A642 Pharmacodynamics of piperacillin-tazobactam (P/T) against *Pseudomonas aeruginosa*: antibacterial effect and risk of emergence of resistance

52nd ICAAC, San Francisco 9-12th Sept 2012

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Abstract

Background: A pharmacodynamic (PD) index target of T>MIC ≥50% is widely used to optimise dosing of P/T, often by prolonged infusion. The published pre-clinical PD data to support this target is poor and there is no data on the likely impacts of this target on risk of emergence of resistance (EOR). We used a pre-clinical in vitro model to define the P/T T>MIC for antibacterial effect (ABE) and EOR against *P.aeruginosa* (*Pa*).

Methods: A dilutional single compartment in vitro pharmacokinetic model (IVPKM) was used to simulate T>MIC in the range 0-100% for P/T. Four strains of *Pa* were employed with MICs of 4, 4, 6 and 6mg/L respectively. ABE was measured by change in viable count over 72h and EOR by changes in population profile from baseline at time 0 by culture on to media containing x2MIC, x4MIC and x8MIC P/T.

Results: The T>MIC at 24h for a bacteriostatic effect was 45% (95%CI 32-53) and equivalent exposures for a -1 or -2 log reduction in Pseudomonal count were 62% (CI 52-72) and 80% (CI 68-96) respectively. At 48h and 72h bacterial killing only occurred at T>MIC ≥70%. T>MIC values in the range 40-60% were always associated with recovery of *Pa* on x4MIC media and viable counts were 5.4 ± 0.3 log CFU/mL at 24h, 5.7 ± 0.6 log CFU/mL at 48h and 7.1 ± 0.3 log CFU/mL at 72h. At T>MIC of 80-100% *Pa* was recovered from x4MIC media in all simulations after ≥48h.

Conclusions: A T>MIC target of 50% is associated with a 0 to -1 log reduction in bacterial counts of *Pa* after 24h exposure to P/T and also EOR as judged by growth on MICx4 media. At times of >24h, T>MIC exposures of up to 70% are associated with bacterial growth and amplification of resistant sub populations. More aggressive T>MIC targets will be needed for *Pa* to increase anti-Pseudomonal activity and prevent EOR.

Introduction

fT>MIC targets of ≥50% are often used to optimise P/T dosing in man.
This has led to the adoption of prolonged or continuous infusion therapies to treat aerobic Gram-negative rods and, most especially, *Pa* infection.
Clinical trials evidence for the superiority of such approaches is lacking with the possible exception of patients with critical illness.
There is little published data on the pre-clinical characteristics of P/T despite its widespread clinical use.

Objectives

To determine the fT>MIC targets for P/T against *P.aeruginosa* (*Pa*) in terms of ABE and risk of emergence of resistance (EOR).

Materials and Methods

Four clinical strains of *Pa;* P/T MICs: 45966 MIC 4mg/L; 46042 MIC 6mg/L; 27853 MIC 4mg/L; 46172 MIC 6.0 mg/L were used.
P/T dose escalation experiments (t½ = 1h, TDS, minimum of 8exps per strain) were performed to simulate T>MIC 0-100%.
A single compartment dilutional IVPKM was used to simulate the pk profiles.
The inoculum was 10^6 CFU/ml and experiments were performed over 72h.
EOR was assessed before and 24hly during the simulation by sub-culture onto x2, x4, x8 P/T MIC containing media. Viable counts (logCFU/mL) were determined over the 72h of P/T exposure.

Results

The fT>MIC relationship to ABE, log change in viable count are shown on Table 1 and Figures 1 and 2.
The fT>MIC for a 24h static effect was 39.8 ± 8.8% and for a -1 log kill 51.4 ± 13.4% (Table 1), -3 log kill was not achieved in 2 of 4 strains even at fT>MIC of 100%.
The fT>MIC for static and cidal antibacterial effects increased markedly 72h with fT>MIC of >80% (Figures 1 and 2).
The risk of EOR, as indicated by recovery of resistant isolates on x4 MIC or x8 MIC plates, varied with drug exposure and time of exposure (Table 2).
At 24h the maximum risk of EOR was with a fT>MIC of 40-60%.
After ≥48h fT>MIC of >20% was associated with EOR.
The absolute bacterial counts on MICx4 or MICx8 recovery plates are shown on Figures 3 and 4.

