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Paper Poster Session

PK/PD of agents against Gram-positives

Comparative pharmacodynamics of ceftaroline and linezolid against *Staphylococcus aureus* in an in vitro dynamic model

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Background: To compare killing kinetics of *S. aureus* exposed to therapeutic and sub-therapeutic doses of ceftaroline and linezolid, human pharmacokinetics of the antibiotics were simulated at the respective ratios of the 24-hour area under the curve (AUC) to the MIC.

Material/methods: MRSA strain ATCC 43300 with MICs of ceftaroline and linezolid equal to their MIC₅₀s (0.5 and 2 mg/L, respectively) was exposed to twice daily antibiotics for three consecutive days at AUC/MICs of 90 and 180 h and 60 and 120 h, respectively. The respective times above MIC were 66% and 87% with ceftaroline and 100% and 100% with linezolid. Peripheral compartments of the hollow-fiber model fitted with computer-assisted systems for antibiotic supply and specimen withdrawal were sampled for antibiotic and bacterial concentrations over 96 to 120 hours. Ceftaroline and linezolid concentrations were determined by HPLC methods. Time courses of viable counts were characterized by the time to 100-fold reduction of the starting inoculum (T_{99%}), maximal reduction in bacterial load (ΔN_{max}) and the area between the control growth curve and the time-kill curves (ABBC) calculated from time zero to 72 h.

Results: Antibiotic concentrations determined throughout each experiment were close to target values. Numbers of surviving *S. aureus* colonies decreased after starting treatment with ceftaroline and linezolid, more rapidly at the therapeutic than sub-therapeutic AUC/MIC ratios. Regardless of the antibiotic exposure, initial decrease in bacterial counts was faster with ceftaroline than linezolid: the respective T_{99%}s were 5 versus 36 h. ΔN_{max} values observed with ceftaroline were more pronounced than linezolid (5.3 versus 3.8 log CFU/ml at therapeutic AUC/MICs and 4 versus 3 log CFU/ml at sub-therapeutic AUC/MICs). These differences were consistent with greater ABBCs that reflect integral antibacterial effects of ceftaroline: 480 (log CFU×h)/ml at the therapeutic value of AUC/MIC and 420 log CFU×h/ml at the sub-therapeutic value compared to ABBCs established with linezolid [330 and 310 (log CFU×h)/ml, respectively].

Conclusions: This study highlights the greater activity of ceftaroline over linezolid both in terms of the rate and extent of *S. aureus* killing. These differences are consistent with 1.35-1.45-fold greater integral anti-staphylococcal effects of ceftaroline compared to linezolid.