Population Pharmacokinetics of Levofloxacin as Prophylaxis for Febrile Neutropenia

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Abstract

**Background** Levofloxacin (LVFX) is widely used against a broad spectrum of bacteria. To prevent the emerging of resistance resulting from its abuse, an optimal method and dosage are needed. In the field of hematological malignancies, LVFX is one of the choices for prophylaxis for febrile neutropenia (FN). There is no consensus about the optimal dosage and method among hematologists.

**Aims** To determine the population pharmacological parameters based on the population pharmacokinetics of LVFX. We considered the optimal dosage and method of LVFX based on various simulations depicted by personal computer.

**Methods** We performed population pharmacokinetic analysis for seven patients receiving LVFX as prophylaxis (200 mg, b.i.d.) for FN with blood sampling. One patient received 100 mg t.i.d. All patients were treated at Kyoto Prefectural University of Medicine.

**Results** Clearance (CL) is 5.8 L/hr, distribution volume (Vd) is 58.5 L, area under the blood concentration-time curve (AUC0-24) is 69.0 μg·hr/mL, t1/2 is 6.9hr, Cmax is 3.4 μg/mL at administration of 200 mg b.i.d. Cmax (peak) of 500 mg, and q.d. is simulated as 8.54 μg/mL.

**Conclusion** For LVFX 500 mg q.d. is predicted to be the most effective dosage and method. Because the predicted Cmax value is similar to that of western countries, the frequency of adverse effects is thought to be same as in western countries. 500 mg, q.d., may also be an optimal dosage and method for Japanese.

**Key words:** population pharmacokinetics, levofloxacin, AUC/MIC, febrile neutropenia

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Introduction

Levofloxacin (LVFX) is widely used in the fields of respiratory treatments, urology and hematology. In Japan, various methods are used, for example, 100 mg, t.i.d., 200 mg, b.i.d. (1, 2). On the other hand, in Western countries, 500 mg, q.d., is primarily used.

Because quinolone is a concentration-dependent drug, the more area under the blood concentration-time curve (AUC)/minimum inhibitory concentration (MIC) value insures more clinical efficacy. Considering the post-antibiotic effects (PAE), the *quaie die* method is optimal, suggested by clinical pharmacology (3). However, in Japan, regulatory authorities have determined that the maximum single dose is 200 mg based on some studies (4-6).

For Japanese patients 500 mg, q.d., may give better clinical outcome. However, the concentration of drug of 500 mg, q.d., may increase rapidly and the frequency of adverse effects such as syncope, hypoglycemia, etc. (7), may progress. Thus, easy-going way bridging is not recommended. To perform clinical trials safely, we should predict the Cmax and

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AUC/MIC values based on the population pharmacokinetics of LVFX 500 mg, q.d., beforehand.

Thus, we measured the peripheral blood concentration of LVFX of eight patients with hematological malignancies receiving LVFX as a prophylaxis and performed a population pharmacokinetic analysis. Based on these results, we simulated drug-concentration curve at 500 mg, q.d.

**Patients and Methods**

**Patients**

Seven patients with hematological malignancies treated at Kyoto Prefectural University of Medicine received LVFX 200 mg, b.i.d., as a prophylaxis for febrile neutropenia (FN). Only one patient received 100 mg, t.i.d. (No. 8). After informed consent, blood concentrations were measured in each patient. The protocol, including the informed consent form for this study, was approved by the institutional review board at the Kyoto Prefectural University of Medicine (No. C-290). Stable concentrations were achieved after about one week, so that we obtained peripheral blood 10 days after administration. The clinical characteristics of the patients are summarized in Table 1.

**Measurement of LVFX**

The SRL Laboratory (Tokyo, Japan) measured the concentration of LVFX. Briefly, the concentration of LVFX in plasma was determined by high-performance liquid chromatography fluorescence method. The assays were linear over a wide concentration range (from 0.01 μg/ml to ∞).

**Population pharmacokinetics**

We performed a population pharmacokinetic analysis with NONMEM software (version VI, level 1.0; Globomax LLC, Hanover, MD). The first order conditional estimate (FOCE) method was used for the parameters estimation. We approximated the drug concentration curve using a linear one-compartment model (ADVAN1, TRANS2) with linear elimination, because bioavailability is thought to be 100% (8). We selected an error model as the exponential model.

