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Assessment of the In Vivo Activity of Human-Simulated Exposure of WCK 4282 (High Dose Cefepime [FEP]-Tazobactam [TZB]) against *Enterobacterales* (EB) and *Pseudomonas aeruginosa* (PA) in the Neutropenic Murine Thigh Infection Model

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ABSTRACT

Background: Carbapenems are often used for infections due to extended-spectrum-β-lactamase (ESBL) and cephalosporinase (CSase)-producers. As increased carbapenem utilization is associated with the development of carbapenem resistance, antimicrobial stewardship has targeted non-carbapenem options. WCK 4282 (FEP 2 g-TZB 2 g) offers pharmacodynamically optimized TZB exposure and demonstrated potent activity *in vitro* against ESBL-phenotype isolates. We describe the pharmacodynamics of a WCK 4282 human-simulated regimen (HSR) in the neutropenic murine thigh infection model.
Methods: 19 clinical strains harboring ESBLs/CSase (EB; n=8 and PA; n=4) or serine-carbapenemases (EB; KPC n=4 or OXA-48-like n=3) were tested in vivo. Per CLSI, 19, 18, and 17 isolates were cefepime, ceftolozane/tazobactam, and piperacillin/tazobactam (TZP) non-susceptible, respectively. Thighs of neutropenic, female, CD-1 mice (3 per group) were inoculated with ~10^7 CFU/mL of bacterial suspension 2 h prior to dosing. Mice received WCK 4282 HSR, FEP HSR, or saline (controls) for 24 h. WCK 4282 HSR and FEP HSR provided plasma exposures in mice that were similar in *f*%T>MIC and *f*AUC to FEP-TZB 2 g-2 g and FEP 2 g, respectively, as IV infusions over 1.5 h q8h in humans. Bacterial densities and their changes at 24 h relative to 0 h controls were determined to assess efficacy and reported as mean±SD $\log_{10}$ CFU/thigh.
Results: Bacterial burdens were 5.81±0.36 at 0 h and 9.29±0.88 at 24 h in untreated controls. WCK 4282 produced potent activity against ESBL/CSase producing EB and PA with WCK 4282 MIC≤16 mg/L; mean change in $\log_{10}$ CFU from 0 h was -1.70±0.77, while growth was observed with FEP alone. WCK 4282 produced variable activity against OXA-48-like harboring EB. Against KPC-harboring EB, WCK 4282 produced stasis to growth. Mean $\log_{10}$ CFU changes are reported in Table 1 and Figure 1.
Conclusion: WCK 4282, a novel TZB containing regimen, resulted in enhance in vitro potency against ESBL/CSase and OXA-48-like producers. Humanized exposures of WCK 4282 produced substantial kill in vivo against ESBL/CSase producers with MICs ≤ 16 mg/L including FEP resistant/TZP non-susceptible PA. These data support further evaluations of WCK 4282 as a carbapenem-sparing regimen for ESBL/cephalosporinase harboring strains.

BACKGROUND

- WCK 4282 is the pharmacodynamically enhanced combination of cefepime and tazobactam administered as 2g - 2g IV every 8 hours as a 1.5 hour (h) infusion.
- WCK 4282 has potent *in vitro* activity against *Enterobacterales* including ESBL-harboring strains.[1]
- The efficacy of human-simulated WCK 4282 exposure was studied in the murine thigh infection model to evaluate the *in vivo* efficacy against EBSL/cephalosporinase-harboring *Enterobacterales* and *P. aeruginosa* as well as serine carbapenemase producing *Enterobacterales.*

METHODS

Antibiotic Compounds

- Commercially available cefepime and analytical grade tazobactam were reconstituted with 0.9% sodium chloride (NS) or phosphate buffer, respectively.
- All antibiotics were administered as separate subcutaneous injections of 0.1 mL.

