

# What is the effect of obesity on the population pharmacokinetics of meropenem in critically ill patients?

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**Objectives:** Severe pathophysiological changes in critical illness can lead to dramatically altered antimicrobial pharmacokinetics (PK). The additional effect of obesity on PK potentially increases the challenge for effective dosing. The aim of this prospective study was to describe the population PK of meropenem in a cohort of critically ill patients including obese and morbidly obese patients.

**Methods:** Critically ill patients prescribed meropenem were recruited into three body mass index (BMI) groups, 18.5-29.9; 30.0-39.9; and  $\geq 40$  kg/m<sup>2</sup>. Serial plasma samples were taken and meropenem concentrations were determined using a validated chromatographic method. Population PK analysis and Monte Carlo dosing simulations were undertaken with Pmetrics®.

**Results:** Nineteen critically ill patients with different BMI categories were enrolled. The patient's mean  $\pm$  SD age, weight and BMI were 49  $\pm$  15.9 years, 95  $\pm$  22.0 kg and 33  $\pm$  7.0 kg/m<sup>2</sup>, respectively.

A two compartment model described the data adequately. The mean  $\pm$  SD parameter estimates for the final covariate model were clearance (CL) 15.5  $\pm$  6.0 L/h, volume of distribution of the central compartment (V<sub>c</sub>) 11.7  $\pm$  5.8 L, intercompartmental clearance from central to peripheral compartments 25.6  $\pm$  35.1 L\*h<sup>-1</sup> and intercompartmental clearance from peripheral to central compartment 8.3  $\pm$  12.2 L\*h<sup>-1</sup>. Higher CL<sub>CR</sub> was associated with a lower probability of target attainment with BMI having little effect.

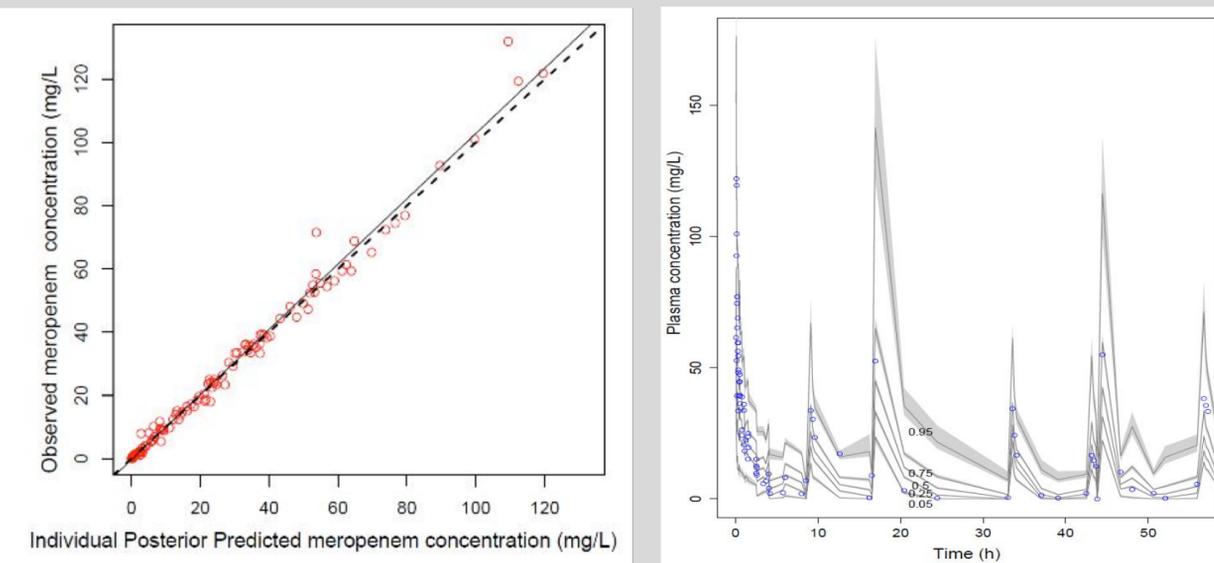


Figure 1: Diagnostic plots for the final population pharmacokinetic covariate model. Left panel, Observed meropenem concentrations versus individual predicted meropenem concentration ( $r^2 = 0.987$ ); Right panel, Visual predictive check.

