In vivo PK/PD of Delafloxacin Against Staphylococcus aureus (SA), Streptococcus pneumoniae (SPN), and Klebsiella pneumoniae (KPN) in the Murine Lung Infection Model

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ABSTRACT

Background: Delafloxacin is a broad-spectrum quinolone for use under the guidance of pharmacokinetic/pharmacodynamic (PK/PD) studies. The goal of the study was to determine the PK/PD targets in the murine lung infection model for SA, SPN, and KPN.

Methods: A diverse group of pathogens including those with phenotypic drug-resistance to other classes. Median free drug AUC/MIC targets were set at 100 for all pathogen groups: SA 0.04, SPN 0.02, and KPN 0.61. One-log-kill targets were 2- to 3-fold higher. These results were consistent with clinical drug selection for drug susceptibility breakpoints for delafloxacin for the treatment of lower respiratory tract infections involving these pathogens.

RESULTS

• Delafloxacin exhibits broad spectrum activity that includes S. aureus (MSSA and MRSA), S. pneumoniae, and K. pneumoniae.
• Clinical trials have shown ototoxicity and paroxysms in patients with acute bacterial skin and structure infection.
• The objectives of our experiments were to characterize in vitro efficacy of delafloxacin using a neutrophilic murine lung infection model for three common respiratory tract pathogens including S. aureus, S. pneumoniae, and K. pneumoniae.
• Specifically, the pharmacokinetic/pharmacodynamic targets of delafloxacin were examined to provide a framework for further development of drug-dosing regimens to optimize delafloxacin therapy for respiratory infections.

CONCLUSIONS

The relationship between PD index AUC/MIC and treatment efficacy is shown in Figure 3a-c. Each data point represents the mean of pharmacokinetic and clinical cure rates. A best fit line based on the Hill equation is included in each graph. The E_{D50} value, (N), and coefficient of determination (R^2) values are presented in the figure legend. Total daily doses necessary to achieve a 1-log kill for are shown in Table 2 below.