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Comparison of the Antibacterial Effects of Two Dosing Regimens of Ceftaroline in Combination With NXL104 Against Enterobacteriaceae

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Abstract

Background: CPT plus NXL is a cephalosporin non β-lactam β-lactamase inhibitor combination with activity against Gram-positive organisms, including MRSA, and Enterobacteriaceae producing a wide range of β-lactamases. Optimal doses and ratios of CPT plus NXL are unknown. We used an in vitro pharmacokinetic model (IVPKM) to simulate 2 human dose regimens and measured their effect on 3 strains of Enterobacteriaceae.

Methods: An IVPKM was used to simulate serum concentrations associated with 400 mg CPT (peak 17 mg/L) and 600 mg CPT (peak 27 mg/L) in combination with 600 mg NXL (peak 25 mg/L), t½ 2 hr, q8h dosing for 96 h. Three strains were used: an ampicillin sensitive (Amp^S) *Escherichia coli* (CPT/NXL MIC 0.08 mg/L), a CTX-M producing *E. coli* (CPT/NXL MIC 0.08 mg/L), and an AmpC hyper-producing *Enterobacter cloacae* (CPT/NXL MIC 1.8 mg/L). The inoculum was 10^6 CFU/mL and simulations were performed in triplicate. Antibacterial effect (ABE) was measured by log change in viable count and the area-under-the-bacterial-kill-curve (AUBKC).

Results: Both regimens produced a >4 log_{10} reduction in viable count by 12 h with the Amp^S *E. coli*. Growth was suppressed to 96 h by the 600 mg CPT regimen but regrowth occurred after 48 h with 400 mg. AUBKC showed that the 600 mg CPT regimen had a superior ABE to the 400 mg (p <0.05). Similar results were observed with the CTX-M producer with suppression of growth with the 600 mg regimen, regrowth with the 400 mg regimen and AUBKC measures showing the 600 mg regimen superior (p <0.05). Against the AmpC producer *E. cloacae* there was a 3-5 log_{10} reduction in count at 12 h with both regimens followed by a 1-3 log_{10} suppression of growth to 96 h with the 400 mg regimen and a 2-4 log_{10} suppression with the 600 mg regimen. Comparison of the AUBKC indicated the 600 mg regimen was superior to the 400 mg (p <0.05).

Conclusions: 600 mg CPT + 600 mg NXL is superior in its ABE to 400 mg CPT + 600 mg NXL against Enterobacteriaceae without β-lactamase, CTX-M producers, and AmpC hyperproducers.

Introduction

- Ceftaroline (CPT), the active component of the prodrug ceftaroline fosamil, is a novel, broad-spectrum cephalosporin exhibiting bactericidal activity against resistant Gram-positive and common Gram-negative organisms. NXL104 (NXL) is an investigational non-β-lactam β-lactamase inhibitor with activity against Class A, C and D β-lactamases. The combination of CPT and NXL, CXL, is currently in early clinical development
- It was previously shown that CPT plus NXL (2 µg/mL) reduces CPT MICs of Enterobacteriaceae with Class A and/or extended-spectrum β-lactamases (ESBL) from >128 to ≤2 µg/mL. Subsequent studies have demonstrated that Enterobacteriaceae strains with KPC serine carbapenemases exhibit an MIC_{90} of 4 mg/L if tested using a 4 mg/L fixed concentration of NXL
- A hollow-fibre pharmacokinetic model has demonstrated proof of concept with ceftazidime and ceftaroline plus NXL, showing activity against AmpC *Enterobacter cloacae* and *Klebsiella* producing CTX-M-15, SHV-5, and TEM-10[1-3]
- Ceftaroline displays linear pharmacokinetics in humans. Single-dose studies indicate C_{max} of 9.9 mg/L, 23 mg/L, and 30.2 mg/L with doses of 250 mg, 750 mg, and 1000 mg, respectively, t½ of 2.5 h, and protein binding <20%. NXL also shows proportional pharmacokinetics, with C_{max} increasing from 2.7 mg/L for a 50 mg dose to 124 mg/L at 2000 mg dose[4,5]
- However, the optimal doses and ratios of CXL are unknown. The aim of this study was to simulate 2 human dose regimens of CXL and to measure their effect on 3 strains of Enterobacteriaceae using an in vitro pharmacokinetic model.

Materials and Methods

Pharmacokinetics

- Regimen 1: CPT 400 mg (C_{max} 17 mg/L) in combination with NXL 600 mg (peak 25 mg/L), t½ of 2 h, q8h dosing for 96 h
- Regimen 2: CPT 600 mg (C_{max} 27 mg/L) in combination with NXL 600 mg (C_{max} 25 mg/L), t½ of 2 h, q8h dosing for 96 h.

