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Abstract (oral session)

Population pharmacokinetics of colistin methanesulfonate (CMS) and colistin in critically ill patients receiving intermittent haemodialysis

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Objectives: Colistin is administered intravenously as an inactive prodrug (CMS). In patients with preserved renal function about 2/3 of the CMS dose is excreted unchanged in urine (1) making difficult to attain effective colistin plasma concentrations (2). However in patients under intermittent haemodialysis (HD), most of the CMS dose has a chance to be converted into colistin to reach relatively high plasma concentrations (3). Yet since CMS and colistin are efficiently removed during HD (4), steady-state concentrations cannot be maintained. The aim of this study was to assess colistin pharmacokinetics (PK) in critically ill patients receiving intermittent haemodialysis (HD) in order to suggest optimal dosing regimen. Methods: Eight (n=8) HD patients, including 2 anuric with a median age of 65 years and weight of 80 kg, received multiple doses of CMS (median 0.5 MUI/8h). Concentrations of CMS and colistin were measured (5) outside HD sessions, after the 1st dose and at steady-state, in plasma (n=87) and urine (n=6). Data were submitted to PK Population analysis with Monolix software. CMS and colistin HD clearance were set at 90 and 135 mL/min (4). Results: A PK model with one compartment for both CMS and colistin, assuming negligible renal clearance of colistin, adequately fitted the data. CMS renal and non renal clearances were estimated to 4 and 95 mL/min respectively and colistin clearance to 38 mL/min. Colistin concentrations slowly reached a pseudo-steady-state at typically 1.4 µg/mL between two consecutive HD sessions, with very little fluctuations. Simulations using parameters model show that colistin concentrations above breakpoints should be reached more rapidly after infusing the daily dose of CMS at once than in 3 times, with still limited fluctuations (0.5-2.0 µg/mL after CMS 1.5 MIU/24h, or 1.0-4.0 µg/mL after CMS 3 MIU/24h). Conclusions: Relatively high and efficient colistin concentrations may be obtained in HD patients between two consecutive HD sessions but once-daily administrations of CMS should probably be preferred to dose fractionation.