A- 506 Comparison of the Antibacterial Effects of Two Dosing Regimens of Ceftolozane (TOL) in Combination with Tazobactam (TAZ) against Enterobacteriaceae

KE Bowker, AR Noel, MLG Attwood, ST Tomaselli, AP MacGowan,
BCARE, Department of Microbiology, North Bristol NHS Trust, Bristol, UK.
karen.bowker@nbt.nhs.uk

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Abstract

Introduction:
TOL/TAZ is an anti-pseudomonal cephalosporin combined with the ß.lactamase inhibitor - tazobactam. The addition of tazobactam protects ceftolozane from hydrolysis by a range of clinically important ß.lactamases and broadens coverage to include most ESBL producing Enterobacteriaceae. Optimal doses of TOL/TAZ to prevent resistance are uncertain. We used an *in vitro* pharmacokinetic model (IVPKM) to simulate 2 human dose regimens and measured their effect on 3 strains of Enterobacteriaceae and potential emergence of resistance (EoR) over 7 days. **Methods:** A one compartment IVPKM was used to simulate free drug serum concentrations associated with 1G TOL/0.5G TAZ (Cmax 46.4/16.0mg/L) and 2G TOL/1G TAZ (Cmax 89.6mg/L/25.6mg/L) TOL t½ 2.5hr, TAZ t½ 1hr. Dosing was q8hrly for 7d (168 h). Three strains were used: a wild type (Amp S) *E. coli* (MIC 0.25mg/L), two CTX-M 15 producing *E.coli* (MIC both 0.25mg/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). EoR was assessed by growth on nutrient agar plates containing x2, x4, x8 TOL/TAZ MIC 24hrly over 7days. **Results:** Both regimens produced a >4 log reduction in viable count (below the limit of detection) by 4h for the WT strain; for the CTXM producers a >4log drop was noted at 12h for 1G/0.5G TOL/TAZ and by 8h for the 2G TOL/1G TAZ regimen. Growth remained suppressed through day 7 by both regimens. No difference was observed between the regimens using AUBKC24 or AUBKC168 (p=>0.05). No EoR was detected with either regimen at any time point for any of the 3 organisms. **Conclusions**: For wild type and ESBL producing strains TOL/TAZ was effective in reducing bacterial load >/= 4 log whether given 1G/0.5G or 2G/1G 8hrly over 7d. There was no EoR.

Introduction

- TOL/TAZ is an anti-pseudomonal cephalosporin combined with the ß.lactamase inhibitor - tazobactam.
- The addition of 4mg/L TAZ protects TOL from hydrolysis by a range of clinically important ß.lactamases and broadens coverage to include most ESBL producing Enterobacteriaceae.
- Optimal doses of TOL/TAZ to prevent resistance are uncertain.
- We used an *in vitro* pharmacokinetic model (IVPKM) to simulate 2 human dose regimens and measured their effect on 3 strains of Enterobacteriaceae and potential emergence of resistance (EoR) over 7 days.

Materials and methods

- A dilutional one compartment IVPKM using 50% MHB was used to simulate free drug serum concentrations associated with 1G TOL/0.5G TAZ (Cmax 46.4/16.0mg/L) and 2G TOL/1G TAZ; (Cmax 89.6/25.6mg/L) TOL t½ 2.5hr, TAZ t½ 1hr, Tmax 1h; dosing was q8hrly for 7d (168 h).
- 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.
- Concentrations of TOL and TAZ were confirmed by HPLC throughout 0-24h.

Materials and methods

- Three strains were used: a wild type (Amp S) *E. coli* SMH 44913 (TOL/TAZ MIC 0.25mg/L), two CTX-M 15 producing *E.coli* (TOL/TAZ MICs both 0.25mg/L) SMH 47202 (hyper producer) and SMH 49439 (moderate producer).
- The inoculum was 10^6 CFU/ml and simulations and MICs were performed in triplicate.
- Antibacterial effect (ABE) was measured by log change in viable count relative to the starting inoculum and the area-under-the-bacterial-kill-curve (AUBKC) at time 24h, 48h, 72h and 168h. Comparison of the AUBKC was performed using the Mann Whitney test.
- Emergence of resistance (EoR) was assessed by growth on nutrient agar plates containing x2, x4, x8 TOL/TAZ MIC 24hrly over 7days at 0h, 24, 48, 72, 96, 120, 144 and 168h.

