04922

Drug repurposing for identification of new efflux inhibitors and/or antibiofilm agents against *Staphylococcus aureus* and *Staphylococcus epidermidis*

05. New antibacterial agents, PK/PD & Stewardship

5a. Mechanisms of action, new compounds, preclinical data & basic pharmacology of antibacterial agents (incl. investigational and non-traditional therapeutics)

Likely attendance

Onsite

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Background

Staphylococcus aureus (SA) and *Staphylococcus epidermidis* (SE) are frequent pathogens causing nosocomial infections. Efflux-mediated resistance and biofilm formation may contribute to the emergence of resistance in these species and resilience of such infections to chemotherapeutics. In this work, we applied an *in silico* drug repurposing strategy to identify drugs that can target efflux and/or biofilm formation, to be then assessed *in vitro* for their efflux inhibitory and/or antibiofilm activities.

Methods

A list of targets, corresponding to all SA and SE membrane transporters and biofilm-associated proteins was used to interrogate the DrugBank database and generate a list of approved drugs targeting these proteins or their homologues. Representative candidate drugs were chosen for validation in an experimental model based on reference and isogenic strains differing in *norA* expression (gene encoding the main staphylococcal efflux pump NorA). To assess efflux inhibitory activity, the drugs MICs were determined by broth microdilution and each drug (at ¼ MIC) tested for its ability to reduce MICs of selected antimicrobials (NorA substrates and non-substrates). Drugs with significant effect (≥ four-fold MIC reduction) were further tested for synergism with those antimicrobials by checkerboard assays and their potential to inhibit biofilm formation by the crystal violet adhesion method.

Results

We identified over 200 drugs that potentially target SA and/or SE membrane transporters or biofilm-associated proteins. Seven of these candidate drugs were tested: desipramine, chloroquine, atovaquone, topiramate, amlodipine, tariquidar and sulpiride. All drugs showed high MICs (>64 mg/L) against all staphylococcal strains. Tariquidar, amlodipine, desipramine and chloroquine reduced the MICs of NorA substrates in *norA*-overexpressing SA and SE strains, suggesting they possess efflux inhibitory activity. Moreover, amlodipine

and tariquidar presented significant synergism with some NorA substrates. Amlodipine was the only drug able to abolish biofilm formation in SA, whereas desipramine and chloroquine were more effective against SE biofilms.

Conclusions

This work reveals amlodipine, desipramine and chloroquine as new potential dual target drugs and tariquidar as a potent efflux inhibitor in staphylococci. These drugs may, in the future, be included in the fight against antimicrobial-resistant *S. aureus* and *S. epidermidis* infections.

J. Neves and C. Antunes contributed equally to this work.

Keyword 1
New and non-traditional drugs
Keyword 2
Antimicrobial resistance (AMR)
Keyword 3
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Conflicts of interest

Do you have any conflicts of interest to declare?
No