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Pharmacokinetics of meropenem in critically ill patients receiving continuous venovenous haemofiltration: A randomised controlled trial of continuous infusion versus intermittent bolus administration

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ABSTRACT

The objective of this study was to describe the pharmacokinetics of meropenem, administered by continuous infusion (CI) or intermittent bolus (IB), in critically ill patients receiving continuous venovenous haemofiltration (CVVH) and to evaluate the frequency of pharmacokinetic/pharmacodynamic target attainment with each dosing strategy. This was a prospective, randomised controlled trial in critically ill patients receiving CVVH and administered meropenem by CI or IB. Serial meropenem concentrations in plasma and ultrafiltrate were measured after administration of a standard total daily dose (4 g/day on Day 1, followed by 3 g/day thereafter) on two occasions during antibiotic therapy. Meropenem pharmacokinetic parameters were calculated using a non-compartmental approach. Sixteen critically ill patients receiving CVVH concurrently treated with meropenem were randomised to CI ($n = 8$) or IB dosing ($n = 8$). IB administration resulted in higher maximum concentrations (C_{max}) [64.7 (58.9–80.3) and 64.8 (48.5–81.8) mg/L, respectively] on both sampling occasions compared with CI ($P < 0.01$ and $P = 0.04$, respectively). CI resulted in a higher meropenem steady-state concentration (C_{ss}) on occasion 1 [26.0 (24.5–41.6) mg/L] compared with the minimum concentration (C_{min}) observed for IB patients [17.0 (15.7–19.8) mg/L; $P < 0.01$]. CVVH contributed to ca. 50% of meropenem total clearance in these patients. The administered meropenem doses resulted in plasma drug concentrations that were >4× the targeted susceptibility breakpoint (2 mg/L) for 100% of the dosing interval, for both groups, on both occasions. CI could be an alternative to IB for meropenem administration in critically ill patients receiving CVVH.

1. Introduction

Effective antibiotic dosing is considered one of the key interventions to reduce mortality in critically ill patients with severe sepsis or septic shock [1]. Administration by continuous infusion (CI) is one of the approaches advocated to improve β-lactam drug exposure in critical illness [2–8], particularly in an era of emerging bacterial resistance and limited availability of new antibiotics. Multiple studies have evaluated this method of β-lactam administration in various critically ill subgroups, demonstrating that CI achieves the required drug concentrations more consistently than conventional intermittent bolus (IB) dosing [6–10].

Existing literature on β-lactam CI generally excludes critically ill patients treated with renal replacement therapy (RRT), a group for which additional data are urgently required as substantial amounts of drug may be cleared by this extracorporeal technique [11]. Indeed, previous data have shown that standard carbapenem dosing regimens were insufficient for critically ill patients receiving RRT [12]. As such, CI may offer a more effective dosing option, increasing the likelihood of achieving therapeutic concentrations in this patient group.

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The objectives of this study were therefore to describe the pharmacokinetics of meropenem administered by CI or IB to critically ill patients receiving continuous venovenous haemofiltration (CVVH). We also aimed to describe the frequency of pharmacokinetic/pharmacodynamic (PK/PD) target attainment of meropenem with each method of administration.

2. Patients and methods

This was a prospective, randomised controlled pharmacokinetic study performed in a 12-bed intensive care unit (ICU) of a major tertiary hospital in Malaysia (Kuantan, Pahang, Malaysia). The study was approved by the local ethics committee, and consent to participate was obtained from the patient's legally authorised representative.

2.1. Patient selection and data collection

All adult patients (age ≥18 years) admitted to the ICU with severe sepsis or septic shock and receiving CVVH for oligouric or anuric renal impairment were eligible for enrolment. Meropenem was prescribed at the discretion of the treating physician. Patients were randomised to receive the same dose of meropenem, administered by either CI or IB, using random allocations selected from sequentially numbered opaque sealed envelopes.

2.2. Meropenem administration

All patients received meropenem (DBL™ Meropenem for Injection; Hospira Healthcare, Chennai, India). Patients in the CI group ($n = 8$) were administered a loading dose of 1 g of meropenem in 20 mL of 0.9% sodium chloride over 30 min via a central line, followed immediately by CI over 24 h (125 mg/h). Owing to stability issues, meropenem was prepared every 8 h by diluting 1 g of meropenem in 100 mL of 0.9% sodium chloride. Patients in the IB group ($n = 8$) received 2 g of meropenem as a 30-min infusion via a central line for the first dose, followed by 1 g every 8 h thereafter. In both groups, meropenem was administered using a volumetric infusion pump controller, and all patients received a total dose of meropenem of 4 g/day on Day 1 and 3 g/day thereafter.

