Pharmacokinetics of PTK 0796 (BAY 73-6944) in Mouse, Rat, and Cynomolgus Monkey

Paratek Pharmaceuticals, Inc., Boston, MA

Abstract 2655
Poster F-759
Pharmacokinetics of PTK 0796 in Mouse, Rat and Cynomolgus Monkey

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ABSTRACT

The pharmacokinetic behavior of PTK 0796 was evaluated in CD-1 mice, Sprague-Dawley rats, and Cynomolgus monkeys. PTK 0796 was prepared as a solution in sterile water or in Phasmolys (USP Multiple Electrolytes Injection Type 1). Rat ascending dose pharmacokinetic studies were conducted using a single dose of four different concentrations administered as bolus injections. Blood samples were obtained at predetermined time points in EDTA-containing tubes. The samples were centrifuged, and the plasma was withdrawn and stored at -20 °C for liquid chromatography and mass spectrometry analysis. The pharmacokinetic behavior of PTK 0796 was evaluated in CD-1 mice, Sprague-Dawley rats, and Cynomolgus monkeys. PTK 0796 was prepared as a solution in sterile water or in Phasmolys (USP Multiple Electrolytes Injection Type 1). Rat ascending dose pharmacokinetic studies were conducted using a single dose of four different concentrations administered as bolus injections. Blood samples were obtained at predetermined time points in EDTA-containing tubes. The samples were centrifuged, and the plasma was withdrawn and stored at -20 °C. The plasma T½ (elim) was determined in the mouse, rat, and monkey.

INTRODUCTION

We have studied the single dose IV pharmacokinetics of PTK 0796 (BAY 73-6944) in mice, rats, and Cynomolgus monkeys. Noncompartmental analysis of tissue and plasma concentrations of PTK 0796 (BAY 73-6944) suggested a potential for PTK 0796 (BAY 73-6944) as a once-daily IV therapy against other susceptible or multiply antibiotic-resistant organisms.

RESULTS

Single Dose IV Bolus Pharmacokinetics

Mouse. Male CD-1 mice were injected IV with PTK 0796 via a lateral tail vein with a single dose of 10 mg/kg. Blood samples were obtained at 5, 30, 60, 120, 240, 480, 960, and 1440 min post-dosing. The samples were analyzed by LC-MS/MS, and pharmacokinetic values were calculated.

Rat. The pharmacokinetic behavior of PTK 0796 in Sprague-Dawley rats following an IV injection of PTK 0796/0.9% saline at 5, 10, 20, or 40 mg/kg was characterized in plasma and tissue samples collected at various time points following the injection. The pharmacokinetic parameters, Cmax, AUC, and elimination half-life (t1/2) were calculated using noncompartmental analysis. Plasma concentration-time data were analyzed using WinNonlin 4.0.1, using a noncompartmental model. An IV dose model was used for the plasma data, and an extravascular input model was used for the tissues.

METHODS

Pharmacokinetic behavior of PTK 0796 was evaluated in CD-1 mice, Sprague-Dawley rats, and Cynomolgus monkeys. PTK 0796 was prepared as a solution in sterile water or in Phasmolys (USP Multiple Electrolytes Injection Type 1). Rat ascending dose pharmacokinetic studies were conducted using a single dose of four different concentrations administered as bolus injections. Blood samples were obtained at predetermined time points in EDTA-containing tubes. The samples were centrifuged, and the plasma was withdrawn and stored at -20 °C for liquid chromatography and mass spectrometry analysis. The pharmacokinetic behavior of PTK 0796 was evaluated in CD-1 mice, Sprague-Dawley rats, and Cynomolgus monkeys. PTK 0796 was prepared as a solution in sterile water or in Phasmolys (USP Multiple Electrolytes Injection Type 1). Rat ascending dose pharmacokinetic studies were conducted using a single dose of four different concentrations administered as bolus injections. Blood samples were obtained at predetermined time points in EDTA-containing tubes. The samples were centrifuged, and the plasma was withdrawn and stored at -20 °C. The plasma T½ (elim) was determined in the mouse, rat, and monkey.

RESULTS

In all species, PTK 0796 exhibited a bi-exponential decline with a rapid distribution phase and an extended elimination phase. In mouse and rat, the plasma T½ (elim) were 5.6 hr and 3.8 hr, respectively. AUC was determined in the mouse, rat, and monkey.

Table 1. Pharmacokinetic Parameters in Mice Following Single IV Bolus Dose of PTK 0796

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Cmax (g/ml)</th>
<th>AUC (Hr·g/ml)</th>
<th>T½ (0-24) (Hr)</th>
<th>t1/2 (0-24) (Hr)</th>
<th>t1/2 (IV Bolus) (Hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2.22</td>
<td>20.30</td>
<td>1.15</td>
<td>0.83</td>
<td>2.54</td>
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<tr>
<td>10</td>
<td>4.36</td>
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<td>1.31</td>
<td>0.83</td>
<td>2.54</td>
</tr>
<tr>
<td>20</td>
<td>7.66</td>
<td>68.03</td>
<td>1.56</td>
<td>0.83</td>
<td>2.54</td>
</tr>
<tr>
<td>40</td>
<td>11.99</td>
<td>106.74</td>
<td>1.99</td>
<td>0.83</td>
<td>2.54</td>
</tr>
</tbody>
</table>

In the lung, concentrations were found to be 10 to 20-fold that of the plasma and similar in all species. Pleural fluid was evaporated to dryness. The samples were reconstituted in Methanol: Water 1:1, and protein was precipitated from the plasma and tissue samples by addition of Acetonitrile containing tubes. The samples were centrifuged, and the plasma was withdrawn and stored at -20 °C. Noncompartmental analysis of tissue and plasma concentrations of PTK 0796 (BAY 73-6944) suggested a potential for PTK 0796 (BAY 73-6944) as a once-daily IV therapy against other susceptible or multiply antibiotic-resistant organisms.

Structure of PTK 0796 (BAY 73-6944)

Initiation of therapy was determined to be one to two-fold higher than in plasma. AUC, AUC,......

Table 2. Pharmacokinetic Parameters in Rats Following Single IV Bolus Dose of PTK 0796

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Cmax (g/ml)</th>
<th>AUC (Hr·g/ml)</th>
<th>T½ (0-24) (Hr)</th>
<th>t1/2 (0-24) (Hr)</th>
<th>t1/2 (IV Bolus) (Hr)</th>
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<tr>
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<td>43.68</td>
<td>0.83</td>
<td>0.83</td>
<td>2.47</td>
</tr>
<tr>
<td>40</td>
<td>11.99</td>
<td>68.03</td>
<td>0.83</td>
<td>0.83</td>
<td>2.47</td>
</tr>
</tbody>
</table>

In this study, PTK 0796 was shown to have an elimination phase half-life after IV dosing of more than 10 hr. Plasma concentrations were greater than 1 µg/ml for 24 hr.

CONCLUSIONS

• In all species, after IV administration, plasma concentrations of PTK 0796 (BAY 73-6944) exhibited a broad exposure decay with a rapid distribution phase followed by a slower elimination phase.
• The elimination half-life appeared to increase in higher species.
• When administered as an IV bolus to rats, PTK 0796 (BAY 73-6944) distributed rapidly into tissues, kidney and lung were found to have concentrations 6 to more than 20-fold higher than plasma. Elimination half lives of 4 to 5 hr were observed.
• In rats, concentrations of PTK 0796 (BAY 73-6944) in tissues appeared to be of microbiologic significance for between 6 and 20 hr depending on dose.
• The elimination half life achieved values of 10 hr in the plasma of Cynomolgus monkeys.