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A new approach to predict anti-staphylococcal effects of antibiotic combinations using an in-vitro dynamic model

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Background: Data obtained using checkerboard techniques do not always predict the activity of antibiotic combinations, possibly because the “optimal” ratio of the combined agents might not correspond to clinically attainable ratios. To explore if susceptibility testing with linezolid (LZD) + rifampicin (RIF) at concentration ratios that correspond to the respective ratios of 24-hour area under the concentration – time curve (AUC), *Staphylococcus aureus* was exposed to linezolid and rifampicin in an in vitro dynamic model that simulates single and combined treatments at therapeutic and sub-therapeutic ratios of AUC_{LZD} and AUC_{RIF}.

Material/methods: Susceptibility of *S. aureus* to LZD and RIF was tested for the single agents and their combinations at the therapeutic LZD-to-RIF concentration ratio (4:1, AUC_{LZD} 240 µg×h/ml to AUC_{RIF} 60 µg×h/ml) and at sub-therapeutic concentration ratios of 2:1 (AUC_{LZD} 120 µg×h/ml to AUC_{RIF} 60 µg×h/ml), 4:1 (AUC_{LZD} 120 µg×h/ml to AUC_{RIF} 30 µg×h/ml), 8:1 (AUC_{LZD} 120 µg×h/ml to AUC_{RIF} 15 µg×h/ml; AUC_{LZD} 240 µg×h/ml to AUC_{RIF} 30 µg×h/ml) and 16:1 (AUC_{LZD} 240 µg×h/ml to AUC_{RIF} 15 µg×h/ml). Using the same AUC_{LZD} and AUC_{RIF} (single drug treatments) and AUC_{LZD} to AUC_{RIF} ratios (combination treatments), twice daily dosing of LZD and once-daily dosing RIF given alone and in combination was simulated. The central compartment of the model was sampled daily for viable counts and antibiotic concentrations from the beginning of simulated treatments to120 hr.

Results: RIF enhanced susceptibility of *S. aureus* to LZD in a concentration-dependent manner. At LZD-to-RIF concentration ratios of 2:1 and 4:1 the MIC of LZD dropped 67 times compared to the MIC determined without RIF (2 µg/ml); at the concentration ratios of 8:1 and 16:1, i.e. at a smaller

proportion of RIF in the combinations, – 16 and 8 times, respectively. Unlike RIF, LZD did not influence the rifampicin susceptibility of *S. aureus*: MICs of RIF determined with and without LZD were similar (0.008-0.016 μg/ml). In simulations of multiple-dose pharmacokinetics of LZD-RIF combinations, killing of *S. aureus* was more rapid and intensive compared with single treatments, possibly as a result of lowering the MIC of LZD and thereby increasing the actual AUC/MIC ratios. Indirectly, this assumption is confirmed by the observation that the areas between the control growth and time-kill curve (ABBCs) determined in both combined and single treatments could be plotted against AUC/MIC expressed as LZD concentrations on the same sigmoid graph (r^2 0.94).

Conclusions: These findings suggest that the antibacterial effects of LZD-RIF combinations can be predicted by AUC/MICs of LZD using its MIC determined at pharmacokinetically-derived LZD-to-RIF concentration ratios.