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MEETING ABSTRACT

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Pharmacokinetics of trimethoprim-sulfametrole during continuous haemofiltration

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Background: Trimethoprim-sulfametrole (TMP-SMT, Rokiprim®) is a combination with a broad antimicrobial spectrum comprising numerous Gram-positive and Gram-negative bacteria as well as *Pneumocystis jirovecii*. In critically ill patients, the most important indications are respiratory tract infections caused by highly resistant pathogens such as *Pneumocystis jirovecii* or *Stenotrophomonas maltophilia*. Renal failure with an indication for continuous haemofiltration (HF) is common in critically ill patients. The influence of HF on pharmacokinetic on SMT is unknown so far, and data on TMP is scarce. The chemical and pharmacokinetic properties of SMT and TMP, however, suggest relevant elimination by HF that may lead to subtherapeutic plasma levels.

Methods: Pharmacokinetics were determined in plasma and ultrafiltrate samples of patients on HF and of patients with approximately normal renal function off HF. In addition, the extracorporeal clearance by HF (CL_{HF}) was calculated using pre- and post-filter plasma levels, and from the sieving coefficient (SC). TMP-SMT was measured by high-pressure liquid chromatography and UV detection after sample preparation by solid phase extraction. SMT was detected at 250 nm and TMP at 306 nm. Quantification was validated according to the European Medicine Agency (EMA) guidelines. The lower limit of quantification was 0.5 mg/l (SMT) and 0.1 mg/l (TMP).

Results: So far, two patients requiring HF and four patients off HF have been enrolled. In one patient on HF, sampling was performed after the first dose. The other patient on HF as well as the patients off HF were at steady state. For SMT, $t_{1/2}$ was 7.4 h and 10.2 h, total CL amounted to 1.9 l/h and 2.2 l/h, and apparent volume of distribution during terminal phase (V_z) was 20.5 l and 7.7 l, after single and repeated dose, respectively, on HF. Off HF SMT, $t_{1/2}$ amounted to 9.7 ± 3.3 h (mean \pm standard deviation), total CL was 0.8 ± 0.4 l/h and V_z was 4.35 ± 2.11 l. For TMP, $t_{1/2}$ was 10.4 h and 26.9 h, total CL was 5.9 l/h and 5.3 l/h, and V_z was 87.8 l and 20.0 l after single and repeated dose, respectively on HF. Off HF, a $t_{1/2}$ of TMP of 16.7 ± 7.9 h, a total CL of 4.0 ± 1.5 l/h and a V_z of 22.6 ± 9.3 l were observed. For SMT, CL_{HF} was 1.6 l/h and 1.8 l/h (84% and 68% of total CL)

after single and multiple doses, respectively. CL_{HF} of TMP amounted to 1.8 l/h and 1.9 l/h (31% and 30% of total CL), respectively. CL_{HF} , calculated from SC, was somewhat lower for both drugs, suggesting that moderate adsorption to the haemofilter takes place.

Discussion: Considerable amounts of SMT and TMP are eliminated by HF resulting in an enhanced total CL in comparison with patients off HF. CL_{HF} was similar for SMT and TMP. If this is confirmed by data from a larger number of patients, higher doses have to be considered for this clinical condition.

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