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PK/PD studies

Appraisal of potential effect of subcutaneous administration on antibiotics pharmacokinetics-pharmacodynamics

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Objectives: Subcutaneous (SC) infusion of antibiotics may constitute an interesting alternative to oral or intravenous (IV) administration in elderly patients (1). However only ceftriaxone and amikacin are officially approved for SC administration in France and the lack of pharmacokinetic (PK) data constitutes a major obstacle (1). The aim of this study was to identify the absorption rate limiting steps in order to predict antibiotics PK after SC infusion, and also to predict the pharmacokinetic-pharmacodynamic (PK-PD) consequences for concentration dependent and time dependent antibiotics.

Methods: Data obtained in intensive care patients treated by ertapenem IV and SC were used (2). A new population PK analysis was performed using a two-compartment model with multiple zero-order infusions after IV administrations and by adding a depot compartment after SC administration to take into account the transfer of drug from the SC tissue to the plasma with a first-order absorption rate constant (Ka). PK simulations were performed after changing the IV infusion or SC absorption rates with Berkeley Madonna software.

Results: These simulations suggest that for most antibiotics candidates for SC administration (1), absorption from the tissue would be the rate limiting step for their appearance in the systemic circulation. Consequently SC infusion would shift the plasma concentration-time profiles to the right with major reduction of peak concentration (C_{max}) and delayed time to peak (t_{max}). The expected reduction of C_{max}/MIC after SC administrations could dramatically reduce the antimicrobial efficacy of concentration dependent antibiotics such as amikacin. By contrast the dosing interval during which drug concentrations exceeds the MIC would not be significantly affected by the route of administration, suggesting that time dependent antibiotics such as ertapenem or ceftriaxone, should be good candidates for SC infusion.

Conclusion: SC administration may represent an interesting alternative to IV infusion or oral administration for patients with reduced vascular access, that should be preferentially indicated for time dependent antibiotics.

References:

[1] Forestier E et al., *Clin Microbiol Infect*, in press

[2] Frasca D et al., *Antimicrob Agents Chemother*. 2009