Comparison of anti-MRSA antibiotics (vancomycin, linezolid, daptomycin, rifampin) and anti Gram-positive fluoroquinolones (moxifloxacin, delafloxacin) against MSSA and MRSA in models of young and mature biofilms

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INTRODUCTION

Biofilm-related infections by S. aureus represent a major problem in the hospital. Antibiotic activity is, however poorly characterized against this particular form of infection.

We have set up a model of young and mature biofilms allowing comparison of the activity of anti-staphylococcal antibiotics on a pharmacodynamic basis.

We selected conventional anti-MRSA agents and compared them to fluoroquinolones, for which high diffusibility and strong bactericidal character may offer advantages in this respect. Moxifloxacin was compared to the investigational fluoroquinolone delafloxacin, which is highly potent against Gram-positive organisms (1).

METHODS

• Antibiotic activity was concentration-dependent against both viable bacteria and biofilm mass, and was globally lower
• For 24 h–biofilms, E_max values were reduced, with only daptomycin, rifampin, and delafloxacin reaching a 50 %
• Assessment of bacterial viability within biofilms: florescence signal (λexc 560 nm; λem 590 nm) associated to the reduction of resazurin (blue, non-fluorescent) into resorufin (pink) by viable bacteria (2).
• Determination of total biofilm mass: crystal violet staining and measure of absorbance at 570 nm (3).

RESULTS

Pharmacological descriptors of concentration-effect relationships.

Upper panel: maximal efficacy (E_max) maximal decrease in signal extrapolated for an infinitely large concentration.
Lower panel: relative potency (EC): drug concentration needed to reach a 75 % decrease in the signal (6h-biofilm) or a 25 % of the signal (24h-biofilm), as interpolated from the sigmoidal regression of the concentration-effect curve. Dotted line: highest concentration tested. EC values are × to this value

• Biofilms grew over time, with a 4-fold and 14-fold increase in viable bacteria, and a 14-fold and 26-fold increase in biofilm mass between 6 and 24 h for MSSA and MRSA, respectively.
• Antibiotic activity was concentration-dependent against both viable bacteria and biofilm mass, and was globally lower against 24 h-biofilms than against 6 h-biofilms.
• For 6 h-biofilms, maximal efficacy (E_max) towards viable bacteria and biofilm mass reached > 80 %, except for linezolid against MSSA and moxifloxacin against MRSA. With respect to potency, a 75 % reduction in the signal (EC75) was obtained at concentrations close to the MIC or even lower for rifampin and delafloxacin, except for linezolid which did not reach this effect against the matrix.
• For 24 h-biofilms, E_max values were reduced, only daptomycin, rifampin, and delafloxacin reaching a 50 % reduction in viability and only daptomycin (towards MSSA) and vancomycin (against MRSA) reaching this effect towards the matrix. With respect to potency, a 25 % reduction in viability (EC25) was obtained for concentrations of 1-10 X MIC against MSSA and 0.1-1 X MIC against MRSA, for all drugs except moxifloxacin, which required higher concentrations. High concentrations were needed to act upon the matrix.

CONCLUSIONS

• Activity of antibiotics is markedly defeated against mature biofilms and is strain-dependent, probably reflecting differences in the nature and/or the physicochemical properties of the biofilm produced.
• Daptomycin, rifampin, and delafloxacin were the most effective drugs tested in this model. The high intrinsic activity of these antibiotics, especially that of delafloxacin (lowest MICs), may offer an additional advantage in combatting biofilms with respect to the concentrations that could be achieved in vivo.

REFERENCES

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