P510 The Antibacterial Effects (ABE) of Two Dosing Regimens of Ceftolozane (TOL) in Combination with Tazobactam (TAZ) in comparison with meropenem (MER) against *Pseudomonas aeruginosa* (PA)

ASM MICROBE, Boston, 16-20th June, 2016

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Amended Abstract

Background:
TOL/TAZ is an anti-pseudomonal cephalosporin (TOL) combined with a B.lactamase inhibitor (TAZ). TOL has marked in vitro potency against PA being active against many multi-drug resistant and extensively drug resistant strains. With anti-pseudomonal antibiotics, emergence of resistance (EoR) is a significant issue, hence it is important to optimise dosing regimens to limit this risk. We used an in vitro pharmacokinetic model (IVPKM) to simulate two human dose regimens of TOL/TAZ and measured their effect on 3 strains of PA and potential EoR over 7 day exposure.

Methods:
A one compartment IVPKM was used to simulate free drug serum concentrations associated with 1G TOL/0.5GTAZ (Cmax 58/16mg/L) and 2G TOL/IG TAZ (Cmax 112/32); TOL t½ 2.5h, TAZ t½ 1h. Dosing was q8hly for 7d (168h). MER 2G (Cmax 100mg/L); t½ 1h was also simulated. 3 strains of PA were used, one wild type strain, one with AmpC hyper-expression and the other with a MER MIC 6mg/L: TOL/TAZ MICs were 0.5, 1 and 2mg/L. The inoculum was 10^6 CFU/ml and simulations were performed in triplicate. ABE was measured by log change in viable count and area-under-the-bacterial-kill-curve (AUBKC) over 168h. EoR was assessed by growth on nutrient agar plates containing x2, x4 MIC of the test antibiotic 24hly over 7 days.

Results:
Both TOL/TAZ regimens produced a >4 log reduction in viable count (below the limit of detection) by 12h for all three PA strains. Some regrowth occurred with all three strains after 24h with the TOL/TAZ 1G/0.5G regimen resulting in a log drop of 0-1 log at 168h. Regrowth also occurred with all three strains with the 2G/1G regimen after 48h with a 1-2 log drop at 168h. The 1G/0.5G was less effective at producing pathogen clearance than the 2G/1G regimen against all strains (AUBKC 168h 1G/0.5G 320±90; 2G/1G 172±117 log CFU/mL.h $p<0.01$). MER 2G q8h was less effective than either TOL/TAZ regimen (ANOVA $p<0.01$). EOR on MICx2 plates was only present with MER from 96h and did not occur with either TOL/TAZ regimen.

Conclusions:
TOL/TAZ was effective at reducing PA bacterial load. The 2G/1G regimen was more effective than 1G/0.5G.
Both TOL/TAZ regimens were more effective than MER 2G in reducing bacterial load and preventing EoR.

Introduction

- TOL/TAZ is an anti-pseudomonal cephalosporin (TOL) combined with a B.lactamase inhibitor (TAZ). TOL has marked in vitro potency against PA being active against many multi-drug resistant and extensively drug resistant strains.
- With anti-pseudomonal antibiotics, emergence of resistance (EoR) is a significant issue, hence it is important to optimise dosing regimens to limit this risk.
- We used an in vitro pharmacokinetic model (IVPKM) to simulate two human dose regimens of TOL/TAZ and measured their effect on 3 strains of PA and potential EOR compared to MER over 7 days exposure.

Materials and methods

- A one compartment IVPKM was used to simulate free drug serum concentrations associated with 1G TOL/0.5TAZ (Cmax 58/16mg/L) and 2G TOL/IG TAZ (Cmax 112/32mg/L); TOL t½ 2.5h, TAZ t½ 1h and MER 2G (Cmax 100mg/L); t½ 1h,
- Dosing was q8hly for 7d (168h).
- 3 strains of PA were used; wild type strain (SMH 38475), AmpC hyper-expression (SMH 47237), meropenem isogenic mutant MIC 6mg/L (SMH 17286).
- The inoculum was 10^6 CFU/ml and simulations were performed in triplicate.
- ABE was measured by log change in viable count and area-under-the-bacterial-kill-curve (AUBKC) over 168h. Changes in population analysis profile as measured by EoR was assessed by growth on nutrient agar plates containing x2, x4 MIC of the test antibiotic 24hly over 7 days.

Results

- Comparison of the ABE for the 3 regimens using log reduction in viable count and AUBKC are shown on Tables 1 and 2 and Figure 1. For all 3 strains there was a rapid reduction in count by 6h, however regrowth occurred after 24h.
- Statistical comparison using AUBKC as the ABE measure showed the 2G/1G TOL/TAZ regimen was significantly smaller than the other two regimens (ANOVA $p<0.05$) at 168h.
- No EoR was noted with either TOL/TAZ regimen on x2MIC plates at 168h however EoR was seen with MER with all 3 strains (Table 3). EoR was seen on x4 MER MIC plates on 1/3 occasions for strain PA 38475.

