Pharmacokinetics / Pharmacodynamics of Finafloxacin in the Murine Thigh Infection Model with S. aureus and E. coli

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Abstract

Background: Finafloxacin (FIN), a new fluoropenicillin (FQ), in clinical development, has the unique property of being activated under acidic conditions, unlike other marketed FQs. Since local acidic environments are a hallmark of bacterial infection, FIN may have an advantage over existing agents in treating these infections. This study was performed to determine the PK/PD parameter that best predicts efficacy in the thigh infection model. Methods: Mice were treated with FIN or other FQs at pH 5, 6 and 7. For E. coli, dose-ranging was performed at pH 5 and 6 with a pH 7 used as a control. FIN was administered SC from 1 to 200 mg/kg to determine PK parameters for FIN and the other FQs at each pH. E. coli and Staphylococcus aureus (MSSA) strains were used. Dosed mice were challenged with 1 log higher inocula at each of the dose fractionations in order to determine the PK/PD parameter that is most predictive of efficacy.

Methods and Materials

FIN was administered SC at 1 – 100 mg/kg in order to determine PK parameters (Cmax, AUC, T>MIC) and their relationship to administered dose. PK was performed in neutropenic, untreated controls was determined and related to the PK parameters at each dose. Summary and Conclusions

FIN was more active than the other FQs tested at pH 5. The static dose for both the MSSA and Ec was 10.7 mg/kg. The correlation coefficients of the PD parameters to efficacy in the thigh infection for the 24 hr AUC/MIC, Cmax and T>MIC were 0.97 and 0.99 for FIN and 0.72 for MerLion (TL) and 0.57 and 0.75 for TL and 4.6 mg/kg for MSSA, and 0.77 and 0.77 for MSSA and 4.6 mg/kg for Ec, respectively. The dose at which the PD parameter and the PK parameter achieved the best fit was 23 for the AUC/MIC and 22.6 for the 4.6. The efficacy of FIN in the neutropenic thigh model for both MSSA and Ec, correlating best to the AUC/MIC, and further investigation is warranted to determine the effect of pH on the PK/PD relationship of these parameters.

References


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