Poster T-04

The Exposure-Response Relationship of Enmetazobactam, Combined with Cefepime, is Best Described by *f*T > C_T in a Murine Thigh Infection Model

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Abstract

Background Third-generation cephalosporin (3GC)-resistant Enterobacteriaceae are categorized as critical priority pathogens, with extended-spectrum beta-lactamases (ESBLs) as main resistance determinants. Enmetazobactam (EMT, formerly AAI101) is a novel ESBL inhibitor developed in combination with cefepime (FEP) targeting 3GC-resistant Enterobacteriaceae as an empiric carbapenem sparing option. Here, the PK-PD index of EMT was assessed in a murine thigh infection model.

Methods A FEP-resistant CTX-M-15-producing isolate of *K. pneumoniae* was used in a 26 h neutropenic mouse thigh infection model. EMT was administered in a matrix design of fractionated total dosages of 6, 20, 60, 200 and 600 mg/kg given q4h, q8h, q12h, and q24h. FEP was concomitantly administered at 100 mg/kg q4h. Terminal bioburden was quantified 26 h post infection. PK parameters of EMT were determined in infected animals and exposures from simulated PK profiles expressed as the fraction of free drug above a threshold concentration *f*T > C_T, free-drug area under the concentration-time profile *f*AUC/C_T, and free-drug maximum concentration *f*C_{max}/C_T, where C_T was fixed at 2 µg/ml.

Results Increasing the fractionation of EMT was associated with greater reductions in bioburden for all total doses tested. The exposure-response (E-R) relationship determined by regression analysis was best described by *f*T > C_T, followed by *f*AUC/C_T, and *f*C_{max}/C_T when applying the standard error of the regression (S) as a goodness-of-fit measure.

Conclusion The PK-PD index for EMT in the neutropenic mouse thigh infection model, in combination with FEP, is *f*T > C_T. These findings corroborate previous studies in a hollow-fibre infection model.

Background

- 3GC-resistant Enterobacteriaceae are categorized as critical priority pathogens (1). Main resistance determinants for 3GC-resistance are ESBLs, including CTX-M, SHV and TEM (2).
- ESBLs increased significantly in clinical isolates of Enterobacteriaceae over the past years and mainstay empiric therapies, including piperacillin-tazobactam, are losing efficacy (3).
- Carbapenems are now recommended as definitive therapy for infections caused by ESBL-producing Enterobacteriaceae (4). Widespread carbapenem consumption, however, promotes the selection of carbapenem resistance, and carbapenem resistance is associated with increased mortality and length of hospital stay (3, 5).
- Enmetazobactam is a novel extended-spectrum beta-lactamase inhibitor with a mechanism of action that differs from tazobactam (6). Cefepime-enmetazobactam is intended as an empiric carbapenem-sparing option in settings where ESBL-producing Enterobacteriaceae are prevalent.
- The safety and efficacy of cefepime 2 g-enmetazobactam 0.5 g vs piperacillin 4 g-tazobactam 0.5 g administered every 8 h as 2 h iv infusion is currently being investigated in a randomized, double-blind, non-inferiority Ph3 study in adults with cUTI or AP.
- The objective of this study was to determine the PK-PD index of enmetazobactam, when combined with cefepime, in a neutropenic mouse thigh model infected with a clinical ESBL-producing isolate of *K. pneumoniae*.

Methods

Susceptibility testing Cefepime-enmetazobactam MICs were determined in quintuplicate by broth microdilution following CLSI guidelines with enmetazobactam fixed at 8 µg/ml.

PK sampling and simulations Cefepime-enmetazobactam was administered to infected animals. Blood samples were collected in triplicate and analyzed by LC-MS/MS. Pooled observations were fitted to a linear, two-compartmental model.

Neutropenic murine thigh infection model Thighs of immunocompromised mice were infected intramuscularly. Treatment was initiated 2 h post-infection by intravenous injection. Animals of pre-treatment groups were euthanized 2 h post infection and animals of treatment groups 26 h post infection. Colony forming units were converted to the $\log_{10}$ of the group geometric mean and the terminal bioburden was expressed as the difference between pre-treatment and treatment groups ($\Delta\log_{10}$(CFU/g)).

Exposure-response modelling The terminal bioburden as $\Delta\log_{10}$(CFU/g) was modelled as a function of enmetazobactam exposure (*f*Ex) expressed as *f*T > C_T, *f*AUC / C_T, or *f*C_{max} / C_T by fitting a sigmoid curve to the equation:

$$\Delta log_{10}(CFU/g) = -E_{min} + (E_{max} - E_{min})\frac{f\mathrm{Ex}^{\gamma}}{f\mathrm{Ex}^{\gamma} + \mathrm{EC}_{50}{}^{\gamma}}$$

Results

Table 1. Susceptibility of the *K. pneumoniae* isolate used in this study

Identifier	beta-lactamase	MIC (µg/ml)			
		FEP	FEP-EMT(8)	MEM	PTZ
#1077711	CTX-M-15	>32	1	4	>128

Table 2. Estimates of enmetazobactam and cefepime two-compartment PK model parameters from mice infected with *K. pneumoniae* isolate #1077711.