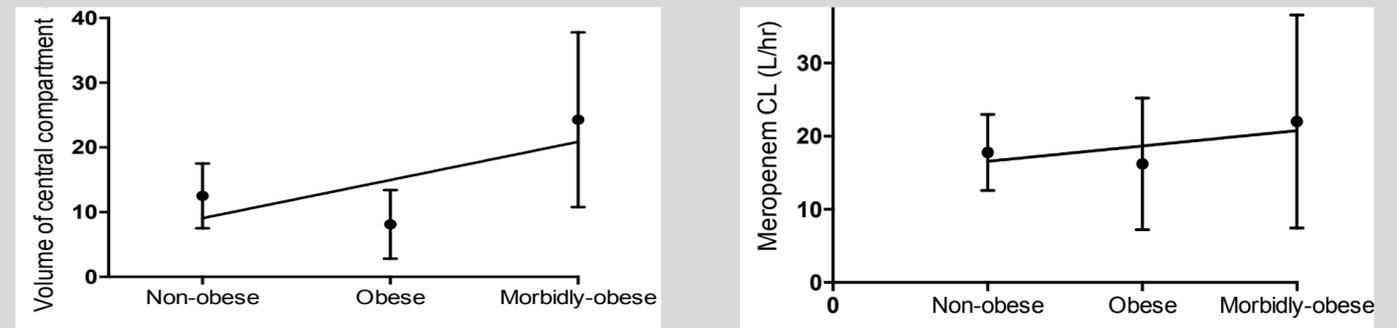


Figure 2. Left panel: Relationship of volume of distribution of the central compartment (V<sub>c</sub>) to the mean (SD) body weight of the pre-specified body mass index (BMI) categorisations (non-obese, obese and morbidly-obese; linear regression  $r^2$  0.4961). Right panel: Relationship of meropenem clearance to the mean (SD) body weight of the BMI categorisations (linear regression  $r^2$  0.4915)

	Minimum Inhibitory Concentration*											
	1 mg/L			2 mg/L			4 mg/L			8 mg/L		
	Non-Ob	Ob	M-Ob	Non-Ob	Ob	M-Ob	Non-Ob	Ob	M-Ob	Non-Ob	Ob	M-Ob
<b>500 mg dosing intermittent infusion q 8h</b>												
CL <sub>CR</sub> 30 to 50 mL/min	+	+	+	+	+	+	+	+	+	-	-	-
CL <sub>CR</sub> $\geq$ 150 mL/min	-	-	-	-	-	-	-	-	-	-	-	-
<b>500 mg dosing prolonged infusion q 8h</b>												
CL <sub>CR</sub> 30 to 50 mL/min	+	+	+	+	+	+	+	+	+	-	-	-
CL <sub>CR</sub> $\geq$ 150 mL/min	+	+	+	+	+	+	-	-	-	-	-	-
<b>1000 mg dosing intermittent infusion q 8h</b>												
CL <sub>CR</sub> 30 to 50 mL/min	+	+	+	+	+	+	+	+	+	+	+	+
CL <sub>CR</sub> $\geq$ 150 mL/min	-	-	+	-	-	-	-	-	-	-	-	-
<b>1000 mg dosing prolonged infusion q 8h</b>												
CL <sub>CR</sub> 30 to 50 mL/min	+	+	+	+	+	+	+	+	+	+	+	+
CL <sub>CR</sub> $\geq$ 150 mL/min	+	+	+	+	+	+	+	+	+	-	-	-
<b>2000 mg dosing intermittent infusion q 8h</b>												
CL <sub>CR</sub> 30 to 50 mL/min	+	+	+	+	+	+	+	+	+	+	+	+
CL <sub>CR</sub> $\geq$ 150 mL/min	-	+	+	-	-	+	-	-	-	-	-	-
<b>2000 mg dosing prolonged infusion q 8h</b>												
CL <sub>CR</sub> 30 to 50 mL/min	+	+	+	+	+	+	+	+	+	+	+	+
CL <sub>CR</sub> $\geq$ 150 mL/min	+	+	+	+	+	+	+	+	+	+	+	+

(+), PK/PD target achieved; (-), PK/PD target not-achieved; CL<sub>CR</sub>, creatinine clearance of mild-to-moderate renal impairment (30-50 mL/min) and normal or augmented renal function (CL<sub>CR</sub>  $\geq$  150 mL/min); Non-ob, non obese (BMI = 18.5-29.9 kg/m<sup>2</sup>); Ob, obese (BMI = 30-39.9 kg/m<sup>2</sup>); M-Ob, morbidly obese (BMI  $\geq$  40 kg/m<sup>2</sup>); q 8h, three times daily dosing.  
\* Meropenem target MIC was used according to EUCAST break-points (2 mg/L)

Table 1. Meropenem probability of target attainment for intermittent and prolonged infusion at different renal function and dosing regimens.

**Conclusions:** Although obesity was found to be associated with an increased V<sub>c</sub>, dose adjustment based on CL<sub>CR</sub> appears more important than patient BMI.