Comparative Pharmacodynamics of Ceftaroline and Linezolid against *Staphylococcus aureus* in an *In Vitro* Dynamic Model

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Background

- Ceftaroline (CPT) is a new bactericidal cephalosporin with a broad spectrum of antimicrobial activity and low MIC values against methicillin-resistant *S. aureus* [1]. Direct comparisons of CPT with linezolid (LZD), the only recently approved agent in recent times for the treatment of infections caused by multidrug-resistant gram-positive bacteria [2], have not been reported in studies using *in vitro* dynamic models.
- To compare killing kinetics of *S. aureus* exposed to therapeutic and sub-therapeutic doses of CPT and LZD, human pharmacokinetics of the antibiotics were simulated at the respective ratios of the 24-hour area under the curve (AUC) to the MIC.

Materials/Methods

- MRSA strain ATCC 43300 with MICs of CPT and LZD equal to their MIC_{50}s (0.5 and 2 mg/L, respectively [3]) was exposed to twice-daily antibiotics for three consecutive days in the hollow-fiber dynamic model.
- Pharmacokinetic profiles that mimic time courses of CPT or LZD in humans after a 1-hour infusion were simulated with their respective half-lives (2.3 [4, 5] and 6 [6] h).
- Target AUC/MIC ratios were 90 and 180 h for CPT (CPT90 and CPT180) and 60 and 120 h for LZD (LZD60 and LZD120). The respective times above MIC were 66% and 87% with CPT and 100% and 100% with LZD.
- The highest AUC/MIC ratios (CPT180 and LZD120) were close to values achievable in humans treated with CPT (600 mg twice daily; the respective AUC/MIC ratio 112 mg×h/L [7]/0.5 mg/L = 224 h) or LZD (600 mg twice daily; 228 mg×h/L [8]/2 mg/L = 114 h).
- 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 72 hours.
- CPT and LZD concentrations in the peripheral unit of the model were determined by a HPLC assay. Isocratic separation was performed at 40°C (CPT) or 35°C (LZD) on a Luna C18(2) column (Phenomenex, Torrance, CA, USA). The mobile phase consisted of 12 mM (for CPT) or 20 mM (for LZD) solution of ammonium acetate, previously adjusted to pH 3.5 with acetic acid, and acetonitrile - (volume ratio 82.6:17.4 for CPT or 71:29 for LZD). The column effluent was monitored with a UV-detector (Waters 2489, Waters Associates, Milford, MA, USA) at 278 nm (CPT) or 251 nm (LZD).
- Time courses of viable counts were characterized by the time to 100-fold reduction of the starting inoculum ($T_{99\%}$), maximal reduction in bacterial burden (ΔN_{max}) and the area between the control growth curve and the time-kill curves (ABBC) [9] calculated from time zero to 72 h.

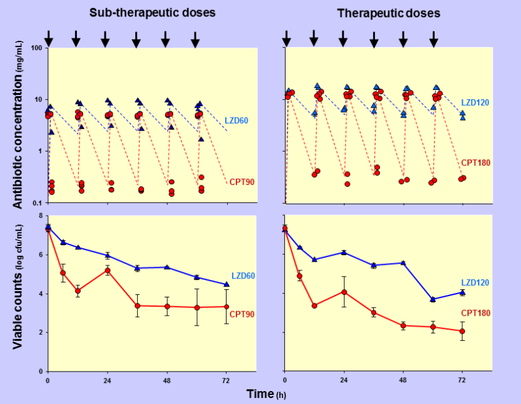
Results

- Antibiotic concentrations determined throughout each experiment were close to target values (Figure, upper panel).
- Numbers of surviving *S. aureus* colonies decreased after starting treatment with CPT and LZD, more rapidly at the therapeutic than sub-therapeutic AUC/MIC ratios (Figure, bottom panel).

The study performed at the Department of Pharmacokinetics & Pharmacodynamics, Gause Institute of New Antibiotics, was supported by a grant from Russian Science Foundation (#14-15-00970)

- Regardless of the antibiotic exposure, initial decrease in bacterial counts was faster with CPT than LZD: the respective $T_{99\%}$s were 5 *versus* 36 h. ΔN_{max} values observed with CPT were greater than LZD (5.3 *versus* 3.2 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 CPT: 480 h×log CFU/mL at the therapeutic value of AUC/MIC and 420 h×log CFU/mL at the sub-therapeutic value compared to ABBCs established with LZD (330 and 310 h×log CFU/mL, respectively).

Figure. **Simulated pharmacokinetics and time courses of *S. aureus* exposed to ceftaroline and linezolid**



Upper panel: dotted lines – expected concentrations, points – HPLC-determined concentrations. The arrows reflect antibiotic dosing.

Conclusion

- This study highlights the greater activity of CPT over LZD both in terms of the rate and extent of *S. aureus* killing. These differences are consistent with the 1.35-1.45-fold greater integral anti-staphylococcal effects (expressed as ABBC) of ceftaroline compared to linezolid.
- When making these comparisons, total antibiotic concentrations were not corrected for protein binding not only because of similar protein binding of CPT and LZD (approximately 20% [10] and 31% [11], respectively), but also because such corrections are consequently unreliable [12]. As shown earlier [13, 14], attempts to interpret the pharmacodynamics of antibiotics using reported percentages of protein binding are fraught with overestimation of protein binding effects and underestimation of the true antimicrobial activity, both *in vitro* and *in vivo*.

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