A1-1367 The magnitude of the pharmacodynamic index required for a 24h bacteriostatic effect for *S.aureus* is associated with increased risk of resistance

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Introduction

- Pre-clinical pharmacokinetic/pharmacodynamic (pK/pD) models are widely used to define the relationship between antibacterial drug exposure and antibacterial effect (ABE)– usually measured by changes in pathogen viable count.
- These investigations allow the dominant pD index to be defined (fAUC/MIC, fT>MIC) and the size of the index to provide a bacteriostatic or bactericidal effect established.
- Correlations with human pD studies indicated the size of the pD index best related to human microbiological cure is a 0 to -1 log kill in neutropaenic pre-clinical models.
- Such pD index targets are subsequently used in setting clinical breakpoints for different pathogen groups.
- The impact of these antibiotic exposures on pathogen population profiles and subsequent risks of emergence of resistance (EoR) have not been adequately studied.

Methods

- An *in vitro* pK model was used to simulate free drug concentrations of antibiotic associated with standard dosing. These were daptomycin (dapt) 6mg/kg/d Cmax 6.4mg/L, t½ 8h;moxifloxacin (moxi) 400mg Cmax 1.6mg/L, t½ 8h; razupenem (razu) 1g BD Cmax 58mg/L, t½ 2h; telavancin (tela)10mg/kg/day Cmax 11mg/L, t½ 7.5h; tomopenem (tomo)1.5g TDS Cmax 90mg/L t½ 2h.
- Using these drug pK, a series of dose ranging studies were performed involving 8-14 dose simulations for each strain tested.
- A range of *S.aureus* strains were used – dapt 6 strains, moxi 7 strains, razu 5 strains, tela 5 strains and tomo 6 strains. 10% Mueller-Hinton Broth was used in all experiments.
- ABE was measured by log change in viable count at 24 hr and EoR by growth on agar containing MICx2 and MICx4 concentrations of the relevant antibiotic.

Results

- The size of the pD index for static and cidal effects at 24h is shown on Table 1.
- The shaded boxes highlight the pD targets for a -1 log drop in *S.aureus* viable count at 24h.

Results

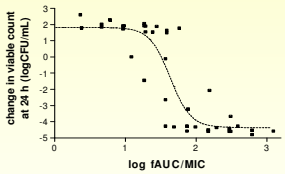
- The relationship between the size of the pD index
- and the risk of emergence and the number of resistant
- bacteria is shown on Figure 1 dapt, Figure 2 moxi, Figure 3 razu, Figure 4 tela and Figure 5 tomo.

Table 1 The size of the pharmacodynamic index for bacteriostatic and bactericidal effects at 24h

Agent	daptomycin	moxifloxacin	razupenem	telavancin	tomopenem
dominant pD index	fAUC/MIC	fAUC/MIC	fT>MIC (%)	fAUC/MIC	fT>MIC (%)
size of the pD index for 24hr static effect	37.2 ± 16.5	21.4 ± 11.6	5 ± 1.4	43 ± 17	8 ± 5
-1 log drop	**40.6 ± 17.8**	**28.8 ± 14.3**	**12.5 ± 5.8**	**50 ± 17**	**12 ± 8**
-2 log drop	45.0 ± 18.8	43.5 ± 25.9	21.9 ± 11.1	67 ± 21	16 ± 9
-3 log drop	49.8 ± 19.2	83.7 ± 67.9	36.6 ± 20.1	-	21 ± 3

Figure 1 Daptomycin

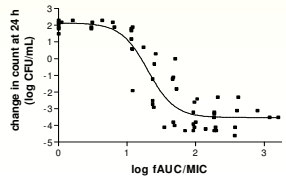
fAUC/MIC ratio relationship to change in viable count at 24hrs - S aureus



fAUC/MIC	number of experiments	% experiments with growth on MICx2 plates	bacterial count on MICx2 plates
1-15%	15	73(11)	4.1 ± 1.2
15-30	6	33(2)	5.9
30-50	6	17(1)	2.5
50-100	8	0	<2
≥100	8	0	<2

Figure 2 Moxifloxacin

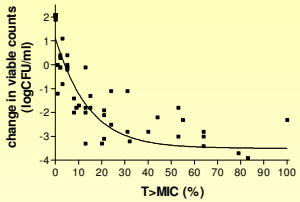
fAUC/MIC ratio relationship to change in viable count at 24hrs - S aureus



fAUC/MIC	number of experiments	% experiments with growth on MICx4 plates	bacterial count on MICx4 plates
0.5-10	11	73(8)	4.3 ± 1.3
20-30	5	60(3)	3.9 ± 0.8
30-40	3	67(2)	3.6
>40	6	17(1)	4.7

Figure 3 Razupenem

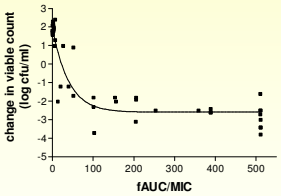
T>MIC relationship to change in viable count at 24hrs - all MRSA strains



T>MIC (%)	number of experiments	% experiments with growth on MICx2 plates	bacterial count on MICx2 plates
0.5-2.5	6	83(5)	4.3 ± 0.8
2.5-5.0	6	83(5)	4.8 ± 0.8
5.0-10	5	60(3)	4.1 ± 0.6
10-15	6	33(2)	3.4
15-35	7	43(3)	3.2 ± 0.2
>35	15	0	<2

Figure 4 Telavancin

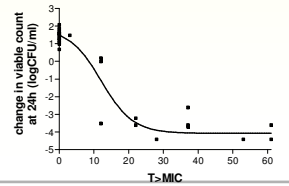
fAUC/MIC ratio relationship to change in viable count at 24hrs - S aureus



fAUC/MIC	number of experiments	% experiments with growth on MICx2 plates	bacterial count on MICx2 plates
1-3	8	100(8)	5.6 ± 1.9
3-10	3	100(8)	4.7 ± 0.6
10-50	8	50(4)	4.3 ± 1.1
50-175	7	29(2)	4.2
175-400	7	14(1)	2.1
>400	5	0	<2

Figure 5 Tomopenem

fT>MIC relationship to change in viable count at 24 hr - S aureus



fT>MIC	number of experiments	% experiments with growth on MICx2 plates	bacterial count on MICx2 plates
1-10%	11	100(11)	4.0 ± 1.1
10-20	3	100(3)	3.5 ± 1.1
20-30	5	20(1)	2.5
≥30	21	5(1)	2.5

Conclusions

- The pD index targets associated with a -1 log drop in *S.aureus* viable counts at 24h are related to changes in population profiles in 17-67% of exposures with dapt, 33% with moxi, 33% with razu, 29-50% with tela and 100% tomo.
- Viable counts after these exposures on MICx2-4 containing agar increase from <2 logs pre exposure to 3-4 logs at 24h.
- The use of pD index targets for microbiological efficacy in therapy of *S.aureus* infection are associated with a significant risk of EoR.

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