Revival of old antibiotics: Pharmacokinetic study of multiple-dose intravenous Polymyxin B in patients with severe burn injury undergoing continuous renal replacement therapy

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An old antibiotic Polymyxin B has been increasingly used as a last resort for MDR (multidrug-resistant) Gram-negative bacilli. However, for patients with severe burned injury, Polymyxin B dosing recommendations are scarce, especially when these patients undergoing continuous renal replacement therapy (CRRT). Therefore, the aim of the present study was to address the urgent need to investigate the clinical pharmacokinetics of Polymyxin B among patients with severe burned injury on continuous venovenous haemodialysis (CVVH) after intravenous administration of unadjusted dosage regimens.

Six patients with full-thickness burns up to 99% TBSA (total body surface area) receiving CVVH and Polymyxin B (50 mg of Polymyxin B twice daily) were included in this study. Blood and effluent samples were collected over 12 h to determine Polymyxin B1 and B2 which was the main component of Polymyxin B using the validated ultra-performance liquid chromatography tandem mass spectrometry assay. Pharmacokinetic parameters were based on 8 sampling time points during the eighth 12 h, and peak and trough samples thereafter. Pharmacokinetic analysis was carried out through computerized programs using the DAS 2.0 method.

Peak plasma concentrations after dilution with 50 mg Polymyxin B was 2.986 ± 1.130 mg/L. The concentrations of Polymyxin B1 were ~3.2-fold higher than the concentrations of Polymyxin B2 (data not shown).The total clearance (scaled linearly by body weight) was 0.052 ± 0.093 L/h/kg, and the apparent volume of Polymyxin B1 was higher in samples from patients (mean standard deviation, 0.62 ± 0.23 L/kg) than in plasma samples from non-burned critically ill patients (range, 0.34~0.50 L/kg). The mean of the AUC for unbound Polymyxin B1 was 15.10 ± 8.213 mg·h/L.

Polymyxin B1 was filtrated and could therefore be measured in the effluent, of which 7.5 ± 4.8 % were dialysis clearance. In the thigh infection model, the fAUC/MIC values for 2-log bacterial killing were approximately 20 for Pseudomonas aeruginosa and Acinetobacter baumannii. Therefore, assuming that these PK/PD data for colistin are similar for Polymyxin B, no one in the study group would reach an fAUC/MIC of approximately 20 on day 4 when the causative pathogen MIC is 2 mg/L under the studied dosage.

Severe burned patients had decreases in the maximum concentration of the drug in plasma (33%) and increases in the volume of distribution and total clearance compared to non-burned critically ill patients. Thus, in such burned patients(>99% TBSA), Polymyxin B at 120 to 140 mg twice daily would be required to achieve drug exposures similar to those for non-burned critically ill patients receiving 75 mg at least. In addition, even if some drug can be cleared via CVVH, the amount eliminated is not high enough to warrant the administration of a supplemental dose after haemodialysis.

Table 1 Mean pharmacokinetics of Polymyxin B1 following the multiple dose of 50 mg to the patients with severe burn injury during CRRT ($x \pm s$, n=6).

Parameters	Plasma pre-dilution	Plasma after-dilution	Effluent
C_{min}(mg/L)	0.4535 ± 0.3400	0.4198 ± 0.2005	0.03899 ± 0.02113
C_{max}(mg/L)	3.147 ± 1.653	2.986 ± 1.130	0.2481 ± 0.1561
T_{max}(h)	1.1 ± 0.4	1.0 ± 0.3	1.0 ± 0.0
$t_{1/2}$ (h)	6.5 ±1.7	6.8 ± 2.1	7.9 ± 3.8
Cl(L/h/kg)	0.050 ± 0.078	0.052 ± 0.0092	-
Vd(L/kg)	0.59 ± 0.34	0.62 ± 0.23	-
AUC_{ss} (mg·h/L)	16.31 ± 10.23	15.10 ± 8.213	1.028 ± 0.4309

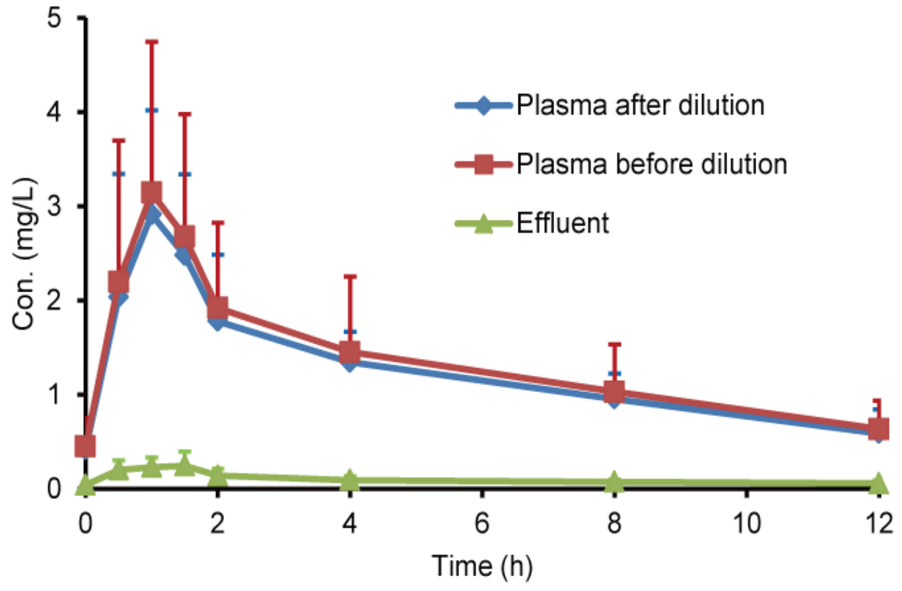

Figure 1 Concentration–time profiles of the study population. Polymyxin B1 concentrations after intravenous infusions of 50 mg, sampled from the pre-filter, post-filter and the effluent ports during 12 h of CVVH ($x \pm s$, n=6).

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