MIC Determination

- MICs were performed in Mueller Hinton Broth. NXL was added at a fixed concentration of 2 µg/mL.

Strains

- 3 strains were used: *Escherichia coli* ATCC 25922 (CXL MIC 0.08 mg/L), CTX-M-producing *E. coli* (CXL MIC 0.08 mg/L), and AmpC-hyperproducing *E. cloacae* (CXL MIC 1.8 mg/L)
- The inoculum was 10^6 CFU/mL and simulations were performed in triplicate
- Antibacterial effect (ABE) was measured by log change in viable counts (d24, d48, d72, d96), and the area-under-the-bacterial-kill-curve (AUBKC) at 24, 48, 72, and 96 h.

Emergence of Resistance

- Emergence of resistance was assessed by plating aliquots onto nutrient agar plates containing 1x, 2x, 4x, and 8x MIC of the test strain at 24, 48, 72, and 96 h
- Concentrations were confirmed using a bioassay with Diagnostic Sensitivity Agar, with *E. coli* NCTC 10418 as the indicator organism.

Results

Figure 1a. Antibacterial Effect of CPT 400 mg/NXL 600 mg and CPT 600 mg/NXL 600 mg Against ATCC *Escherichia coli* 25922

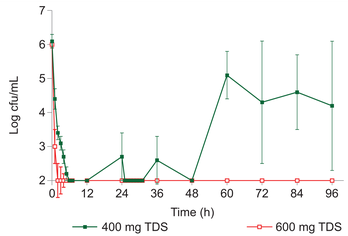

Figure 1b. Antibacterial Effect of CPT 400 mg/NXL 600 mg and CPT 600 mg/NXL 600 mg Against CTX-M-15-producing *Escherichia coli*

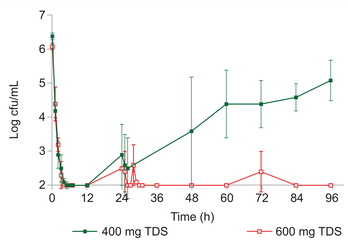

Figure 1c. Antibacterial Effect of CPT 400 mg/NXL 600 mg and CPT 600 mg/NXL 600 mg Against AmpC-producing *Enterobacter cloacae*

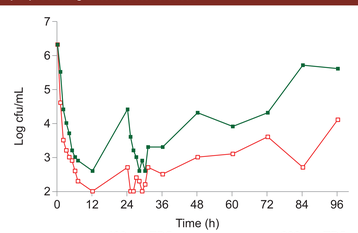

Table 1. CPT/NXL (400/600) vs CPT/NXL (600/600) Against *Escherichia coli* ATCC 25922 (MIC 0.08 mg/L)

Antibacterial effect measure	CPT/NXL 400/600 mg	CPT/NXL 600/600 mg	p value
d12	-4.1 ± 0.2	-4.0 ± 0.1	ns
d24	-3.4 ± 0.7	-3.8 ± 0.3	ns
d36	-3.5 ± 0.9	-4.0 ± 0.1	ns
d48	-3.6 ± 1.0	-4.0 ± 0.1	ns
d72	-1.9 ± 1.9	-4.0 ± 0.1	ns
d96	-1.9 ± 1.9	-4.0 ± 0.1	ns
dmax	-4.1 ± 0.2	-4.0 ± 0.1	ns
AUBKC 24	60.5 ± 3.4	53.8 ± 1.8	0.040
AUBKC 48	118.6 ± 3.9	69.9 ± 26.0	0.036
AUBKC 72	221.1 ± 24.3	69.9 ± 26.0	0.0018
AUBKC 96	327.4 ± 60.0	69.9 ± 26.0	0.0024

AUBKC = area-under-the-bacterial-kill-curve; ns = not significant.

Table 2. CPT/NXL (400/600) vs CPT/NXL (600/600) Against CTX-M-producing *Escherichia coli* (MIC 0.08 mg/L)

Antibacterial effect measure	CPT/NXL 400/600 mg	CPT/NXL 600/600 mg	p value
d12	-3.9 ± 1.1	-4.1 ± 0.1	ns
d24	-3.5 ± 0.9	-3.7 ± 0.6	ns
d36	-4.4 ± 0.1	-4.1 ± 0.1	0.013
d48	-2.9 ± 1.8	-4.1 ± 0.1	ns
d72	-2.0 ± 0.7	-3.7 ± 0.4	0.015
d96	-1.3 ± 0.6	-4.0	0.035
dmax	-4.4 ± 0.1	-4.1 ± 0.1	0.002
AUBKC 24	63.9 ± 9.8	56.3 ± 3.7	ns
AUBKC 48	123.0 ± 15.6	74.3 ± 17.4	0.0114
AUBKC 72	233.7 ± 38.6	74.3 ± 17.4	0.0017
AUBKC 96	337.0 ± 41.4	74.3 ± 17.4	0.0002

AUBKC = area-under-the-bacterial-kill-curve; ns = not significant.

