Pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis

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Objectives: To evaluate the pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis (CVVHD) after intravenous administration of unadjusted dosage regimens.

Patients and methods: Two critically ill patients had eight blood samples collected during a 12 h interval on days 8 and 10 of polymyxin B therapy. Dialysate was collected every hour during the 12 h dosing interval. Polymyxin B binding in plasma was determined by rapid equilibrium dialysis. Concentrations of polymyxin B in plasma and dialysate samples were quantified using a validated ultra-performance liquid chromatography-tandem mass spectrometry assay.

Results: Respective maximum plasma concentrations in patients 1 and 2 were 8.62 and 4.38 mg/L; total body clearances (scaled linearly by body weight) were 0.043 and 0.027 L/h/kg, respectively, of which 12.2% and 5.62% were dialysis clearance, respectively. The corresponding volumes of distribution of polymyxin B at steady state were 0.50 and 0.34 L/kg, respectively, and protein binding in pooled plasma samples was 74.1% and 48.8%, respectively.

Conclusions: Our findings indicate that the recommended polymyxin B doses should not be reduced for patients on CVVHD.

Keywords: continuous renal replacement therapy, plasma protein binding, colistin, creatinine clearance, renal insufficiency

Introduction

Over the last decade, ‘old’ polymyxin B and polymyxin E (colistin) have been increasingly used worldwide due to the prevalence of polymyxin-only-susceptible multidrug-resistant (MDR) Gram-negative bacilli.¹,² Most modern pharmacokinetic knowledge of polymyxins is from colistin. Although colistin pharmacokinetics in patients on different types of haemodialysis has been examined,³–⁶ colistin pharmacokinetics cannot be directly extrapolated to polymyxin B because colistin is administered as its inactive prodrug, colistin methanesulfonate (CMS), resulting in a complex pharmacokinetic interplay between CMS and the formed antibacterial entity colistin.⁵ There is still a dearth of information on polymyxin B pharmacokinetics, which has substantially limited optimization of its dosage regimens in patients, in particular those on renal replacement therapy.¹

In the product information there is no information on whether polymyxin B dosage regimens should be adjusted in patients on renal replacement therapy.¹ Since polymyxin B is predominantly non-renalily cleared,³ dosage adjustment in patients with renal replacement therapy may not be warranted. On the contrary, such patients may even need higher doses if the contribution of extracorporeal clearance to total body clearance is large. Here we report the pharmacokinetics of polymyxin B in two

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patients on continuous venovenous haemodialysis (CVVHD) receiving unadjusted dosage regimens, which are recommended by the product information for patients with normal renal function.

**Patients and methods**

**Patients**

The study was approved by the Ethics Committees of Hospital de Clínicas de Porto Alegre and Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil. Informed consent was obtained from legal representatives of the patients.

Patient 1 was a 20–30-year-old woman [body weight 50.8 kg; body mass index (BMI) 21.1] with an APACHE II score of 25. She was under mechanical ventilation and received intermittent 1 h intravenous infusions of 75 mg of polymyxin B (Eurofarma®) twice daily (3.0 mg/kg/day; 1 mg = 10 000 U), as empirical antimicrobial therapy in a febrile neutropenia episode. She was also receiving intravenous meropenem. Renal dysfunction developed during sepsis prior to polymyxin B treatment. Two days after commencing polymyxin B, CVVHD was initiated with an extracorporeal circuit containing a B Braun–Diacap® α Polysulfone HI PS 18 haemofilter. The dialysate and blood flows were 1.8 L/h and 150 mL/min, respectively. Polymyxin B therapy continued for 14 days.

Patient 2 was a 60–70-year-old man with septic shock. His body weight was 250 kg (BMI 77.2) and the APACHE II score was 21. As a consequence of septic shock, he developed acute renal failure and CVVHD was initiated. Two days later, haemodialysis was modified to intermittent. During this dialysis regimen, a carbapenem-resistant Acinetobacter baumannii (polymyxin B MIC 0.5 mg/L) was detected in a blood culture on day 14 after hospital admission. He was under mechanical ventilation and the primary source of the infection was possibly a ventilator-associated pneumonia. On day 18 intravenous polymyxin B [Eurofarma®, as intermittent 4 h infusions of 250 mg twice daily (2.0 mg/kg/day)] was initiated with co-administration of intravenous ceftazidime. CVVHD was re-commenced on day 8 of polymyxin B therapy and performed with a B Braun–Diacap® α Polysulfone HI PS 18 haemofilter, and dialysate and blood flows were 2.0 L/h and 150 mL/min, respectively. The dose of polymyxin B was not changed during the 15 day treatment.

**Sample collection**

On day 8 (i.e. day 6 of CVVHD; patient 1) and day 10 (i.e. day 2 of CVVHD; patient 2) of polymyxin B therapy, eight blood samples (3 mL each) were collected immediately before starting a polymyxin B infusion, 5 min and 0.5, 1, 2, 4 and 8 h after completing the polymyxin B infusion and immediately before commencing the next dose. Blood samples were centrifuged and the resultant plasma immediately stored at −80°C. Dialysate (5 mL) was collected every hour during the 12 h dosing interval and immediately stored at −80°C.

