A-1029 Pharmacodynamics of ceftolozane/tazobactam against Gram-negative bacilli

AR Noel, KE Bowker, ST Tomaselli, A P MacGowan,

BCARE, Department of Microbiology, North Bristol NHS Trust, Bristol, UK.

alan.noel@nbt.nhs.uk

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Introduction

➢Ceftolozane (TOL) (formerly CXA101, FR264205) is a parenteral cephalosporin currently being developed for cUTI and IAI.

➢TOL is 4-8 times more potent in vitro against *P. aeruginosa* than ceftazidime and is 8-32 fold more potent than ceftazidime against imipenem or ciprofloxacin resistant isolates.

➢TOL has wide activity in vitro against Enterobacteriaceae but poor activity against ESBL producing strains and KPC producing *Klebsiella pneumoniae.*

➢Addition of 4mg/L tazobactam (TAZ) in vitro produces marginal improvement in TOLs activity against *P.aeruginosa* but significantly reduces TOL MICs for ESBL producing *E.coli*, *K.pneumoniae* and *Proteus* spp.

➢In Phase I studies TOL had linear pharmacokinetics in the range 250-2000mg. After 1000mg the Cmax is 58mg (1hr), AUC0-∞ 52mg/L.h, t½ 2.3h Protein binding (pb) is about 20%.

➢TAZ 500mg in combination with TOL has a Cmax of 20-25mg/L, AUC0-α 20-25mg/L, t½ 0.67h, pb 23%.

➢The pK profile from this 2:1 mg:mg ratio produces a TOL/TAZ concentration ratio of 2.94:1

➢T>MIC is the dominant PD index for TOL, T>MIC for static effect at 24h are 26± 2% for Enterobacteriaceae and 24±3% for *P.aeruginosa*.

➢There is no published PD data on the combination of TOL plus TAZ.

➢**The objectives of this study were -**

1.Develop an in vitro pK model capable of simultaneously producing human like free drug serum pK profiles for TOL and TAZ.

2.Compare the TOL-TAZ exposure response relationships in terms of T>MIC against a range of Gm-negative aerobes with and without ESBL and other β.lactamase production.

Table: MIC and %fT>MIC for each strain tested

Strain	Agent(s) tested	MIC (mg/L) TOL	MIC (mg/L) TOL plus 4mg/L TAZ	%fT>MIC at 24h for Static effect	-1 log drop	-2 log drop	-3 log drop
E.coli 10909/NIHJ	TOL	0.12	0.12	21.5	25.2	28.5	32.8
	TOL+TAZ (2:1)		0.12	23.5	25.5	28.2	30.5
E.coli 44913	TOL	0.06	0.12	49.1	50.1	50.5	51.0
	TOL+TAZ (2:1)		0.12	49.6	50.1	50.2	50.9
P.aeruginosa 38475	TOL+TAZ (2:1)	0.5	0.5	24.8	30.9	37.6	45.8
	doripenem	0.24*		37.0	42.0	48.0	62.0
E.coli 47204	TOL+TAZ (2:1)	4.0	0.19	81.9	93.1	>100	>100
	TOL+TAZ (4mg/L CI)		0.19	26.2	34.2	43.6	63.8
	TOL+TAZ (hp)		0.19	21.4	30.1	40.1	58.5

Materials and methods

➢A dilutional *in vitro* pK model was used to simulate a range of *f*T>MIC serum concentrations (0–100%) of TOL based on the pK of 1000 mg q8h TOL plus 500mg TAZ dosing in humans. The initial Cmax for TOL was varied to produce the T>MIC required for each individual model; the TAZ was modelled as a 2.94:1 concentration ratio.

➢Due to the difference in half-lives between TOL and TAZ (2.5h and 1h respectively), the model was supplemented with TOL throughout each dosing period via a separate dosing chamber to achieve the required profile.

➢Three strains of *E.coli* (44913 Ampicillin resistant; 10909NIHJ fully susceptible and 47204 (CTX-M producer) and one strain of *P.aeruginosa* 38475 were used (no TOL resistance mechanisms). The inoculum was 10^6 CFU/mL.

➢Antibacterial effect (ABE) was measured by log change in viable count at 24h, 48h, 72h and 96h relative to the starting inocula (log CFU/mL).

