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### **Risk of colistin underdosing in patients with acute kidney injury-results of a single and multiple dose PK study in critically ill patients undergoing extended dialysis**

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**Objectives:** Due to the lack of new antibiotics for the treatment of critically ill patients with multidrug-resistant bacteria, interest on “old” antibiotics like Colistin re-emerged. Dosing of Colistin in critically ill patients undergoing renal replacement therapy is based on scarce data. We aimed to perform a prospective clinical study on dosing of intravenous Colistin in critically ill patients with AKI undergoing extended dialysis to develop dosing recommendations for this patient cohort.

**Methods:** So far three subjects (2F: body weight 53kg and 35kg/ 1M: body weight 85kg) with anuric AKI being treated with extended daily dialysis were enrolled in this prospective, open-label, observational pharmacokinetic study. Pharmacokinetics on the first day and between the 5<sup>th</sup> and 9<sup>th</sup> day of treatment were performed. Blood samples were collected via an arterial catheter before intravenous administration of CMS, Colistins inactive prodrug, after the start of infusion, as well as at the start of and throughout the extended dialysis session (on days of treatment an average of 8.2 hours with a polysulfone high-flux dialyzer [F60S (surface area, 1.3 m<sup>2</sup>; mean blood and dialysate flow of 210/180 ml/min respectively)]. Additional blood samples were drawn pre- and post-dialyzer in order to calculate the dialyzer clearance. Furthermore, samples from the total spent dialysate were taken. This was repeated on day 5-9 of treatment.

**Results:** Peak levels of Colistin after a loading dose of 6 million units on day # 1 were 3.83-10.01 µg/ml and CMS concentration was 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). Dialyzer clearance of Colistin ranged between 37-120 ml/min and 14-220 ml/min for CMS, 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 157-191 mg on day # 5-9.

**Conclusion:** Our data suggest that extended dialysis eliminates Colistin effectively and to a larger extent than previously reported for intermittent haemodialysis. Thus, 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, especially in critically ill patients. After a loading dose of 6 million units on day # 1, a dose of 3 times 3 million units Colistin yields therapeutic drug levels and does not lead to accumulation of this toxic antibiotic if daily extended dialysis with the above mentioned coordinates is performed.

#### **Biography**

Jan T Kielstein studied Medicine at the Otto-von-Guericke University, Germany, University of Chicago and Tufts University, Boston. In 1996 he started his clinical training at the Hannover Medical School, Germany. After board certifications in Internal Medicine and Nephrology he was Postdoctoral research fellow in the Vascular Biology Program at Stanford University from 2004-2007. In 2007 he became Assistant Professor of Medicine in the Department of Nephrology and Hypertension at the Hannover Medical School. Since 2011 he is an Associate Professor, heading Critical Care Nephrology Division since 2014. He published more than 190 papers and serves as a section Editor at *NephroDialTranspl*.

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