0.519
CrCL (mL/min)	97.6 ± 44.2	86.1 ± 53.7	111.4 ± 22.0	0.662
SOFA score	7.9 ± 4.3	11.7 ± 1.6	3.4 ±1.0	***0.007***
Vc (L)	13.5 ± 3.2	12.0 ± 2.7	15.3 ± 2.9	0.082
CL (L/h)	14.5 ± 7.4	9.6 ± 4.4	20.3 ± 5.8	***0.004***
Kcp	1.9 ± 1.4	1.2 ± 0.4	2.6 ± 1.7	0.247
Kpc	4.0 ± 4.4	1.6 ± 0.6	6.9 ± 5.2	***0.017***

Abbreviation: CrCL, creatinine clearance; SOFA, sequential organ failure assessment; Vc, volume of distribution of the central compartment; CL, clearance; Kcp, rate constant from central to peripheral compartment; Kpc, rate constant from peripheral to central compartment.

**Data is presented in mean ± standard deviation.*

#*p value is obtained from Mann-Whitney U test.*