Alterations in transmembrane pressures during continuous venovenous haemofiltration significantly contribute to the pharmacokinetic variability of meropenem

pronounced permeabilizing effect of tobramycin in combination with imipenem leading to extensive outer membrane disruption, higher periplasmic imipenem concentrations and rapid up-regulation of inducible AmpC β-lactamase in *P. aeruginosa*.[8]

While ceftolozane/tazobactam has shown much higher stability against AmpC hydrolysis and slower development of resistance compared with other antibacterials, including carbapenems,[1,9] our case adds to the few documented clinical cases of the development of ceftolozane/tazobactam resistance upon exposure to ceftolozane/tazobactam.[1,10] The high level of resistance observed in our isolate is likely driven by multiple mutations in the AmpC region causing structural changes, along with AmpD-associated derepression of AmpC. While the development of high-level resistance to ceftolozane/tazobactam after exposure is worrisome, our severely neutropenic patient rapidly cleared bacteraemia on a combination of a pharmacodynamically driven dose of ceftolozane/tazobactam[7] and tobramycin with resultant synergy. It emphasizes the importance of strategic dosing and the potential benefit of combination therapy when combating refractory cases of MDR *P. aeruginosa* infection.

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Transparency declarations

None to declare.

References

1 Fraile-Ribot PA, Cabot G, Mulet X *et al*. Mechanisms leading to *in vivo* ceftolozane/tazobactam resistance development during the treatment of infections caused by MDR *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 2018; **73**: 658–63.

2 Cabot G, Bruchmann S, Mulet X *et al*. *Pseudomonas aeruginosa* ceftolozane-tazobactam resistance development requires multiple mutations leading to overexpression and structural modification of AmpC. *Antimicrob Agents Chemother* 2014; **58**: 3091–9.

3 Rodriguez-Martinez JM, Poirel L, Nordmann P. Extended-spectrum cephalosporinases in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2009; **53**: 1766–71.

4 Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. *Clin Microbiol Rev* 2009; **22**: 582–610.

5 Fodor E, Hajdú E, Nagy E. Use of Etest to assess synergy of antibiotic combinations against clinical isolates of *Pseudomonas* spp. *Int J Antimicrob Agents* 2005; **25**: 183–4.

6 Ang JY, Abdel-Haq N, Zhu F *et al*. Multidrug-resistant *Pseudomonas aeruginosa* infection in a child with cystic fibrosis. *Antimicrob Agents Chemother* 2016; **60**: 5627–30.

7 Rico-Caballero V, Almarzoky Abuhussain S, Kuti JL *et al*. Efficacy of human-simulated exposures of ceftolozane/tazobactam alone and in combination with amikacin or colistin against multidrug-resistant *Pseudomonas aeruginosa* in an *in vitro* pharmacodynamic model. *Antimicrob Agents Chemother* 2018; **62**: e02384-17.

8 Yadav R, Bulitta JB, Schneider EK *et al*. Aminoglycoside concentrations required for synergy with carbapenems against *Pseudomonas aeruginosa* determined via mechanistic studies and modeling. *Antimicrob Agents Chemother* 2017; **61**: e00722-17.

9 Van Duin D, Bonomo RA. Ceftazidime/avibactam and ceftolozane/tazobactam: second-generation β-lactam/β-lactamase inhibitor combinations. *Clin Infect Dis* 2016; **63**: 234–41.

10 Haidar G, Philips NJ, Shields RK *et al*. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: clinical effectiveness and evolution or resistance. *Clin Infect Dis* 2017; **65**: 110–20.

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Alterations in transmembrane pressures during continuous venovenous haemofiltration significantly contribute to the pharmacokinetic variability of meropenem: a case series of three patients

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Sir,

Meropenem is a broad-spectrum carbapenem β-lactam antibiotic that is removed via continuous venovenous haemofiltration

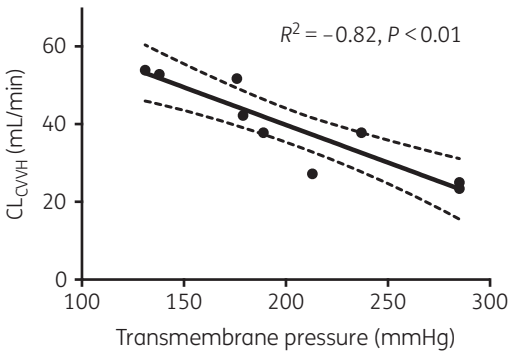

Figure 1. Transmembrane pressure versus extracorporeal clearance of meropenem by the AN69ST haemofilter at nine different timepoints in three critically ill patients (patients A, B and C). The broken lines represent the 95% CI for the regression coefficient of the extracorporeal clearance. An inverse relationship was observed between transmembrane pressure and CL_{CVVH}. The regression coefficient was −0.82 (95% CI = −0.98 to −0.61) and $P < 0.01$. $y = -0.19x + 78.5$.

