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

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Background: In critically ill patients where severe pathophysiological changes can lead to dramatically altered pharmacokinetics, the added effect of obesity on drug disposition creates significant uncertainty for prescribers. The objective of this study is to describe the population pharmacokinetics of meropenem in a cohort of critically ill patients including obese patients.

Material/methods: This was a pharmacokinetic study at a tertiary referral hospital. Critically ill patients with a clinical indication for meropenem were eligible for inclusion. We aimed to recruit at least 6 patients in three body mass index (BMI) categories, (1) normal weight (18.0-29.9 kg/m^2), (2) obese (30.0-39.9 kg/m^2) and (3) morbidly-obese ($\geq$40.0 kg/m^2). We collected serial plasma samples and measured meropenem concentrations using a validated chromatographic method. A population pharmacokinetics analysis was undertaken with Pmetrics®.

Results: One hundred and fourteen plasma concentrations were collected from 19 critically ill patients (11 male and 8 female) with six normal, seven obese and six morbidly obese patients. The mean ± SD age, weight, height and BMI of the subjects were 49.4 ± 15.9, 95 ± 22.0, 170.8 ± 12.2 and 32.7 ± 7.4 respectively. A two compartment linear model with zero order input with drug clearance described by calculated creatinine clearance and volume of distribution of the central compartment (Vc) described by total body weight normalised to 80kg. The mean ± SD parameter population pharmacokinetic estimates were clearance (CL) (all subjects 16.7 ± 6.5 L/h; normal weight 18.0 ± 7.4 L/h; obese 16.1 ± 7.9 L/h; morbidly obese 16.0 ± 4.4 L/h), Vc (all subjects 25.5 ± 8.9 L; normal weight 24.8 ± 12.8 L; obese 22.6 ± 6.9 L; morbidly obese 29.7 ± 5.4 L), inter-compartmental clearance constants from central to peripheral (Kcp) (all subjects 2.6 ± 3.2 L/h; normal weight 2.1 ± 3.1 L/h; obese = 3.0 ± 2.8 L/h; morbidly obese 2.6 ± 4.1 L/h) and peripheral to central compartments (Kpc) (all subjects 17.3 ± 11.0 L/h; normal weight 19.8 ± 11.7 L/h; obese 16.5 ± 11.6 L/h; morbidly obese 15.7 ± 11.3 L/h).

Conclusions: Morbid obesity was associated with a higher meropenem Vc in critically ill patients. Changes in clearance between different BMI categories were associated with changes in calculated creatinine clearance. We recommend therapeutic drug monitoring of meropenem to optimise dosing in order to ensure therapeutic antibiotic exposures in these challenging patients.