A1051 Pharmacodynamics of minocycline against *Staphylococcus aureus* studied in an in vitro pharmacokinetic model of infection

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Abstract

Minocycline (MIN) is a widely used oral therapy for mild to moderate MRSA infection which can be safely treated with non-parenteral antibiotics. Despite a long tradition of use to treat Staphylococcal infection, there is little data to support present dosing regimens and no data on the risks of emergence of resistance. Clinical breakpoints, both in Europe and USA, are based on historic data. Our objective was to provide modern information on the pharmacodynamic index size for minocycline and *S.aureus* with a view to re-assessing established clinical breakpoints and potential dose regimens.

Methods:

An in vitro dilutional pharmacokinetic model was used to perform a series of dose ranging studies against 4 strains of *S.aureus* (MIN MIC 0.19-0.5mg/L, all susceptible by EUCAST breakpoints S≥0.5mg/L). Antibacterial effect was measured by changes in viable count over 72h and changes in population profile by recovery on MICx4 or MICx8 plates after 24, 48 and 72h MIN exposure.

Results:

The fAUC/MIC at 24h for static and -1 log reductions in viable count were 11.5±6.1 and 18.1±8.1 respectively. For -2 log reduction in viable count, the fAUC/MIC was >200 for two strains, and 33.1 and 42.8 for the two others. fAUC/MIC targets were modestly increased after 72h being 12.9±2.9, static effect; 17.7±5.2, -1 log drop; 2 log drop values were >75, and 32.1 and 18.2 for the other two strains. There were no changes in population profiles indicated by growth on MICx4 or MICx8 plates at 24, 48 or 72h.

Conclusions:

A suitable fAUC/MIC target related to static -1 log drop for MIN is 10-15. This target was not associated with any change in population profiles and would suggest a clinical breakpoint of S≤0.25-0.5mg/L for a dose of 100mg 12 hrly.

Introduction

- MRSA remains an important human pathogen and its incidence remains high both in North America and Europe.
- Many MRSA infections, especially those in the community, are best managed with oral antimicrobial chemotherapy.
- Although many MRSA clones are susceptible to oral agents such as cotrimoxazole, clindamycin and tetracyclines, only linezolid has a firm clinical trial with a pharmacokinetic and pharmacodynamic evidence base.

As part of the EU 7th Framework Programme (FP7) project AIDA (preserving old antibiotics for the future) we used an in vitro pharmacokinetic (pK) model to establish the minocycline fAUC/MIC associated with antibacterial effect (ABE) for MRSA as well as performing 10 day human dose simulations.

Materials and methods

- An in vitro single compartment dilutional pK model was employed to simulate a range of fAUC/MIC ratios of minocycline (MIN) based on the pharmacokinetics of 100mg q12h in man. The fCmax modelled was 0.6mg/L, t½ 12hr and fAUC 11.06mg/L.h for a 100 mg dose.
- Four MRSA strains 45494 MIN MIC 0.12mg/L, 43241 MIN MIC 0.25mg/L, 33827 MIN MIC 0.5mg/L, 33922 MIN MIC 1.0mg/L and *S.aureus* ATCC29213 MIN MIC 0.l9mg/L were used, the inoculum used was 10^6 CFU/ml.
- ABE was measured by log change in viable count at 24h (d24), 48h (d48) and 72h (d72) relative to the starting inocula (log CFU/ml). A sigmoid Emax model using Boltzmann equation was used to relate fAUC/MIC with ABE.
- Changes in population profiles were assessed by growth on agar plates containing x2, x4 and x8, the MIN MIC at 24h, 48h and 72h. The limit of detection was 10^2CFU/ml.
- With strain 45494 a 10 day exposure experiment was performed.

Results

- The fAUC/MIC for static, -1 log drop and -2 log drop in initial viable counts at 24h and 72h are shown on the Table.
- The fAUC/MIC ABE for each strain tested is shown on Figures 1, 2, 3, 4 and 5.
- There was no emergence of resistance with any strain or MIN exposure.
- A summary showing the data from all five strains is shown on Figure 6.
- The ABE of MIN over 10 days is shown on Figure 7.

Table: fAUC/MIC and ABE relationship

		AUC/MIC for					
		24hr			72hr		
Strain	MIC (mg/L)	static effect	-1 log drop	-2 log drop	static effect	-1 log drop	-2 log drop
43241	0.25	11.2	20.5	41.5	13.9	20.1	31.7
33827	0.5	3.2	7.3	>200	10.3	13.9	19.5
ATCC29213	0.19	9.0	17.4	51.2	29.8	56.6	105.0
45494	0.12	19.0	29.3	>200	36.5	47.7	>200
33922	1.0	19.2	38.2	>200	17.0	27.8	55.6
Avg ± SD		12.3 ± 6.8	22.5 ± 11.8	46.4*	21.5 ± 11.2	33.2 ± 18.4	52.9**± 37.6

*Average of two observations,** average of four observations

Figure 1: Strain 43241

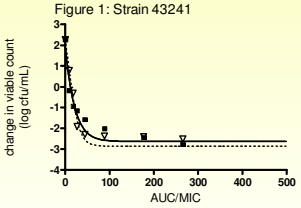


Figure 2: 33827

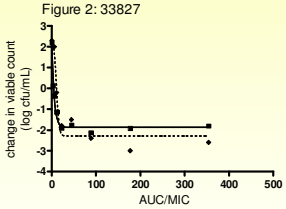


Figure 3: ATCC 29213

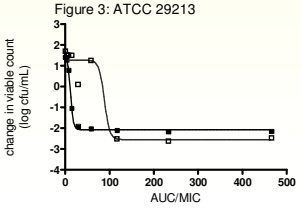


Figure 4: 45494

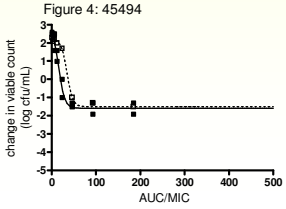


Figure 5: 33922

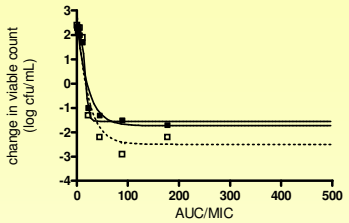


Figure 6: pooled strains (n=5)

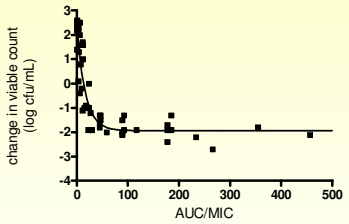
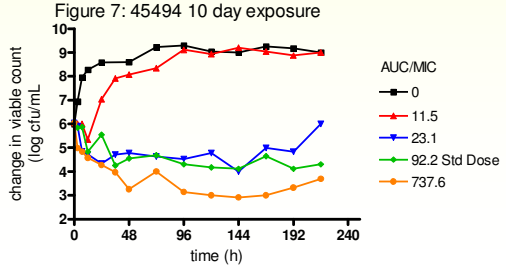


Figure 7: 45494 10 day exposure



Conclusions

- A suitable fAUC/MIC target for sSSTI due to MRSA would be 10-25, i.e. the exposure associated with a static -1 log drop at 24h.
- This fAUC/MIC was not associated with any change in MRSA population profiles.
- The effect of MIN over 10 days was not associated with changes in population profiles at achievable fAUC/MIC in man.

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