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Poster presentation

Efficacy of linezolid (LZD), vancomycin (VAN) and its combinations with rifampin (RIF) in the treatment of experimental meningitis due to methicillin-resistant *Staphylococcus aureus*

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Objective

To study the *in vitro* and *in vivo* activity of LZD, VAN and its combinations with RIF in a rabbit meningitis model, caused by two strains of *S. aureus* with different susceptibilities to glycopeptides.

Methods

In vitro

MICs (mg/L): Strain A (LZD = 2, VAN = 1, RIF = 0.018) and B (LZD = 4, VAN = 8, RIF = 512). The bactericidal activity and synergy (time-kill curves) were studied over 24 h. Drugs were tested for a range of concentrations according to their MICs and achievable human serum levels (1/4x-4xMIC) against both strains.

In vivo

New Zealand rabbits (2.5–3 kg) were used, with an inoculum of 8.5–9 Log cfu/mL. PK/PD parameters (blood and CSF) were determined (Cmax [mg/L]; AUC [mg.h/L]; t1/2 [h]; t > MIC [h]; AUC/MIC) after a single dose of each antimicrobial on infected rabbits. In the therapy experiments, animals (n = 6 per schedule) were grouped in untreated (CON), or treated with LZD (20 mg/kg), VAN (25 mg/kg every 4 hours, 4 doses), RIF (15 mg/kg) every 24 hours (1 dose), LZD+RIF or VAN+RIF. CSF variables analyzed at 0, 4, 6 and 24 h of treatment were: bacterial concentration (Log10 cfu/mL), WBC (cells/mL), lactate (mmol/L) and protein concentration (g/L). Statistical Analysis: Wilcoxon and Anova test were used.

Results

In vitro

The following schedules were bactericidal: Strain A: LZD (4xMIC) and the following combinations RIF (2xMIC)+LZD(4xMIC), RIF (1xMIC)+LZD (1/2xMIC), RIF (1/2xMIC)+LZD (1xMIC); and strain B: VAN (4xMIC, 2xMIC) and the combinations of both drugs with RIF.

In vivo

PK/PD Cmax (μg/mL): Blood: LZD 20.84, VAN 59.59, RIF 52.38, CSF: LZD 4.64, VAN 4.12; RIF 1.22. Percentage of penetration: LZD 19%; VAN 15%; RIF 3.8%.

Bacterial concentration (0, 4, 6, 24 h): Strain A: CON (4.94, 4.48, 4.76, 4.65), LZD (4.96, 4.71, 4.81, 4.27), VAN (5.25, 4.62, 4.30, 4.95), RIF (5.32, 5.65, 5.19, 4.80), LDZ+RIF (4.85, 4.90, 4.82, 4.17) and VAN+RIF (5.34, 5.30, 5.36, 4.61); Strain B: CON (5.19, 4.67, 4.81, 4.37), LZD (4.85, 4.37, 4.18, 3.67), VAN (5.00, 5.63, 4.79, 4.79) and LDZ+RIF (5.02, 4.90, 4.53, 4.21). For Strain B, LZD and LZD+RIF significantly reduced bacterial concentra-

tion (24 h vs. 0 h, $p < 0.05$). LZD reduced the CSF lactate and proteins levels (24 h *vs*. 0 h, $p < 0.05$).

Conclusion

In this model of experimental meningitis caused by a GISA strain, linezolid and linezolid plus rifampin were effective reducing the CSF bacterial concentration and inflammatory parameters.