Prospective single and multiple dose pharmacokinetic study of intravenous colistin in critically ill patients with acute kidney injury (AKI) undergoing extended daily dialysis (EDD)

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Background

- acute kidney injury (AKI) affects up to 25% of all intensive care unit patients and is caused in 50% by sepsis
- lack of new antibiotics for the treatment of multidrug-resistant bacteria renewed interest in “old” antibiotics like colistin
- dosing of IV colistin in these patients undergoing renal replacement therapy is based on scarce data

Aim of the study

- to study pharmacokinetics of colistin after IV administration in patients with AKI on and off renal replacement therapy
- to develop dosing recommendations for this patients cohort and to establish the safety of this dosing recommendations

Patients and Methods

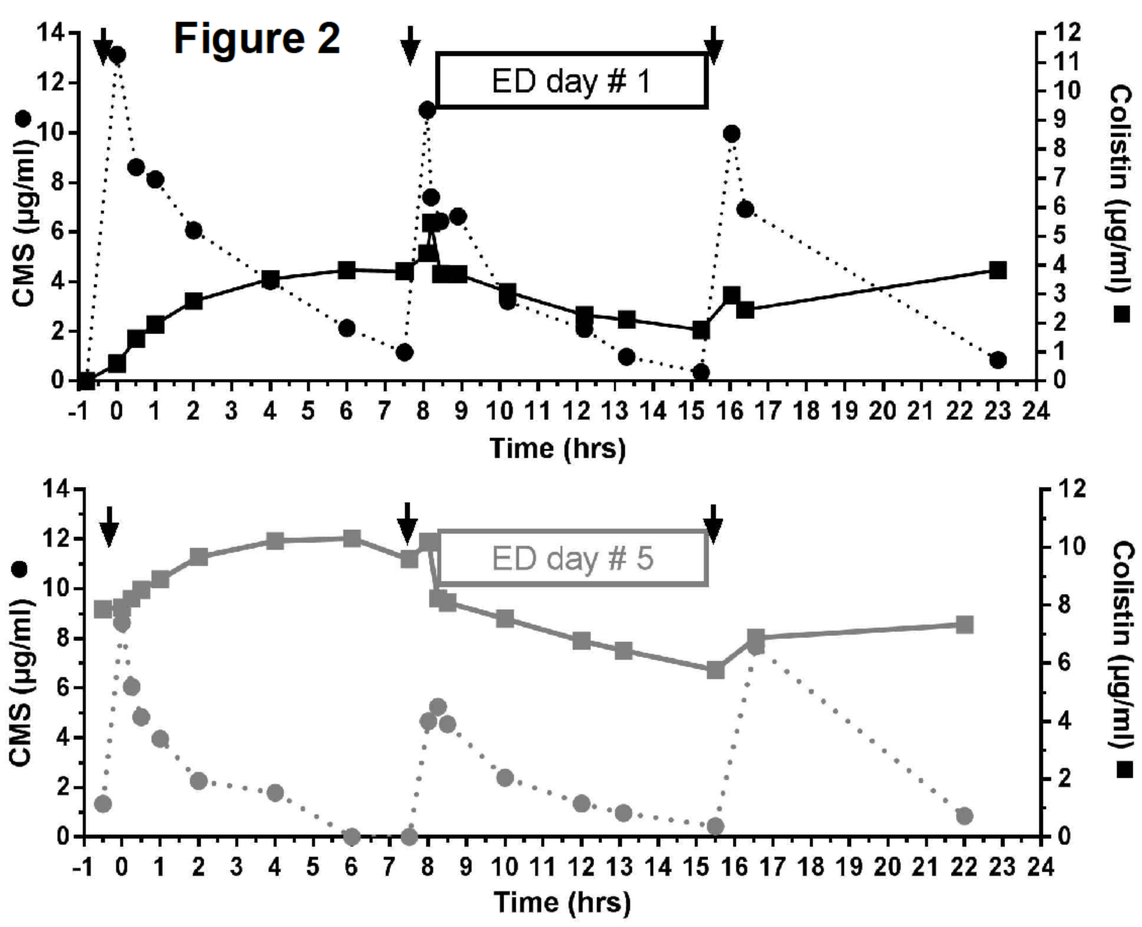
- so far three subjects (2F: body weight 53kg and 35kg/ 1M: body weight 85kg) with anuric AKI being treated with EDD were enrolled in this pharmacokinetic study
- pharmacokinetics on the first day and between the 5th and 9th day of treatment were performed
- blood samples for colistin and CMS were collected via an arterial catheter before IV administration of CMS (prodrug), after the start of infusion, as well as at the start of and throughout the extended dialysis
- EDD: duration 8.2 h; polysulfone high-flux dialyzer (F60S 1.3 m^2); Q_B/Q_D: 210/180 ml/min **(Figure 1)**
- dialyzer clearances were calculated; amount of drugs in the collected spent dialysate was measured

Figure 1

Results

- peak levels of colistin after a loading dose of 6 million units on day # 1 were 3.83-10.01 µg/ml (CMS: 13.14-24.76 µg/ml)
- even after five to nine days of treatment with 3 million units q 8 hours, there was neither an accumulation of colistin (peak level day # 5-9: 8.96-10.71 µg/ml) nor an accumulation of CMS (peak level day # 5-9: 7.68-14.07 µg/ml); example shown in **Figure 2**
- dialyzer plasma clearances ranged between 28-88 ml/min for colistin depending on the blood and dialysate flow
- after dialysis, 108-246 mg colistin could be recovered in the spent collected dialysate on day # 1 and 158-204 mg on day # 5-9

Figure 2



Discussion

- extended daily dialysis eliminates colistin to a larger extent than intermittent hemodialysis
- dosing colistin as recommended for a regular hemodialysis is inadequate and would result in a significant under-dosing, which could be associated with a substantial risk
- after a loading dose of 6 million units on day # 1, a dose of 3 million units every 8 hours yields therapeutic drug levels and does not lead to accumulation of this toxic antibiotic

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