Bacterial Isolates

- 19 clinical isolates of serine β-lactamase harboring *Enterobacterales* and *P. aeruginosa* with previously determined MIC were studied (**Table 1**).
- Per CLSI interpretation, 19, 18, and 17 isolates were cefepime, ceftolozane/tazobactam, and piperacillin/tazobactam (TZP) non-susceptible, respectively.

Neutropenic Murine Thigh Model

- Female CD-1 mice (mean weight 20-22 g) were used in the model.
- Neutropenia was induced with cyclophosphamide 150 mg/kg on day -4 and 100 mg/kg on day -1.
- Uranyl nitrate 5 mg/kg was given on day -3 to include a predictable level of renal dysfunction of study compounds to aid in humanizing antimicrobial exposures.
- Mice were inoculated 2 hours prior to study drug administration via intramuscular injection of ~10^7 CFU/mL of bacterial suspension.
- Euthanasia was performed via CO_2 inhalation and ultimately cervical dislocation.

Plasma Pharmacokinetic Studies

- Mice were pre-treated and infected as outline above.
- Blood was collected via cardiac puncture and centrifuged to separate plasma.
- Cefepime and tazobactam plasma concentrations were measured with LC-MS/MS.
- WCK 4282 HSR and cefepime HSR provided plasma exposures in mice that were similar in *f*%T>MIC and *f*AUC to cefepime/tazobactam 2g-2g and cefepime 2g, respectively, as IV infusions over 1.5 h q8h in humans.
- Dosing regimens simulating human plasma exposures were determined and confirmed for cefepime as monotherapy and WCK 4282 combination using immumocompromised, infected mice.

In Vivo Efficacy Studies

- For each isolate, 4 groups of 3 mice were utilized.
- Control groups were sacrificed at 0 h and 24 h.
- Treatment groups received human-simulated regimens of either cefepime alone or in combination with tazobactam (WCK 4282) for 24 h.
- Both thighs were aseptically harvested, homogenized in NS, and serially diluted before plating to measure bacterial burdens.
- Efficacy was evaluated as $\log_{10}$ change in cfu/thigh at 24 h compared with 0 h controls.

Table 1. Characteristics of studied *Enterobacterales* and *P. aeruginosa* isolates. Modal MICs are reported (mg/L).

Isolate #	FEP	WCK 4282	TZP	C/T	IPM	β-lactamases Encoded
EC 728	64	16	>128	>128	1	CMY, TEM, PBP3 insert
EC 731	>128	8	>128	64	0.5	TEM, PBP3 insert
EC 732	>128	8	>128	64	0.12	CTX-M Gr-1/2, PBP3 insert
EC 736	32	16	>128	128	0.125	CMY, PBP3 insert
EC 737	>128	8	>128	>128	0.25	CMY, TEM
EC 739	>128	4	64	32	0.5	MIR-1/ACT-1, DHA-1/DHA-2, CTX-M GR-1
EC 740	>128	8	>128	64	0.25	CMY, TEM
EC 741	>128	4	>128	32	0.25	Not determined
PSA 1880	16	16	128	2	2	AmpC, CTX-M Gr-1/2
PSA 1881	>128	16	16	>128	1	AmpC, VEB
PSA 1882	>128	16	16	>128	16	AmpC, VEB, CTX-M, OXA-1, OXA-2
PSA 1884	64	16	32	>128	4	AmpC, OXA-1, CTX-M
EA 59	16	16	>128	16	32	KPC, TEM
KP 906	32	32	>128	128	16	KPC, SHV, TEM
KP 909	32	16	>128	128	16	KPC-3, SHV, TEM
KP 910	32	16	>128	>128	16	KPC, SHV, TEM
EC 734	>128	8	>128	128	1	OXA-48/181, TEM, PBP3 insert
KP 908	128	16	>128	>128	8	OXA-181, CTXM Gr-1, CMY, SHV
KP 911	64	16	>128	128	8	OXA-181, CMY, SHV, TEM, CTXM Gr-1

FEP = cefepime; WCK 4282 = cefepime/tazobactam; TZP = piperacillin/tazobactam; C/T =ceftolozane/tazobactam; IPM = imipenem

RESULTS

Figure 1. Observed concentrations of cefepime and tazobactam in murine plasma versus predicted murine plasma profiles and predicted human plasma profiles for (a) cefepime (with and without tazobactam) and (b) tazobactam (in combination with cefepime).