Table 1 Piperacillin-tazobactam fT>MIC for antibacterial effect at 24h

	Strain & MIC					
ABE	45966	46042	27853	46172	Average	Pooled data
	MIC 4mg/L	MIC 6mg/L	MIC 4mg/L	MIC 6mg/L		
Static effect	32.5	52	40.3	34.2	39.8 ± 8.8	34.2
-1 log drop	36.9	69	53	47	51.4 ± 13.4	47.6
-2 log drop	40.5	83	67.8	60.4	62.9 ± 17.7	63.8
-3 log drop	>100	>100	91.3	95.3	-	>100

Table 2 Risk of changes in population profiles of *P.aeruginosa* strains related to time of drug exposure and fT>MIC

Proportion of experiments where growth occurred on x4 MICor x8 MIC recovery plates at fT>MIC:-						
	24h		48h		72h	
fT>MIC (%)	MIC x4	MIC x8	MIC x4	MIC x8	MIC x4	MIC x8
0	0 (0/6)	0 (0/6)	0 (0/6)	0 (0/6)	33 (2/6)	0 (0/6)
>0 - 20	57 (4/7)	29 (2/7)	57 (4/7)	29 (2/7)	86 (6/7)	71 (5/7)
>20 - 40	75 (6/8)	63 (5/8)	100 (8/8)	100 (8/8)	100 (8/8)	100 (8/8)
>40 - 60	86 (12/14)	71 (10/14)	100 (13/13)	100 (13/13)	100 (13/13)	100 (13/13)
>60 - 80	67% (4/6)	33% (2/6)	100 % (6/6)	100 % (5/5)	100 % (5/5)	100 % (6/6)
>80 - 100	20% (2/10)	10% (1/10)	100% (4/4)	100% (3/3)	100 % (5/5)	100 % (5/5)

Fig 1:Piperacillin-tazobactam fT>MIC relationship to antibacterial effect at 24 h for *P.aeruginosa*

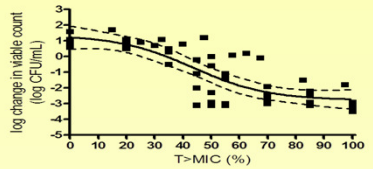


Fig 2: Piperacillin/tazobactam fT>MIC relationship to antibacterial effect at 72h for *P.aeruginosa*

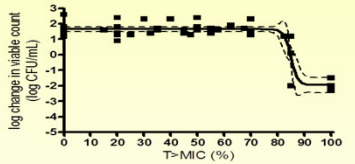


Fig 3:Piperacillin-tazobactam fT>MIC relationship to change in population profile for *P.aeruginosa*

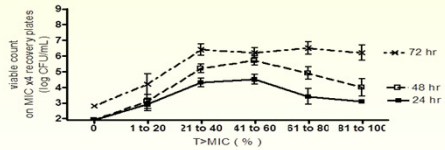
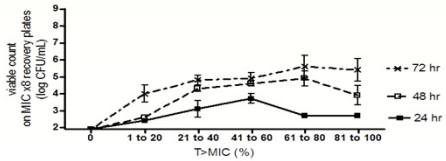


Fig 4: Piperacillin-tazobactam fT>MIC relationship to change in population profile for *P.aeruginosa*



Conclusions

A fT>MIC of 50% for P/T is associated with a -1 log reduction in *Pa* viable counts at 24h.
fT>MIC targets of >80% are required for static or -1 log kill over 72h.
fT>MIC in the range 40-60% maximally amplify resistance by 24h.
At times of drug exposure of ≥48h, even high fT>MIC are associated with EOR.
Higher fT>MIC targets than ≥50% are justified when treating *Pa* with P/T as monotherapy.

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