Pharmacokinetics and safety assessment of tosufloxacin tosilate

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Introduction
Tosufloxacin tosilate is a fluoroquinolone antibacterial agent developed by Toyama Chemical Co., Ltd. Phase I studies of tosufloxacin tosilate were conducted in 1986, followed by double-blind, comparative studies from 1987 through 1988. Tosufloxacin tosilate was approved for the indications of respiratory infections, urinary tract infections, hepatobiliary infections, and gastrointestinal infections, and was launched in 1990. Subsequently, additional indications were approved for Chlamydia trachomatis, urethritis non gonorrhoea, infectious diseases in the field of plastic surgery, typhoid fever, and paratyphoid fever. Twelve years have passed since the launch of tosufloxacin tosilate and it has won the confidence of physicians.

In this article, the pharmacokinetics and safety assessments of tosufloxacin tosilate are described.

Pharmacokinetics in healthy adult subjects

Single-dose administration

Blood concentrations

Blood concentrations and pharmacokinetics of tosufloxacin tosilate following a single oral administration of either tosufloxacin tosilate 150mg (tosufloxacin 102 mg) or 300mg (tosufloxacin 204mg) after a meal in healthy adult volunteers are shown in Fig. 1 and Table 1. Maximum blood concentrations ($C_{\text{max}}$) attained 0.54µg/ml and 1.06µg/ml, respectively, approximately 2h after administration, and blood half-life ($T_{1/2}$) values were 4.85 and 4.44h, respectively. Area under the plasma tosufloxacin concentration-time curve (AUC$_{0-\infty}$) values were 4.95µg·h/ml and 8.97µg·h/ml, respectively. Both the $C_{\text{max}}$ and AUC$_{0-\infty}$ values of tosufloxacin were dose-dependent.

Urinary excretion

Maximum urinary concentrations were attained within 2h after administration after a meal, and the

Effect of a meal

Blood concentrations. Effect of a meal on blood concentrations of tosufloxacin following a single, oral administration either during fasting or after a meal was investigated by the cross-over method. The results are shown in Fig. 3. The $C_{\text{max}}$ value 2h after administration during fasting was 0.37µg/ml, and the $C_{\text{max}}$ value 2h after administration after a meal was 0.60µg/ml. The $C_{\text{max}}$ value after administration after a meal was higher than that after administration during fasting. The $T_{1/2}$ value was 3.77h after administration during fasting, and 3.59h after administration after a meal. No significant differences in $T_{1/2}$ were seen between these dosage regimens.

Urinary excretion. Maximum urinary concentrations were attained within 2h after administration after a meal, and the
peak value was 64.1 µg/ml, while the peak value of 44.1 µg/ml was attained between 4 and 6 h after administration during fasting. The urinary recovery rate up to 24 h after administration after a meal was 45.8%, while that up to 24 h after administration during fasting was 28.0%. The values obtained after a meal were higher than those seen during fasting at all time periods (Fig. 3).

Repeated administrations (blood concentrations and urinary excretion)

The results for blood concentrations following repeated oral administration of tosufloxacin tosilate 150mg three times daily for 7 days after a meal in healthy adult individuals are shown in Fig. 4. The blood concentrations in the morning prior to administration ranged from 0.24 µg/ml to 0.34 µg/ml after day 2 of administration and the levels were sustained on days 4 and 7. For urinary excretion, the cumulative urinary recovery rate on each day after day 2 of administration sustained broadly consistent values with time. There was no accumulation of the drug caused by repeated administrations (Fig. 5).

**Pharmacokinetic studies in special populations and patients**

**Elderly**

Blood concentrations, pharmacokinetic parameters, and urinary recovery rates following a single oral administration of tosufloxacin tosilate 150mg after a meal in elderly volunteers without apparent hepatic and renal dysfunction are shown in Fig. 6, Fig. 7, and Table 2, respectively. In elderly subjects, Cmax attained was 0.45 µg/ml 2.93 h (Tmax) after administration. The T1/2 value was 4.50h and the AUC value

### Table 1. Pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Dosage and administration</th>
<th>n</th>
<th>Vd/F (l)</th>
<th>Ka (h⁻¹)</th>
<th>Kel (h⁻¹)</th>
<th>Tlag (h)</th>
<th>T1/2 (h)</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (h)</th>
<th>AUC (µg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg Dose after a meal</td>
<td>34</td>
<td>144.3</td>
<td>1.32</td>
<td>0.143</td>
<td>0.11</td>
<td>4.85</td>
<td>0.54</td>
<td>2.00</td>
<td>4.95</td>
</tr>
<tr>
<td>300 mg Dose after a meal</td>
<td>5</td>
<td>143.1</td>
<td>1.38</td>
<td>0.156</td>
<td>0.38</td>
<td>4.44</td>
<td>1.06</td>
<td>2.16</td>
<td>8.97</td>
</tr>
</tbody>
</table>

Vd/F, Distribution volume adjusted by absorption rate because of oral preparation
Ka, Absorption rate constant; Kel, rate constant for the appearance of unchanged drug in the urine; Tlag, log-time
*See text for definitions

![Fig. 1. Blood concentrations of tosufloxacin after administration in healthy adult subjects (administration after a meal)](image1)

![Fig. 2a,b. Urinary concentrations (bars) and urinary recovery rates (circles) of tosufloxacin after administration in healthy adult subjects. a] 150-mg dose (after a meal; n = 6); b] 300-mg dose (after a meal; n = 5)](image2)

![Fig. 3. Effect of a meal by the crossover method administration of tosufloxacin tosilate 150mg (n = 6), a] blood concentrations; b] urinary excretion)](image3)