Table 1: Comparison of the ABE of TOL/TAZ (2/1G and 1/0.5G) and MER 2G

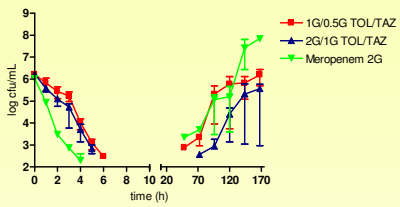
			log reduction in viable count (cfu/mL) at -			
			Ceftolozane/Tazobactam (1G/0.5G)			
strain	Resistance mechanism	MIC (mg/L)	24h	48h	72h	168h
PA 38475	none	1	3.36 ± 0.51	3.38 ± 0.94	3.0 ± 0.87	2.07 ± 2.07
PA 17286	MER isogenic mutant	0.5	2.89 ± 0.63	2.64 ± 0.62	2.18 ± 0.31	0.09 ± 0.36
PA 47237	AmpC hyper expression	2	3.10 ± 0.06	2.70 ± 0.42	1.73 ± 0.20	0.37 ± 0.84
			Ceftolozane/Tazobactam (2G/1G)			
		MIC (mg/L)	24h	48h	72h	168h
PA 38475	none	1	3.94 ± 0.01	2.85 ± 0.37	1.98 ± 0.43	0.02 ± 0.08
PA 17286	MER isogenic mutant	0.5	4.23 ± 0.03	4.23 ± 0.03	3.91 ± 0.54	1.42 ± 1.60
PA 47237	AmpC hyper expression	2	4.14 ± 0.02	4.14 ± 0.02	3.30 ± 0.01	1.77 ± 1.40
			Meropenem 2G			
		MIC (mg/L)	24h	48h	72h	168h
PA 38475	none	1	3.62 ± 0.43	3.51 ± 0.59	3.52 ± 0.58	2.60 ± 0.76
PA 17286	MER isogenic mutant	6	4.03 ± 0.02	3.27 ± 0.79	3.17*	+1.82 ± 0.43
PA 47237	AmpC hyper expression	1	3.14 ± 0.45	2.84 ± 0.82	2.56* 0.24	0.29 ± 0.10

Table 2: Comparison of the AUBKC for TOL/TAZ (2/1G and 1/0.5G) and MER 2G

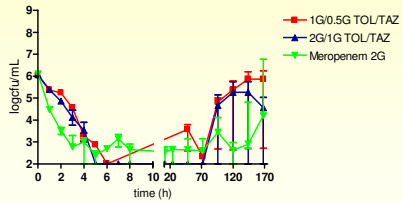
		AUBKC at -		
	Regimen	24h	72h	168h
PA 17286	TOL/TAZ (1G/0.5G)	17.15 ± 2.81	51.72 ± 21.83	348.40 ± 42.84
PA 38475	TOL/TAZ (1G/0.5G)	13.64 ± 0.65	48.35 ± 11.03	268.30 ± 145.34
PA 47237	TOL/TAZ (1G/0.5G)	15.28 ± 6.32	17.93 ± 2.03	304.40 ± 24.36
meaned data n=9		15.36 ± 3.79	47.86 ± 13.73	307.20 ± 84.19
PA 17286	TOL/TAZ (2G/1G)	15.87 ± 1.27	23.79 ± 6.69	191.10 ± 66.58
PA 38475	TOL/TAZ (2G/1G)	11.69 ± 0.47	11.90 ± 0.47	109.40 ± 167.8
PA 47237	TOL/TAZ (2G/1G)	7.99 ± 2.19	17.93 ± 2.03	207.7 ± 95.03
meaned data n=9		11.85 ± 3.65	17.87 ± 6.23	169.41 ± 117.73
PA 17286	MER (2G)	7.57 ± 0.55	32.54 ± 21.69	351.10 ± 91.20
PA 38475	MER (2G)	10.34 ± 1.54	49.53 ± 17.97	200.23 ± 97.21
PA 47237	MER (2G)	22.41 ± 10.10	57.95 ± 18.19	240.10 ± 7.50
meaned data n=9		14.92 ± 8.22	46.67 ± 20.17	263.77 ± 95.06

Figure 1: Comparison of the ABE of TOL/TAZ (2/1G and 1/0.5G) and MER 2G

a) *P.aeruginosa* 17286 TOL/TAZ MIC 0.5mg/L



b) *P.aeruginosa* 38475 TOL/TAZ MIC1.0mg/L



c) *P.aeruginosa* 47237 TOL/TAZ MIC 2.0mg/L

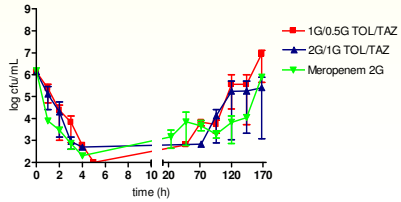


Table 3: Growth on x2MIC plates at 168h

	no of experiments					
	TOL/TAZ (1G/0.5)		TOL/TAZ (2G/0.5)		MER (2G)	
	no of experiments	viable count (log cfu/mL)	no of experiments	viable count (log cfu/mL)	no of experiments	viable count (log cfu/mL)
P.aeruginosa 17286	0/3	<2	0/3	<2	1/3	4.46
P.aeruginosa 38475	0/3	<2	0/3	<2	2/3	3.42
P.aeruginosa 47237	0/3	<2	0/3	<2	3/3	5.02 ± 0.13

Conclusions

- For the 3 *P.aeruginosa* strains tested in this study, the TOL/TAZ 2G/1G regimen was superior to the TOL/TAZ 1G/0.5 regimen and MER 2G.
- Both TOL/TAZ regimens suppressed changes in population analysis profiles.

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ USA