Poster

[P27-1] P27-1: Anti-infective drugs (6): Anti-MRSA and antifungals

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[P27-1-2] Pharmacokinetic/pharmacodynamic evaluation of teicoplanin against Staphylococcus aureus in murine thigh infection model

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Keywords: Teicoplanin, PK/PD

Background

Teicoplanin is a glycopeptide antibiotic commonly used to treat serious infections caused by Gram-positive bacteria including Staphylococcus aureus. However, a detailed pharmacokinetic (PK)/pharmacodynamic (PD) analysis of teicoplanin against S. aureus infections has not been performed, although dosing regimens should be optimized based on PK/PD. This study conducted in vivo analysis to closely examine PK/PD of teicoplanin using a murine thigh infection model.

Methods

Teicoplanin (5–100 mg/kg) was intravenously administered to five-week-old ddY mice with neutropenia. Serum teicoplanin concentrations were measured and analyzed using a one-compartment PK model. An early logarithmic phase bacterial suspension of S. aureus strain ATCC 229213 (3.75×10^6 colony-forming unit/mL) was intramuscularly administered into one posterior thigh muscle. For the thigh-infected mice, teicoplanin was administered at doses of 1 to 120 mg/kg with 4- to and 24-h intervals. The numbers of bacteria were counted and fitted to a standard sigmoid Emax model with three major PK/PD indices: ratio of the maximum free drug concentration to the minimum inhibitory concentration (fCmax/MIC), the ratio of 24-h area under free concentration-time curve to MIC (fAUC24/MIC), and the time that free concentration remained above MIC (fT >MIC).

Results

The mean PK parameters of teicoplanin were 0.149 L/kg for volume of distribution, 0.030 L/h/kg for clearance, 0.199 1/h for elimination rate constant and 3.52 h for half-life. The mean protein binding in serum was 92.3%. The MIC of teicoplanin against the S. aureus strain was 1.5 mg/L. Based on these values, the PK/PD indices of fCmax/MIC ($r^2 = 0.935$) and fAUC24/MIC ($r^2 = 0.924$) correlated with its in vivo effects better than fT >MIC ($r^2 = 0.769$). Values of a static effect (change in log [colony-forming unit/thigh] = 0) and 1-log killing effect were 4.4 and 15.2 for fCmax/MIC, and 30.2 and 69.9 for fAUC24/MIC, respectively.

Conclusions

Teicoplanin showed concentration-dependent bactericidal activities against S. aureus infections. The predictive PK/PD indices for its in vivo effects were fCmax/MIC and fAUC24/MIC. Teicoplanin is considered to be sufficiently bactericidal against S. aureus infections when the target values (fCmax/MIC of 15.2 and

fAUC24/MIC of 69.9) are achieved.