(CVVH).[1] A low molecular weight (437.5 Da), low protein-bound fraction (<2%) and volume of distribution (V) <0.3 L/kg are associated with significant CVVH clearance.[1,2] The likelihood of meropenem crossing the haemofilter membrane is expressed by the sieving coefficient (SC) and is defined as the ratio of meropenem concentration in the ultrafiltrate to the pre-filter plasma concentration.[2,3] SC values between 0.63 and 1.17 have been reported.[4–6] A critical parameter that governs SC is the transmembrane pressure that may vary with operation conditions.[7] However, meropenem doses during CVVH do not consider differences in pharmacokinetic (PK) variability owing to changes in transmembrane pressure and meropenem sieving.[2] This study assessed the relationship between transmembrane pressure changes and extracorporeal removal of meropenem during CVVH.

ICU patients with a clinical diagnosis of acute kidney injury (KDIGO stage 3) requiring CVVH were eligible for inclusion. Meropenem was administered via continuous intravenous infusion (CII).[8] Patient A received 2000 mg/day meropenem via CII after an intravenous loading dose of 1000 mg. Patients B and C were treated with 3000 mg/day meropenem via CII after a loading dose of 1000 mg.[1,4,9] Renal replacement via CVVH was performed.[3] CVVH (PRISMAFLEX system, Gambro®) was conducted using the AN69ST haemofilter with a surface area of 1 m^2. A regional citrate anticoagulation CVVH protocol using an 18 mM citrate solution (Prismocitrate®) with a phosphate-containing replacement fluid (Phoxilium®) was used to prevent circuit and filter clotting.[3] The blood flow and net ultrafiltrate rates were set at 180 and 0 mL/min, respectively. Prismocitrate® 18/0 at 1440 mL/h pre-filter and Phoxilium® at 1600 mL/h were infused at pre-filter and post-filter dilutions, respectively, with an effluent flow rate of 3040 mL/h. CVVH settings were constant throughout the CVVH sessions.

To determine the steady-state PK of meropenem, plasma, pre-filter, post-filter, ultrafiltrate and urine samples were collected at three different timepoints over 24 h and stored at −80°C until batch-wise analysis. Meropenem was measured using validated UPLC–tandem MS. PK parameters included steady-state plasma concentration (C_{ss}), total body clearance (CL_{TOTAL}), clearance by CVVH (CL_{CVVH}), V, residual renal clearance and elimination rate constant (k_{el}).[3] The PK parameters were calculated and modulated using the Mw/Pharm® 3.81 software. A one-compartment model was applied using currently collected data. Operational characteristics of CVVH and transmembrane pressure as measures of convection were monitored and the ultrafiltrate pump rate (UFR; mL/kg/h) and filtration fraction (FF; %) were calculated. Finally, meropenem CL_{CVVH} was plotted against transmembrane pressure (Figure 1).

Three male patients (A, B and C) fulfilled the inclusion criteria. All patients were diagnosed with septic shock due to intra-abdominal infection and required mechanical ventilation. Informed consent was obtained for publication. The patients' ages ranged between 73 and 87 years. Disease severity, as indicated by an APACHE IV score, was as follows: A, 108; B, 86; and C, 72. The BMIs were: A, 33.2 kg/m^2; B, 29.4 kg/m^2; and C, 29.8 kg/m^2. The average CL_{TOTAL} was 1.49 mL/kg/min (0.84, 2.17 and 1.46). The mean CL_{CVVH} of meropenem was 0.45 mL/kg/min (0.55, 0.31 and 0.50) and accounted for ∼30% of CL_{TOTAL} of meropenem. The mean V was 19.9 L (18.8, 20.2 and 20.8). In patient A, the C_{ss} of meropenem after administering 2000 mg of meropenem via CII was 13.3 mg/L, and in patients B and C, the C_{ss} of meropenem was 9.7 and 18.6 mg/L, respectively, after administering 3000 mg via CII. The k_{el} was 0.26, 0.55 and 0.35 h^{-1}. The residual renal clearance was 0 mL/min. Transmembrane pressure values of patients A, B and C are shown in Figure 1. The UFR and FF were 34, 40 and 38 mL/kg/h and 39%, 38% and 36%, respectively. Filter survival at 72 h was 100% with no obvious signs of filter clotting. We observed an unexpected large variability in SC ranging between 0.45 and 0.96 and documented that transmembrane pressures during CVVH treatment were extremely high and inversely correlated to CL_{CVVH} (Figure 1) ($P < 0.01$).