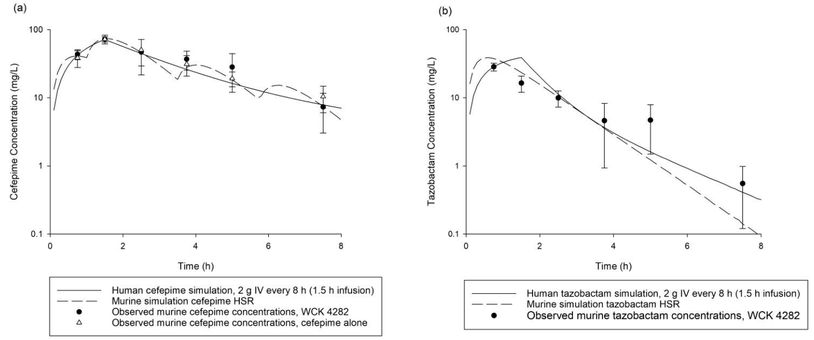
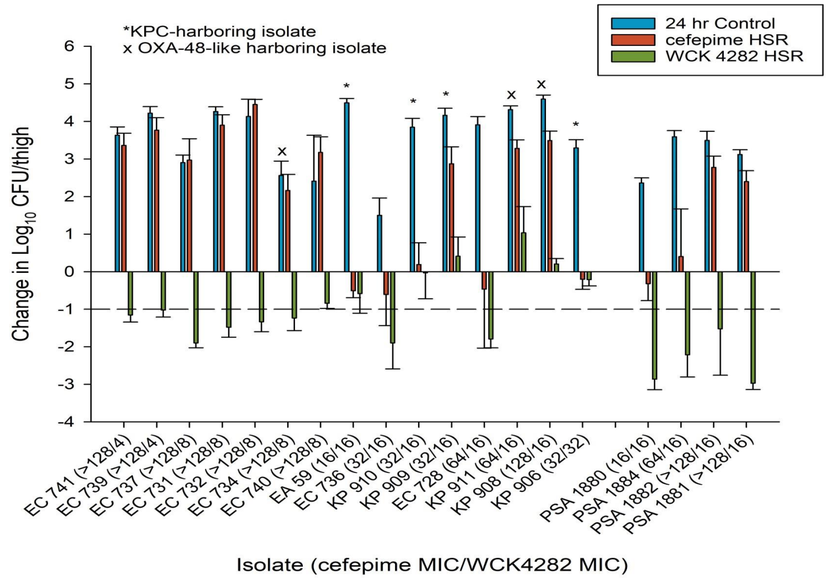


Figure 2. *In vivo* change in $\log_{10}$ cfu/thigh from 0 h controls after 24 h of treatment with saline placebo, human-simulated regimens (HSR) of cefepime or WCK 4282. Data represent means ± SD.



CONCLUSIONS

- **Against ESBL and cephalosporinase harboring- *E. coli* and *P. aeruginosa* (including TZP and C/T-non-susceptible strains) with WCK 4282 MICs ≤16 mg/L, human-simulated plasma exposure of WCK 4282 resulted in substantial bacterial killing.**
- **A 1-$\log_{10}$ bacterial kill threshold was met for 11/12 ESBL/cephalosporinase harboring isolates tested in the murine thigh model predictive of clinical efficacy in severe infections.**
- **WCK 4282 produced variable activity against carbapenemase harboring strains including 1/3 OXA-48-like harboring strains reaching 1-$\log_{10}$ bacterial kill warranting further investigation.**
- **These data support the further development of WCK 4282 as a carbapenem-sparing agent for the treatment of infections with ESBL/cephalosporinase- harboring strains.**

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1. *J Antimicrob Chemother* 2018;73:126-33.

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