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Paper Poster Session
PK/PD of agents against Gram-positives

Standard vs. alternative dosing regimens for linezolid against S. aureus: Potential value of front-loaded regimens

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Background: There is an on-going debate about the suitability of potential alternative dosing strategies for linezolid beyond 600 mg BID. Continuous infusion regimens, but also intensified front-loaded or TID dosing regimens have been hypothesised, but their potential clinical advantage is yet unclear. In order to guide future clinical investigations, the present study aimed at a systematic comparison of these regimens by means of semi-mechanistic PK/PD modelling.

Material/methods: A semi-mechanistic PD model was developed for time-kill curve studies with log-phase *S. aureus* ATCC 29213 covering clinically relevant concentrations from 0-32 mg/L linezolid. This PD model was linked to a published human population PK model for linezolid [1]. The linked PK/PD model was utilised for stochastic simulations of the antibacterial effects after 24 h of treatment with the linezolid standard regimen of 600 mg BID and the following alternative regimens: continuous infusion of 1200 mg over 24 h, 600 mg TID and front-loaded 1200 mg followed by 600 mg BID. The impact of creatinine clearance (CLCR, 60-160 mL/min) and body weight (WT, 60-100 kg) on the antibacterial effect was assessed for each scenario. The probability of target attainment (PTA) was calculated for a bacteriostatic (no net difference from inoculum) and bactericidal effect (≥3 log10 CFU/mL reduction of inoculum) to evaluate and compare the regimens.

Results: Low CLCR and low WT increased PTA of the bacteriostatic effect, but the impact was ≤0.16 in the studied covariate ranges. 600 mg BID stimulated a bacteriostatic PTA of ≥0.85 and bactericidal PTA was ≤0.02. Continuous infusion of 1200 mg/24 h displayed a bacteriostatic PTA of ≤0.29 and bactericidal PTA of ≤0.007. 600 mg TID stimulated a bacteriostatic effect with PTA ≥0.96 and bactericidal PTA was ≤0.04. The front-loaded regimen with 1200 mg followed by 600 mg BID was bacteriostatic with PTA ≥0.96 and bactericidal PTA was ≤0.23.

Conclusions: The continuous infusion regimen was inferior to the standard dosing regimen. Conversely, front-loaded regimens with a doubled initial dose of 1200 mg were superior to the standard regimen and all other evaluated alternative regimens and stimulated a bactericidal effect in a >10-fold higher portion of the population. This superiority possibly originated from the significant contribution of initial concentration-dependent killing of linezolid to the observed effect after 24 h. Clinical evaluation of front-loaded regimens for treatment of *S. aureus* infections is warranted.

[1] Sasaki et al. Antimicrob. Agents Chemother., 55.: 1867–73 (2011).