Parameters	Estimates	
	Enmetazobactam	Cefepime
V1 [ml]	11	13
V2 [ml]	13	3.2
Cl [ml/h]	41	41
Q [ml/h]	8.2	0.9

V1, central volume; V2 peripheral volume; Cl, clearance; Q, intercompartmental exchange factor

Table 3. Terminal bioburden in a 26 h murine thigh infection model challenged with *K. pneumoniae* isolate #1077711 following dose fractionation of different total enmetazobactam doses combined with a fixed dose of cefepime.

Total daily dose (mg/kg/day)		Bioburden as $\Delta\log_{10}$(CFU/g)			
		EMT/FEP dosing frequency (h)			
EMT	FEP	q4/q4	q8/q4	q12/q4	q24/q4
0	0	2.3			
0	600	1.9			
6	600	0.3	1.3	0.8	1.1
20	600	0	0.6	0.9	1.9
60	600	-1.1	0.3	0.7	0.9
200	600	-1.5	-0.8	-0.5	0.6
600	600	-2.3	-1.1	-2.2	-0.4

$\Delta\log_{10}$(CFU/g) = bioburden as $\log_{10}$(CFU/g) difference between the pre-treatment group and treatment groups.

Figure 1. Predicted vs observed plots of enmetazobactam and cefepime two-compartment PK models

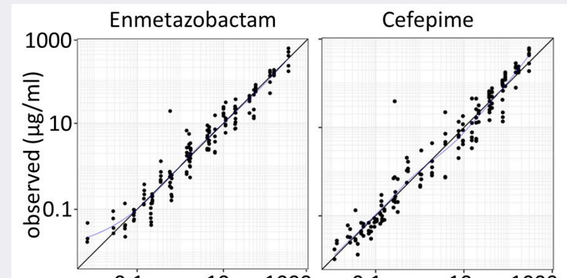
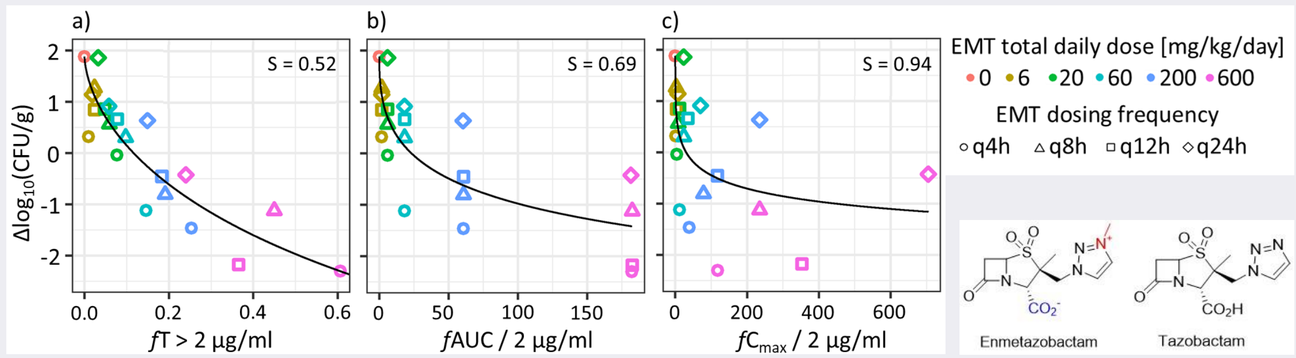


Figure 2. Simulated enmetazobactam exposure-response relationship in a 26 h murine thigh infection model challenged with *K. pneumoniae* isolate #1077711 following dose fractionation of enmetazobactam combined with a fixed dose of cefepime. Y-axes show the bioburden difference between pre-treatment and treatment groups. X-axes show enmetazobactam exposures as (a) *f*T > C_T, (b) *f*AUC/C_T, and (c) *f*C_{max}/C_T with C_T = 2 µg/ml. S, standard error of regression.



Summary

- **Enmetazobactam restored the *in vitro* activity and the *in vivo* efficacy of cefepime against the CTX-M-15 producing *K. pneumoniae* isolate #10777111 (Table 1 and Table 3).**
- **Enmetazobactam and cefepime PK in infected mice were both adequately described by a linear, two-compartment model (Figure 1 and Table 2).**
- **Increasing the total daily dose of enmetazobactam was associated with greater reductions in bioburden for different dosing intervals, and increasing the enmetazobactam dosing frequency was also associated with greater reductions in bioburden for different total daily enmetazobactam doses (Figure 2 and Table 3).**
- **The PK-PD relationship of enmetazobactam was best described by *f*T > C_T µg/ml. These findings corroborate previous studies in a hollow-fibre infection model (7).**

References

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