2.3. Continuous renal replacement therapy

CVVH was performed in all patients using an Aquarius™ system (Edwards Lifesciences, Saint-Prex, Switzerland). Polysulfone®-type haemofilters with a surface area of 1.2 m^2 (Aquamax12™; Baxter Healthcare, Zurich, Switzerland) were used. In all patients, CVVH was started at least 4 h prior to the sampling period. Vascular access was obtained via the internal jugular or femoral vein using a 14-French double-lumen catheter. The ultrafiltrate rate was set at 2000 mL/h [median effluent flow rate, 30.09 mL/kg/h; interquartile range (IQR), 25.00–33.33 mL/kg/h], combining pre- and post-dilution fluid replacement at a 1:1 ratio. The targeted blood flow rate was 200 mL/min. Net fluid removal was between 50 mL/h and 100 mL/h depending on the clinical circumstance. Lactate-containing (PrismaSol®; Gambro, Sondalo, Italy) or lactate-free (Duosol™; B. Braun, Glandorf, Germany) solutions were used as the replacement solution, and the circuit was anticoagulated with heparin (100 U/mL) at the discretion of the attending physician.

2.4. Sample collection

Pharmacokinetic sampling occurred during one 8-h or 24-h dosing interval between Days 1–3 of treatment (occasion 1), and during an 8-h dosing interval between Days 4–6 of treatment (occasion 2). For each sample, 3 mL of blood was collected in a lithium heparin tube, pre-filter, at 0, 15, 30, 45, 60, 120, 240, 480 and 1440 min (CI only) and post-filter at 30, 120 and 480 min on occasion 1. For occasion 2, 3 mL of blood was collected in a lithium heparin tube, pre-filter or at arterial line, at 0, 15, 30, 45, 60, 120, 240, 480 and post-filter at 480 min. Ultrafiltrate samples were collected and measured at 120, 240, 360 and 480 min, and 3 mL aliquots were kept for analysis. All samples were immediately centrifuged at 3000 rpm for 10 min and plasma was separated and frozen at −80 °C.

2.5. Meropenem assay

Meropenem concentrations in plasma and ultrafiltrate were determined by validated assay methods on a Shimadzu Prominence (Shimadzu Corp., Kyoto, Japan) high-pressure liquid chromatography (HPLC) system at the Burns, Trauma and Critical Care Research Centre of The University of Queensland (Brisbane, Australia). The assay was conducted alongside a standard curve and quality control replicates at high, medium and low concentrations. The limit of quantification for meropenem was 0.2 mg/L and linearity was validated from 0.2 mg/L to 100 mg/L (plasma) and from 1 mg/L to 200 mg/L (ultrafiltrate). All results were within 5% for all matrices at all levels, and the assay was validated and conducted according to criteria specified by the US Food and Drug Administration (FDA) guidance on bioanalysis [13].

2.6. Pharmacokinetic analysis

Pharmacokinetic parameter values were estimated using non-compartmental methods. The area under the concentration–time curve from 0 to 8 h in plasma ($AUC_{0-8\ plasma}$) or ultrafiltrate ($AUC_{0-8\ ultrafiltrate}$) was calculated using the linear trapezoidal rule. Total body clearance (CL_{total}) was calculated as dose/$AUC_{0-8\ plasma}$. The maximum concentration for the dosing period (C_{max}) and the minimum concentration for the dosing period (C_{min}) were the observed values. The apparent terminal elimination rate constant (k_e) was determined from log-linear least-squares regression analysis of concentrations from 2 to 8 h (bolus dosing). The apparent volume of distribution during the terminal phase (V_d) was calculated as CL_{total}/k_e, and the half-life ($t_{1/2}$) was calculated as $\ln(2)/k_e$ (bolus dosing). The extraction ratio (ER) across the filter was calculated as the ratio of the meropenem post-filter blood sample concentration to the pre-filter blood sample concentration. The sieving coefficient (S_c) was calculated as the ratio of the concentration of meropenem in the ultrafiltrate to the concentration in the pre-filter blood. Clearance by CVVH (CL_{CVVH}) was calculated using the equation $CL_{CVVH} = A_{CVVH}/AUC_{0-8\ ultrafiltrate}$ (where A_{CVVH} is the total amount of meropenem recovered in the ultrafiltrate in one dosing interval). Clearance not mediated by CVVH ($CL_{non\text{-}CVVH}$) was calculated using the equation $CL_{non\text{-}CVVH} = CL_{total} - CL_{CVVH}$.

2.7. Pharmacodynamic analysis

A susceptibility breakpoint of 2 mg/L for meropenem against common pathogens, based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2013 database [14] was used to determine the frequency of PK/PD target attainment. Based on previous publications [15,16], for IB administration a plasma drug concentration ≥4× the minimum inhibitory concentration (MIC) for more than 40% of the dosing interval (40% $T_{>4\times MIC}$) was considered as a suitable PK/PD target, whereas for CI administration a plasma concentration 5× the MIC breakpoint over the entire dosing interval (100% $T_{>5\times MIC}$) was required.