The increase in transmembrane pressures over time caused by coagulative occlusion and the blocking of pores changed the properties of the filter membrane resulting in a decline in filter efficacy and lower SCs. Therefore, transmembrane pressure is an important determinant of PK variability during extracorporeal meropenem clearance. Administering 2000 and 3000 mg/day of meropenem via CII resulted in sufficient plasma drug concentrations for treating susceptible bacteria (MIC 2 mg/L) using a target plasma concentration of >4× the MIC.[1] Hence, an increase in CVVH transmembrane pressure is an important determinant of PK variability. Despite considerable inter-patient variability in terms of meropenem CL_{CVVH}, the appropriate time above the MIC (100% fT >4× the MIC) can be achieved by administering 2000–3000 mg/24 h via CII. Another issue that emerges from our findings is the risk of neurotoxicity due to higher meropenem levels.[10] Further studies are required to establish this. Real-time prospective therapeutic drug monitoring of meropenem should include transmembrane pressure and real-time SC to correct for the loss of CVVH efficiency or prevent toxic dose regimens.

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References
1 Jamal JA, Mat-Nor MB, Mohamad-Nor FS *et al*. Pharmacokinetics of meropenem in critically ill patients receiving continuous venovenous haemofiltration: a randomised controlled trial of continuous infusion versus intermittent bolus administration. *Int J Antimicrob Agents* 2015; **45**: 41–5.

2 Shaw AR, Mueller BA. Antibiotic dosing in continuous renal replacement therapy. *Adv Chronic Kidney Dis* 2017; **24**: 219–27.

3 Janssen PK, Foudraine NA, Burgers DM *et al*. Population pharmacokinetics of cefuroxime in critically ill patients receiving continuous venovenous hemofiltration with regional citrate anticoagulation and a phosphate-containing replacement fluid. *Ther Drug Monit* 2016; **38**: 699–705.

4 Langgartner J, Vasold A, Glück T *et al*. Pharmacokinetics of meropenem during intermittent and continuous intravenous application in patients treated by continuous renal replacement therapy. *Intensive Care Med* 2008; **34**: 1091–6.

5 Isla A, Maynar J, Sánchez-Izquierdo JA *et al*. Meropenem and continuous renal replacement therapy: in vitro permeability of 2 continuous renal replacement therapy membranes and influence of patient renal function on the pharmacokinetics in critically ill patients. *J Clin Pharmacol* 2005; **45**: 1294–304.

6 Bilgrami I, Roberts JA, Wallis SC *et al*. Meropenem dosing in critically ill patients with sepsis receiving high-volume continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 2010; **54**: 2974–8.

7 Charcosset C, Jaffrin MY, Ding L. Time and pressure dependence of sieving coefficients during membrane plasma fractionation. *ASAIO Trans* 1990; **36**: M594–7.

8 Pea F, Viale P, Cojutti P *et al*. Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe Gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. *Antimicrob Agents Chemother* 2012; **56**: 6343–8.

9 Ulldemolins M, Soy D, Llaurado-Serra M *et al*. Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: influence of residual diuresis on dose requirements. *Antimicrob Agents Chemother* 2015; **59**: 5520–8.

10 Beumier M, Casu GS, Hites M *et al*. Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients. *Minerva Anestesiol* 2015; **81**: 497–506.

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Counting the cost of critical antibiotic shortages

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Sir,

In recent years, medicine shortages in healthcare services have become a common occurrence and pose significant challenges to prescribers and pharmacists. Reasons for medicine shortages are many, including manufacturing issues, product recalls or unavailability of raw materials.[1] Results of a point prevalence survey of medicine shortages in Australian hospitals conducted in April 2017 revealed that 95% of participating hospitals experienced a shortage in the preceding 12 months and the most frequently reported shortages were antimicrobials.[2] The prescribing patterns and economic consequences of these antimicrobial shortages in Australian hospitals are ill-defined. Supplies of piperacillin/tazobactam and gentamicin, two frequently used antibiotics, were interrupted to Australian hospitals in September and October 2017, respectively. We evaluated the impact of these shortages on hospital antibiotic use and associated costs.

A retrospective review comparing the inpatient use (excluding hospital-in-the-home) of alternative antibiotics, 3 months pre-shortage (July–September 2017), 3 months during the shortage (October–December 2017) and 3 months post-shortage (January–March 2018), was undertaken at Austin Health, a tertiary teaching hospital in Victoria. Costs of antibiotics were also analysed before and during the shortage periods. A hospital-wide contingency plan recommended alternatives to piperacillin/tazobactam, mainly intravenous amoxicillin/clavulanate and cefepime, based on clinical indication (Table S1, available as Supplementary data at *JAC* Online). Shortage of gentamicin also occurred; however, this only lasted for 1 week; amikacin was temporarily used as a substitute where indicated, e.g. directed Gram-negative therapy. Aggregate antibiotic use data, expressed as days of therapy (DOT) per 1000