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Population pharmacokinetics of teicoplanin administered in adults by subcutaneous or intravenous route and simulation of optimal loading dose regimen

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Background: Subcutaneous (SC) administration of teicoplanin, although off-label, is not rare and may be convenient. Little is known about the comparative pharmacokinetics (PK) and optimal dosing of intravenous (IV) and SC teicoplanin. The objectives of this study were to perform population PK modeling of teicoplanin in adult patients treated by IV and SC route and to evaluate optimal loading dosage regimens.

Material/methods: This was a retrospective analysis of two datasets: 12 patients hospitalized in intensive care units with rich sampling [1] and 86 elderly patients with sparse sampling. Patients received teicoplanin by IV and/or SC route for infections caused by Gram-positive cocci. Data were analyzed with a population approach in Monolix 4.4. Model evaluation was based on classical criteria including goodness-of-fit and simulation-based diagnostics. Monte Carlo simulations were then performed to evaluate the probability of target attainment (PTA) for four loading dosage regimens of teicoplanin. The pharmacodynamic targets were: 1) through concentration (C_{min}) ≥ 15 $mg.L^{-1}$ and area under the concentration-time curve divided by minimal inhibitory concentration (AUC_{24}/MIC) ≥ 900 [2].

The simulated dosage regimens were as follows: 400, 600, 800, and 1000 mg every 12h during 48h followed by the same dose administered every 24h during 12 days, for both routes.

Results: A total of 844 teicoplanin concentrations from the 98 patients were available. There were 51 males and 47 females with mean age, weight and creatinine clearance (CL) of 78 ± 15 years, 64 ± 14 kg, and 63 ± 53 ml/min, respectively. A linear two-compartment model fitted the data very well. Estimated glomerular filtration rate was found to influence teicoplanin plasma CL. Typical parameter values (between-subject variability) were as follows: SC absorption rate constant 0.039 h^{-1} (77%); plasma CL, 0.305 $L.h^{-1}$ (28%); central volume of distribution, 10 L (55%); intercompartmental CL, 4.42 $L.h^{-1}$ (66%); peripheral volume of distribution, 97.4 L (51%). On day 3, all SC and IV simulated dosing regimens had a PTA of ≥ 90% for the C_{min} target, except 400/12h and 600 mg/12h. PTA were similar for the SC and IV route. Regarding the AUC_{24}/MIC target, all dosage regimens achieved a PTA of 90% for MIC values ≤ 0.25 mg/L, but the PTA dropped dramatically for higher MIC values. However, on day 15, all maintenance dosage regimens were associated with PTA > 90% for MIC values ≤ 1 $\mu g.mL^{-1}$, except 400 mg/24h and 600 mg/24h.

Conclusions: The SC administration of teicoplanin does not alter the PTA compared with IV administration. This study also shows that loading doses of teicoplanin higher than currently recommended should be used to provide earlier and better target attainment.

References: 1. Barbot, A. et al. Intensive Care Med 2003; 2. Matsumoto, K. et al. Clin Pharmacol 2016