Standard doses of intravenous colistin do not achieve therapeutic plasma target levels in adult cystic fibrosis patients : preliminary results from a multicentre, prospective pharmacokinetic study

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Objectives : The polymyxin colistin, commercialized as a prodrug (colistimethate-CMS), is considered a last-resort drug for Pseudomonas aeruginosa (Pa), as it shows no cross-resistance with more conventional antibiotics. Its use is however limited by its neurological and renal toxicities. Optimal dosing for CF patients is still unknown. We, prospectively, evaluated the pharmacokinetic (PK) profile of intra-venous (iv) colistin as well as its safety in adult CF patients presenting an acute exacerbation and colonized with Pa.

Methods : Patients were treated with a conventional dose of CMS (Colistineb®) of 2 MIU tid and a broad spectrum beta-lactam for 10–14 days. Serum trough drug concentrations were measured at day 1–3 and a full PK profile was obtained at steady state between day 3–5. Serum creatinine was assessed before and during treatment. Neurotoxicity was evaluated clinically. CMS, total and unbound colistin A+B concentrations were determined by mass spectrometry (LC-MS/MS method). PK results are expressed as median (quartiles 25–75). The accepted PD target for total unbound colistin is 2 mg/L.

Results : We included 24 patients [14 F, median age (min-max) 34.5 yrs (20–57), body weight 57 kg (40–69), serum creatinine 0.7 mg/dL (0.47– 1.1)]. PK data are at present available from 17 patients. Cmax for CMS was 10.4 (8.4–12.4) mg/L, for total colistin A+B 1.97 (1.31–2.55) mg/L and for unbound colistin A+B 0.55 (0.37–0.69) mg/L. At trough level, all total colistin results (0.48 [0.25–0.67] mg/L) and unbound colistin (0.05 [0.03–0.09] mg/L) were inferior to the MIC of isolated strains and protein binding of colistin was high 87.5 (83.7–90.1) %. No serious adverse events were observed.

Conclusions : Standard dose regimens of iv colistin in CF patients did not reach therapeutic plasma target levels in any patient. Higher dose regimens plus nebulized administration may be required in severe clinical presentations.

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