**In Vivo Pharmacodynamics of MK-2764 / PTK 0796 Against Various Gram-Positive and Gram-Negative Bacteria in the Thighs of Neutropenic and Normal Mice**

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**ABSTRACT**

Background: MK-2764 (PTK 0796) is an oxazolyl-phenyl tetrazole, derived from the tetrazole class of potent antibacterials, that displays high MICs against Gram-positive organisms, particularly Staphylococcus aureus. MK-2764 is highly active in vitro against many Enterobacteriaceae with MICs of 0.06-0.5 mg/L and against many Gram-negative bacteria at concentration ratios of 3:6:12:24 hours. The purpose of this study was to characterize the in vivo pharmacodynamics of MK-2764 against these organisms in the thigh model of neutropenic and normal mice. MK-2764 was administered in a single dose of 1.25, 5, and 20 mg/kg (mg/kg/12h) then tail vein-infused at the mean of 3 mice. The extent of killing of the strain of S. aureus ATCC 10813 was 0.31 log10 units with PTK. Four of the strain of Bacteraemia strains were MRSA with two being community-acquired MRSA (CAMRSA).

**RESULTS**

The pharmacokinetics of MK-2764 in thigh-infected neutropenic mice showed clearance half-life of 4 hours for all doses. AUC/MIC was linear across doses with a correlation coefficient of determination (R²) of 83.5-89.3%. The magnitude of the 24-hr AUC/MIC required for the various strains of pneumococci was 23.8. This value is very similar to the 24-hr AUC/MIC values obtained with fluoroquinolones, other tetracyclines, clindamycin and macrolides with similar characteristics of MK-2764. The impact of the dosing regimen on the PK/PD parameters was evaluated in four strains (MSSA, 2 CA-MRSA, 12 Enterobacteriaceae) with MICs of 0.03 to 2 mg/L. PK of PTK was linear for all doses where plasma Cmax values of 8-100 ng/ml and AUC values of 80-8000 ng/ml were observed. The PK/PD indices that best correlated with efficacy with all 4 strains (R²=81-85%) were the peak/MIC ratio, the 24-hour AUC/MIC ratio, and the coefficient of determination (R²) of the relationship between efficacy and each PK/PD parameter. The coefficient of determination (R²) to the relationship between efficacy and each PK/PD parameter was 81-85%.

**CONCLUSIONS**

The dose-studies have characterized the in vivo pharmacodynamic activity of MK-2764 against various strains of S. pneumoniae. A monotherapy regimen should be evaluated in phase 3 clinical trials.

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**RESULTS**

**Table 1: Pharmacokinetic and pharmacodynamic parameters**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Dose (mg/kg)</th>
<th>Cmax (ng/ml)</th>
<th>AUC (0-24 hr) (ng.hour/ml)</th>
<th>T1/2 (H)</th>
<th>CL (ml/hr/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus ATCC 10813</td>
<td>20</td>
<td>160</td>
<td>5120</td>
<td>4</td>
<td>360</td>
</tr>
<tr>
<td>S. pneumoniae ATCC 49619</td>
<td>20</td>
<td>200</td>
<td>8000</td>
<td>4</td>
<td>400</td>
</tr>
</tbody>
</table>

**Figure 1: Mean time course of killing activity in vivo with a single dose of MK-2764 (mg/kg) in the thigh of normal mice.**

**Figure 2: Effect of single doses of MK-2764 on time course of neutropenic activity with Staphylococcus aureus ATCC 10813 in the thighs of neutropenic mice.**

**Figure 3: Dose-response relationships for 12-hourly dosing of MK-2764 against Staphylococcus aureus ATCC 10813 in the thighs of neutropenic mice.**

**Figure 4: Dose-response relationships for 12-hourly dosing of MK-2764 against Staphylococcus aureus ATCC 43816 in the thighs of neutropenic and normal mice.**

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**CONCLUSIONS**

The dose-studies have characterized the in vivo pharmacodynamic activity of MK-2764 against various strains of S. pneumoniae. A monotherapy regimen should be evaluated in phase 3 clinical trials. **MK-2764 produced a modest new event with 6 doses.**

**The 24-hr AUC/MIC ratio was the PK/PD indice most important for efficacy.**

**The presence of S. aureus had a major impact in reducing the magnitude of the 24-hr AUC/MIC ratio.**

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**REFERENCES**