Population pharmacokinetics of daptomycin in critically ill patients with various degrees of renal impairment

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Résumé en anglais	Objectives The objective of this study was to characterize the pharmacokinetics of unbound and total concentrations of daptomycin in infected ICU patients with various degrees of renal impairment. From these results, the probability of attaining antimicrobial efficacy and the risks of toxicity were assessed. Methods Twenty-four ICU patients with various renal functions and requiring treatment of complicated skin and soft-tissue infections, bacteraemia, or endocarditis with daptomycin were recruited. Daptomycin (Cubicin®) at 10 mg/kg was administered every 24 h for patients with creatinine clearance (CLCR) ≥30 mL/min and every 48 h for patients with CLCR <30 mL/min. Total and unbound plasma concentrations and urine concentrations of daptomycin were analysed simultaneously following a population pharmacokinetic approach. Simulations were conducted to estimate the probability of attaining efficacy (unbound AUCu/MIC >40 or >80) or toxicity (Cmin >24.3 mg/L) targets. Results Exposure to unbound daptomycin increased when the renal function decreased, thus increasing the probability of reaching the efficacy targets, but also the risk of toxicity. Modifications of the unbound fraction (fu) of daptomycin did not affect the pharmacokinetics of unbound daptomycin, but did affect the pharmacokinetics of total daptomycin. Conclusions Daptomycin at 10 mg/kg q24h allowed efficacy pharmacokinetic/pharmacodynamic targets for ICU patients with CLCR ≥30 mL/min to be reached. For patients with CLCR <30 mL/min, halving the rate of drug administration, i.e. 10 mg/kg q48h, was sufficient to reach these targets. No adverse events were observed, but the toxicity of the 10 mg/kg q24h dosing regimen should be further assessed, particularly for patients with altered renal function.
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