Table 3. CPT/NXL (400/600) vs CPT/NXL (600/600) Against AmpC-producing *Enterobacter cloacae* (MIC 1.8 mg/L)

Antibacterial effect measure	CPT/NXL 400/600 mg	CPT/NXL 600/600 mg	p value
d12	-3.7 ± 0.5	-4.2 ± 0.2	ns
d24	-2.0 ± 1.2	-3.6 ± 0.7	<0.05
d36	-3.0 ± 1.9	-3.8 ± 0.5	ns
d48	-2.1 ± 1.2	-3.2 ± 0.3	ns
d72	-2.0 ± 0.9	-2.6 ± 0.3	ns
d96	-0.7 ± 1.2	-2.0 ± 1.2	ns
dmax	-4.3 ± 0.3	-4.3 ± 0.2	ns
AUBKC 24	84.4 ± 11.0	64.5 ± 5.8	0.009
AUBKC 48	167.9 ± 31.2	126.8 ± 13.2	0.036
AUBKC 72	264.7 ± 41.2	212.1 ± 30.9	0.055
AUBKC 96	415.9 ± 43.4	284.1 ± 32.3	0.0126

AUBKC = area-under-the-bacterial-kill-curve; ns = not significant.

- The ABEs of CPT 400 mg and CPT 600 mg plus NXL 600 mg against *E. coli* ATCC 29522, *E. cloacae*, and the CTX-M-producing *E. coli* strains are shown in Figures 1a-c and Tables 1-3, respectively
- Targeted concentrations of CPT in the model were confirmed (data not shown)
- Both regimens produced a >4-log_{10} reduction in viable count by 12 h against the *E. coli* ATCC 29522. Growth was suppressed to 96 h by the 600-mg CPT regimen but regrowth occurred after 48 h with the 400-mg regimen. This was confirmed with the AUBKC, which verified that the 600-mg CPT regimen had superior ABE vs the 400-mg regimen (p <0.05)
- Similar results were observed with the CTX-M-producing *E. coli* with suppression of growth with the 600-mg regimen. After 48 h, regrowth was noted with the 400-mg regimen; d24 and AUBKC measures showed the 600-mg regimen to be superior (p <0.05)
- Against the AmpC-producing *E. cloacae*, a 3- to 5-log_{10} reduction in count at 12 h was observed with both regimens. The 400-mg regimen suppressed 1- to 3-log_{10} growth to 96 h. The 600-mg regimen resulted in a 2- to 4-log_{10} suppression until 96 h
- Comparison of the AUBKC indicated that the 600-mg regimen was superior to the 400-mg regimen (p <0.05)
- No emergence of resistance was noted with either regimen.

Conclusions

- The AUBKC simulating doses of 600 mg CPT plus 600 mg NXL demonstrated a superior antibacterial effect, compared with that of 400 mg CPT plus 600 mg NXL, against Enterobacteriaceae without β-lactamase, CTX-M producers, and AmpC hyperproducers.

References

1. Borgonovi M, Merdjan H, Girard AM, et al. Importance of NXL104 pharmacokinetics (PK) in the pharmacodynamics (PD) of ceftazidime+NXL104 combinations in an in vitro hollow fiber infection model. Presented at the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/ Infectious Diseases Society of America Annual Meeting; October 25-28, 2008; Washington, DC. Poster # A-023.
2. Drusano GL, Castanheira M, Liu W, et al. Pharmacodynamically-linked variable for the combination of ceftaroline plus novexel 104 (NXL104). Presented at the 19th Annual European Congress of Clinical Microbiology & Infectious Diseases; May 16-19, 2009; Helsinki, Finland. Poster #1461.
3. Drusano GL, Castanheira N, Liu W, et al. Optimal administration of ceftaroline (CPT) plus NXL104 (NXL) for cell kill and resistance suppression for *Enterobacter cloacae*. Presented at the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; September 12-15, 2009; San Francisco, CA. Poster #A-002.
4. Ge Y, Hubbel A. In vitro evaluation of plasma protein binding and metabolic stability of ceftaroline (PPI-0903M). Presented at the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; September 27-30, 2006; San Francisco, CA. Poster #A-1935.
5. Ge Y, Redman R, Floren L, et al. Single-dose pharmacokinetics (PK) of ceftaroline (PPI-0903) in healthy subjects. Presented at the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; September 27-30, 2006; San Francisco, CA. Poster #A-1936.

Acknowledgments

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