➢A sigmoid Emax model was used to relate T>MIC with ABE using the Boltzmann equation using Graph Pad Prism™.

Results

➢The pK profiles of 1000mg TOL and 500mg TAZ free drug concentrations are shown on Figure 1.

➢Against *E.coli* strain 10909/NIHJ (Figure 2, 3, Table) *E.coli* strain 44913 (Figure 4, 5, Table) and *P.aeruginosa* strain 38475 (Table) the fT>MIC for 24h bacteriostatic and cidal effects were unchanged by the co-modelling of TOL plus TAZ compared to TOL alone.

➢For *E.coli* 10909/NIHJ the fT>MIC for 24h static effect was 21.5-23.5% and for *E.coli* 44913 49.1-49.6%.

➢For *P.aeruginosa* 38475 the fT>MIC for static effect was 24.8%, markedly lower than the value we previously reported for doripenem. *E.coli* 47204 CTX-M producer had a fT>MIC for static effect of 26.2% in the presence of 4mg/L TAZ given by continuous infusion and 21.4% when average human serum pK associated with 500mg TDS were simulated (Figure 6, 7, Table).

➢When TOL plus TAZ was modelled as a 2.94:1 concentration ratio the T>MIC values were much greater presumably related to the suboptimal amounts of inhibitor present (Figure 8, Table).

Figure 1: CXA -101 and tazobactam meaned measured concentrations (human dose)

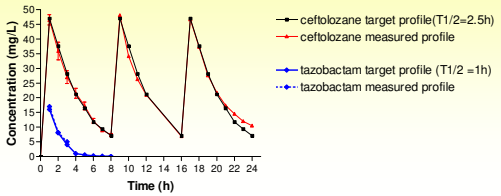


Figure 2:Relationship between ceftolozane alone and fT>MIC for *E.coli* 10909/NIHJ (no resistance mechanism)

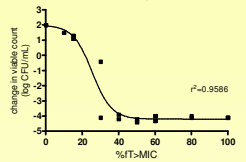


Figure 3: Relationship between ceftolozane and fT>MIC for E.coli 10909/NIHJ (no resistance mechanism)

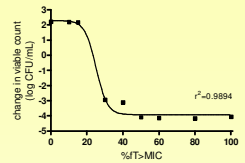


Figure 4: Relationship between ceftolozane alone and fT>MIC for *E.coli* 44913 (ampicillin -R)

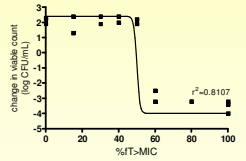


Figure 5: Relationship between ceftolozane plus tazobactam and fT>MIC for E.coli 44913 (ampicillin -R)

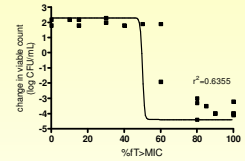


Figure 6: Relationship between ceftolozane plus tazobactam continuous infusion (4mg/L) and fT>MIC for E.coli 47204 (CTX-M)

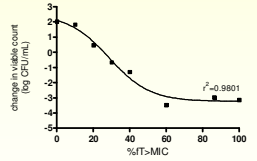


Figure 7: Relationship between ceftolozane plus tazobactam (human serum simulation) TDS for *E.coli* 47204 (CTX-M)

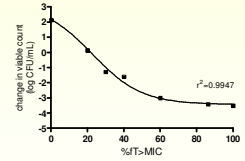
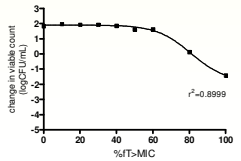


Figure 8: Relationship between ceftolozane plus tazobactam concentration ratio 2.94:1 and fT>MIC for *E.coli* 47204 (CTX-M)



Conclusions

➢The combination of TOL plus TAZ pK could be successfully modelled in an in vitro pK model.

➢The fT>MIC for a bacteriostatic effect at 24h was 21.5-23.5% for *E.coli* 10909/NIHJ – similar to the values observed in an animal model.

➢The fT>MIC for an ESBL producing *E.coli* strain was 21.4-26.4% providing sufficient TAZ was present in dose ranging experiments.

➢The fT>MIC for 24h static effect for *P.aeruginosa* strain compares favourably with the historical fT>MIC for doripenem against the same strain.

Acknowledgement

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