**Results**

**Cases**

Neither syncope nor hypoglycemia was seen in any patient during LVFX treatment. Biochemical examination detected a slight GOT/GPT increase in case no. 3. However, that particular case was suffering from chronic hepatitis type C before the trial.

**Drug concentration**

All patients’ data are described in Table 2 and the drug concentration curve is depicted in Fig. 1.
The concentration drug curve of levofloxacin in peripheral blood.

Table 3. Population Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th></th>
<th>200mg/12hr (patient)</th>
<th>500mg/24hr (simulation)</th>
<th>200mg/12hr (healthy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>5.8</td>
<td>5.8</td>
<td>9</td>
</tr>
<tr>
<td>Vd(L)=CL/K</td>
<td>58.5</td>
<td>58.5</td>
<td>75</td>
</tr>
<tr>
<td>Kel=CL/Vd</td>
<td>0.099</td>
<td>0.099</td>
<td>0.12</td>
</tr>
<tr>
<td>AUC(µg·hr/mL)=D/CL</td>
<td>34.48</td>
<td>86.21</td>
<td>19.88</td>
</tr>
<tr>
<td>AUC(0-24hr)</td>
<td>68.97</td>
<td>86.21</td>
<td>39.76</td>
</tr>
<tr>
<td>t1/2 (hr)=0.693/Kel</td>
<td>6.89</td>
<td>6.89</td>
<td>5.97</td>
</tr>
<tr>
<td>C=D/Vd;Cmax</td>
<td>3.42</td>
<td>8.55</td>
<td>2.04</td>
</tr>
</tbody>
</table>

Population pharmacokinetics

NONMEM analysis presented population pharmacokinetics data (RSE%) as follows: distribution of volume (Vd), and clearance (CL), are 58.5 (13.3) L/hr, and 5.8 (10.7) L, respectively.

The equation on the CL and Vd is:

\[ \text{CL} = 5.8^{*}\exp(\eta_{C}) \]  
\[ \text{Vd} = 58.5^{*}\exp(\eta_{Vd}) \]  

(\eta means inter-individual variability). All population pharmacokinetics parameters are described in Table 3.

Discussion

Recently, pharmacokinetic analysis has developed rapidly together with computer technology. For example, population pharmacokinetic analysis can now be easily performed using the NONMEM software. This software is used globally as an effective tool because NONMEM can calculate exact parameters even with small sampling data (9-11). In the current study, we identified population pharmacokinetics parameters using this powerful tool.

Our results were slightly different from those of a phase I study. The reason may be derived from the difference in the deviation of ages between our patients and healthy ones in a phase I. Tanigawara et al reported that affecting factors for the clearance of LVFX are age, renal function, and weight, with age greater than 65 a particular factor. Among these factors, renal function has been reported to be the most prominent factor (12). The effects of these factors for pharmacokinetics were not studied in the current trial because of small population. Further studies will be needed.

AUC (0-24 hour) is 86.2 µg·hr/mL (500 mg, q.d.). This value is bigger than that of a phase I study with healthy volunteers. Because AUC/MIC is thought to be over 35 in treatment of most bacteria, this method and dosage may be useful for treatment as well as prophylaxis. Considering the utility of empiric, oral, outpatient gatifloxacin monotherapy
at a dose of 400 mg once daily for FN in patients with low risk has been already established (14), 500 mg LVFX may be more potent to treat FN. Cmax of 500 mg, q.d., is 8.54 μg/mL, similar to that of Western countries. Thus, we supposed that the frequencies of adverse effects are almost identical. Cmax of 500 mg, q.d., is also over the supposed mutant prevention concentration (MPC) of *Streptococcus pneumoniae* at 8 μg/mL (13). 500 mg, q.d., will also help to prevent the emergence of resistance.

We concluded that 500 mg, q.d., is safe for Japanese and an effective method for clinical outcomes and the prevention of mutation, if a systemic prophylaxis, and not a selective decontamination of the digestive tract, is needed to put down an occurrence of FN.

In the future, clinical trials should be performed to verify the utility of this administration, because 500 mg, q.d., can affect anaerobes, including *Clostridium difficile*, resulting in pseudomembranous colitis (15, 16).

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**References**