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Removal of colistin during intermittent haemodialysis in two critically ill patients

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Sir,

After being abandoned in the early 1980s because of reported nephrotoxicity and neurotoxicity, colistin is having a second life as a 'salvage' treatment in critically ill patients.[1] It is increasingly used intravenously as a prodrug (colistin methanesulphonate) as a last line of defence against multiresistant Gram-negative bacteria such as *Pseudomonas* and *Acinetobacter* spp.[2] In fact, colistin is composed of ≥30 polymyxins, mainly colistin A and B, and a complex mixture of colistin methanesulphonate derivatives is administered. Specific analytical procedures are mandatory for accurate pharmacokinetic studies and have only recently been made available, explaining the paucity of colistin pharmacokinetic data. The objective of the present study was to document colistin methanesulphonate and colistin removal during intermittent haemodialysis, which has never been investigated, even though this procedure is frequently used in critically ill patients with severe renal failure treated with colistin methanesulphonate.

Two male patients who had acute renal failure requiring intermittent haemodialysis and pulmonary infection with multiresistant Gram-negative bacteria susceptible to colistin are presented. Intermittent haemodialysis sessions (Gambro, AK 200) were performed before colistin methanesulphonate dosing, with a blood flow setting of 300 mL/min and dialysis effluent at 500 mL/min for 4 h, using a 1.6 m^2 B3 polymethylmethacrylate membrane (Toray Industries, Tokyo, Japan). Patient 1 received 1 million international units (MIU) of colistin methanesulphonate every 48 h as 30 min intravenous infusions and haemodialysis sessions were performed every 48 h. Patient 2 received 2 MIU of colistin methanesulphonate every 12 h as 60 min intravenous infusions and haemodialysis sessions were performed every 24 h. Blood samples were collected hourly in the affluent and effluent lines of the extracorporeal circuit during a haemodialysis session on day 17 for Patient 1 and day 2 for Patient 2. Plasma samples were collected and stored frozen at −20°C before being analysed within a week. A recently published liquid chromatography–tandem mass spectrometry ('LC–MS/MS') assay[3] was used for the determination of colistin and colistin methanesulphonate concentrations in plasma, with a limit of quantification of 0.04 mg/L. The between-day variability was characterized at the three levels of concentrations with a precision and accuracy always of <20%. Dialysis clearance (CL_{HD}) was calculated hourly during the whole session for colistin methanesulphonate and colistin as:

$$CL_{HD} = Q(1 - Ht)(C_A - C_E)/C_A$$

where Q corresponds to blood flow, Ht to haematocrit, and C_A and C_E to plasma concentrations in the affluent and effluent lines of the extracorporeal circuit, respectively. Mean ± SD values obtained from four consecutive estimates are reported and are referred to as time-averaged dialysis clearances.

Colistin plasma concentrations determined immediately before starting haemodialysis in Patient 1 were equal to 0.45 mg/L, far below the MIC breakpoint (2 mg/L) published by the European Committee on Antimicrobial Susceptibility Testing.[4] Colistin methanesulphonate concentrations were below the limit of quantification of the assay, consistent with our recent observation that the colistin methanesulphonate

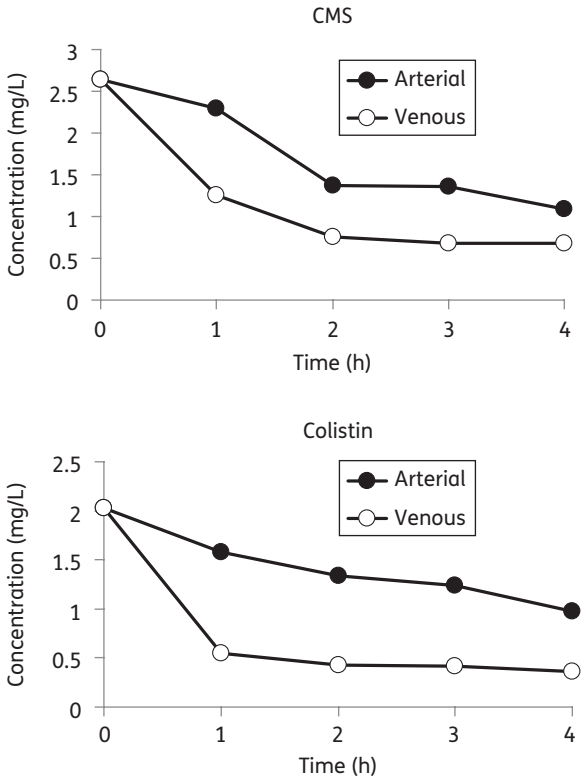

Figure 1. Colistin methanesulphonate (CMS) and colistin concentrations in plasma before and during a 4 h haemodialysis session in the affluent (arterial) and effluent (venous) lines of the extracorporeal circuit in Patient 2.

elimination half-life is much shorter ($t_{½}=0.8\pm0.1$ h) in healthy volunteers than that of colistin ($t_{½}=4.5\pm0.6$ h).[5] It was therefore decided to increase the colistin methanesulphonate dose thereafter and Patient 2 received 2 MIU of colistin methanesulphonate every 12 h compared with 1 MIU of colistin methanesulphonate every 48 h in Patient 1, corresponding to an 8-fold greater maintenance dose associated with a 4-fold reduction of the dosing interval. As a consequence, colistin concentration immediately before haemodialysis in Patient 2 had reached the target, with a value close to the MIC breakpoint at 2 mg/L, and colistin methanesulphonate concentrations could also be quantified in Patient 2 (Figure 1). However, although colistin levels differed between the patients, time-averaged dialysis clearances were equal to 140 ± 36 mL/min in Patient 1 and 134 ± 5 mL/min in Patient 2, i.e. almost identical. Colistin methanesulphonate clearance was estimated to be 90 ± 10 mL/min, which is apparently slightly less than that of colistin, although still quite high. In comparison, continuous venovenous haemodiafiltration previously estimated in another patient[6] was much less efficient for removal, with clearances for colistin and colistin methanesulphonate, respectively, estimated at 11.9 and 11.2 mL/min. However, this renal replacement therapy technique is applied continuously while intermittent haemodialysis is usually applied every 24–48 h, leading to comparable daily clearing capacity.

In conclusion, a colistin methanesulphonate dosing regimen of 1 MIU every 48 h is probably too low in patients with end-stage renal failure under intermittent haemodialysis and 2 MIU every 12 h seems more appropriate. Furthermore, we have demonstrated that both colistin methanesulphonate and colistin are removed efficiently by intermittent haemodialysis, thus preventing the risk of toxicity due to colistin accumulation in these patients. Based on these findings, it should be recommended to readminister colistin methanesulphonate after each session.

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Transparency declarations

None to declare.

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