ABSTRACT

Background and Aim
S. aureus is capable of surviving in mild acidic pH environments, which includes phagolysosomes. Acidity, however, affects also antibiotic activity. We have compared the influence of acid pH on the extracellular and intracellular activities of (α) oxacillin (OXA), a beta-lactam known for its poor accumulation in cells but for an enhanced activity at acid pH, and (β) gentamicin (GEN), which accumulates in phagolysosomes but shows a marked decrease of activity at acid pH.

Methods
MICs were determined in MH Broth adjusted to pH 5.0 to 7.4. Extracellular (MH broth) and intracellular (THP-1 macrophages) activities (expressed as difference in CFU compared to controls) were examined at 24h using a wide range of concentrations to obtain full pharmacological response (Emin, static concentration, Emax).

Results
MICs are shown in Table. Activity was always concentration-dependent (sigmoid dose-response; R²≥0.9), with Emax reaching -5 log (limit of detection) extracellularly and -1 log intracellularly. Static concentrations to obtain full pharmacological response (Emin, static concentration, Emax) as difference in CFU compared to controls) were examined at 24h using a wide range of concentrations to obtain full pharmacological response (Emin, static concentration, Emax).

Conclusion
Acid pH has contrasting effects on GEN and OXA activity in broth, but their static concentrations remain close to the corresponding MIC. Intracellularly, OXA and GEN seem equipotent. The negative effect of acid pH for GEN is probably compensated by its larger accumulation, whereas the opposite combination of effects may take place for OXA.

Contrasting effect of acid pH on the extracellular and intracellular activities of gentamicin and oxacillin against Staphylococcus aureus

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Results

A. pH exerts a negative effect on gentamicin activity by increasing its relative potency (EC50). In contrast, pH decreases Emax of oxacillin. Maximum effect for both drugs (Emax) remain unchanged.

B. Responses become superimposable when plotted as a function of multiples of MIC for each pH value.

C. Intracellularly, Emax and, to a lesser extent, EC50 are lower than extracellularly.

D. For both gentamicin and oxacillin, drug accumulation in the infected compartment compromise for the effect of pH.

Conclusions

• We specifically demonstrate that influence of pH is related to a modulation of the relative potencies (EC50) of the antibiotics studied, without adversely affecting the maximal effects (Emax) once a suitable concentration is reached. This strongly suggest that the effect of pH is mainly related to modulation of binding and/or accessibility of the drugs to their bacterial target.

• These data may help better understanding how the activity of antibiotics could be improved in the clinical arena with respect to intracellular infection and infections in other acidic body sites. Strategies aimed at selecting molecules with low MICs at acidic pH and optimizing exposition of intracellular bacteria taking into account drug accumulation and using extracellular concentrations as high as possible appear as straightforward approaches.

References

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