Results

- The predicted and observed pk profiles of 1G TOL and 2G TOL and, 0.5G and 1G TAZ free drug concentrations are shown on Figures 1 and 2.
- Figures 3a-c show the ABE of 1G TOL/0.5G TAZ and 2G TOL/1G TAZ over 168h.
- Both regimens produced a >4 log reduction in viable count (below the limit of detection) by 4h for the WT strain; for the CTXM producers a >4log drop was noted at 12h for 1G/0.5G TOL/TAZ and by 8h for the 2G TOL/1G TAZ regimen.

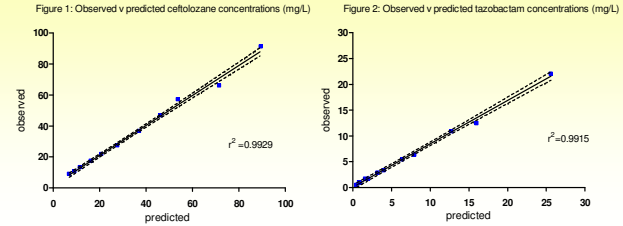
Table 1: the ABE of TOL (1G) and TAZ (0.5G)

1G/0.5G	log reduction in viable count at -				AUBKC 0-24	AUBKC 0-168
	12h	24h	72h	168h		
44913	4.24 ± 0.063	4.24 ± 0.063	4.24 ± 0.063	4.24 ± 0.063	14.86 ± 9.08	14.86 ± 9.08
49439	4.14 ± 0.062	4.14 ± 0.062	4.14 ± 0.062	4.14 ± 0.062	39.41 ± 4.33	39.41 ± 4.33
47202	4.25 ± 0.014	4.25 ± 0.014	4.25 ± 0.014	4.03 ± 0.37	51.61 ± 10.56	105.5 ± 85.5

Table 2: The ABE of TOL (2G) and TAZ (1G)

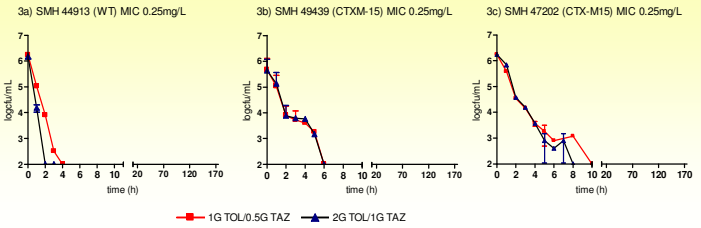
2G/1G	log reduction in viable count at -				AUBKC 0-24	AUBKC 0-168
	12h	24h	72h	168h		
44913	4.24 ± 0.063	4.24 ± 0.063	4.24 ± 0.063	4.24 ± 0.063	14.86 ± 9.08	14.86 ± 9.08
49439	4.16 ± 0.035	4.16 ± 0.035	4.16 ± 0.035	4.16 ± 0.035	42.16 ± 0.34	39.41 ± 4.3
47202	4.25 ± 0.014	4.25 ± 0.014	3.92 ± 0.56	4.25 ± 0.014	53.99 ± 3.95	110.7 ± 99.9

Figures 1 and 2 predicted and observed TOL and TAZ concentrations



- Growth remained suppressed through day 7 by both regimens for strains 49439 and 44913; strain 47202 (CTXM-15 hyper producer) showed a 2log regrowth on 1/3 occasions at 144 and 168h with the 1G/0.5G TOL/TAZ dose however no change in population profile was detected
- Similarly with the 2G TOL/1G TAZ regimen a 2-3log regrowth was seen at 72h and 96h in 1/3 experiments but was below the limit of detection at 120h; however at 96h growth ($3\log_{10}$) was observed in 1/3 experiments on MIC x8 plates but not thereafter.
- No statistical difference was observed between the regimens using AUBKC24 or AUBKC168 (p=>0.05).

Figures 3a-c : Comparison of the ABE of 1G/0.5G TOL/TAZ and 2G TOL/1G TAZ regimens.



Conclusions

- For wild type and ESBL producing strains TOL/TAZ was effective in reducing bacterial load >/= 4 log whether given 1G/0.5G or 2G/1G 8hrly over 7d.
- Both regimens suppressed emergence of resistance in 5/6 experiments.

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