**Determination of polymyxin B concentrations and plasma protein binding**

Polymyxin B concentrations in plasma and dialysate samples were quantified using a validated ultra-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay. The accuracy and reproducibility (coefficient of variation) of the method were within 99.9% and 8.42%, respectively, and the limit of quantification was 0.050 mg/L. Polymyxin B binding in plasma was determined by rapid equilibrium dialysis in Teflon® equilibrium dialyser cells (DIANORM® Macro 15). Polymyxin B concentrations in the plasma (Cp) and buffer (C₀) reservoirs were determined (see above) and plasma protein binding was calculated as (1 − C₀/Cp) × 100%.

**Pharmacokinetic analysis**

Non-compartmental pharmacokinetic analysis was conducted using WinNonlin® Pro (version 5.3). Recovery of polymyxin B in dialysate was calculated as the amount of unchanged drug recovered across the dosing interval divided by the dose.

**Results**

Concentrations of polymyxin B in plasma and dialysate are shown in Figure 1. The maximum plasma concentrations were 8.62 and 4.38 mg/L in patients 1 and 2, respectively, and the corresponding total body clearances (including CVVHD clearances) were 2.17 and 6.66 L/h (0.043 and 0.027 L/h/kg, scaled linearly by body weight). In the CVVHD dialysate, 12.2% and 5.62% of the dose was recovered as unchanged polymyxin B during the 12 h dosing interval and the CVVHD clearances were 0.264 and 0.374 L/h (0.0052 and 0.0015 L/h/kg) in patients 1 and 2, respectively. The corresponding volumes of distribution of polymyxin B at steady state were 0.50 and 0.34 L/kg. The half-life of polymyxin B is not reported here, as the period of sample collection (i.e. 12 h) did not allow reliable estimation of the terminal half-life. Protein binding in pooled plasma samples was 74.1% (at 3.03 mg/L at the end of equilibrium dialysis) in patient 1 and 48.8% (at 2.09 mg/L) in patient 2.

**Discussion**

Polymyxin B has been increasingly used, particularly in critically ill patients, as a last resort for MDR Gram-negative bacilli. Renal replacement therapies are commonly required in the critically ill. Dosage adjustments of polymyxin B for such therapies have been empirically performed so far. There is only one case report on polymyxin B pharmacokinetics in a patient receiving CVVHD, in which a non-specific microbiological assay was used to quantify polymyxin B in samples. In that study, serum concentrations of polymyxin B were reported to range from 6.25 to 50 mg/L and no polymyxin B was detected in the dialysate. There was no information on the accuracy, reproducibility or sensitivity of the microbiological assay employed. Nevertheless, a Cmax of 50 mg/L in plasma has never been observed in recent clinical pharmacokinetic studies or our current study using specific liquid chromatography assays. To the best of our knowledge, we are the first to reveal the pharmacokinetics of polymyxin B in patients on CVVHD using a specific, accurate and precise LC-MS/MS assay.

The observed difference between patients in total body clearance (expressed in L/h) is due to body weight in the highly obese patient 2; after linear scaling by body weight, the total body clearances were similar (0.043 L/h/kg for patient 1 versus 0.027 L/h/kg for patient 2). In patients not receiving renal replacement, polymyxin B total body clearance appears insensitive to renal function, as less than 1% of a dose is excreted as unchanged drug in urine. Interestingly, in the two patients in the present report, CVVHD clearances represented 12.2% and 5.62% of the respective total body clearances, but were still a minor part of the total clearance. The explanation for the greater contribution of extracorporeal elimination to total body clearance lies in the respective mechanisms involved in processing polymyxins in kidneys (glomerular filtration followed by extensive carrier-mediated tubular reabsorption).
versus a CVVHD cartridge (diffusional and/or convective movement of polymyxin from blood to dialysate without a carrier-mediated mechanism to return the polymyxin from dialysate to blood). Although data on dosage adjustment for renal dysfunction or renal replacement therapy are lacking in the polymyxin B package insert, adjustments have been suggested for anuric patients. Our study demonstrated that in patients on CVVHD receiving the currently recommended dosage regimen for patients with 'normal' renal function (2.0–3.0 mg/kg/day), the area under the plasma concentration versus time curve (i.e. the time-averaged exposure) across a day (69.2 and 75.1 mg·h/L for patients 1 and 2, respectively) was very similar to the median of 73.0 (range 41.2–123.4) mg·h/L in five patients with creatinine clearances of 34–246 mL/min who received 2.0–2.5 mg/kg/day. It should be noted that the dosage regimen of polymyxin B for the obese patient was calculated based on the actual body weight. Considering the plasma protein binding in patient 2 (48.8%), the MIC for the infecting organism (0.5 mg/L) and current knowledge of the pharmacokinetics/pharmacodynamics of polymyxins, the average unbound plasma exposure of polymyxin B in this patient was most likely adequate. However, this conclusion requires re-evaluation for pathogens with higher MICs.

In summary, our findings suggest that, in general, polymyxin B doses should not be reduced for patients on CVVHD and large prospective clinical studies are urgently needed to optimize this last-line therapy.

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**Transparency declarations**

None to declare.

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