Peritoneal Clearance and Optimum Dosage Regimen of Levofloxacin in Patients under Continuous Ambulatory Peritoneal Dialysis

Madoka KANAMORI *1 Kiyoshi MIHARA*1
Kazuhiro HANADA *1 Takashi YASUDA*2
Tomoya FUJINO *2 Takeo SATOH*2
and Hiroyasu OGATA*1

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*1 Meiji Pharmaceutical University Department of Clinical Pharmacy
2-522-1 Noshio, Kiyose-si, Tokyo 204-8588, Japan
*2 St. Marianna University School of Medicine, Department of Medicine,
Division of Nephrology & Hypertension

Introduction: We investigated the clinical significance of the peritoneal clearance of levofloxacin, which is used to treat exit-site infections caused by Pseudomonas aeruginosa in patients under continuous ambulatory peritoneal dialysis (CAPD), and proposed an optimum dose and dosage interval for treating these patients.

Methods: We measured the concentrations of levofloxacin in the plasma, the drainage from peritoneal dialysis and the plasma ultrafiltrate by HPLC in 6 patients receiving CAPD, and determined the plasma unbound fraction (fuB). We also estimated the total clearance (CLtot/F), distribution volume (Vd/F) and peritoneal clearance (CLpd) in each patient.

Results: The mean (S. D.) CLtot/F, Vd/F, CLpd, and fuB were 22.6 (7.34) ml/min, 76.3 (21.9) L, 3.42 (0.831) ml/min, and 69.7 (13.76) %, respectively. We examined the possible factors affecting the peritoneal clearance of levofloxacin, but did not find any definite trends.

Discussion: The average CLpd was about 17% of the CLtot, but in some patients it was above 20%. It seems that the peritoneal clearance values should not be ignored in clinical practice. The minimum plasma concentration of levofloxacin in the steady state in patients under CAPD given 100 mg of levofloxacin every 24 h was 2.7 ± 0.72 μg/ml, which exceeded the MIC50 of the drug for P. aeruginosa. Administration of the drug at a dose of 100 mg every 48 h, a common clinical practice, may not be adequate to maintain a blood concentration high enough to attain an appropriate antibacterial effect.

Key words: Continuous ambulatory peritoneal dialysis, levofloxacin, peritoneal clearance, exit-site infections

*1 明治薬科大学薬学科薬学薬剤学 〒204-8588 東京都清瀬市野塚 2-522-1
*2 聖マリアンナ医科大学内科学腎臓・高血圧内科
Introduction

Patients receiving continuous ambulatory peritoneal dialysis (CAPD) may develop infections at the catheter site (exit-site infections). Infections of the exit-site not extending into the abdominal cavity must be treated with systemic antibiotics. In many cases, however, exit-site infections are caused by bacteria that are resistant to multiple drugs, and only a few drugs can be used. The new drug quinolone levofloxacin, an oral antibacterial agent, has proved effective against most Gram-positive bacteria and Gram-negative bacilli, seldom causing adverse drug reactions. One of the Gram-negative bacteria often detected as a causative agent in exit-site infections in patients under CAPD is *Pseudomonas aeruginosa*; the MIC\textsubscript{50} of levofloxacin against this bacterium is 1.56 \mu g/ml, and the MIC is 6.5 \mu g/ml\textsuperscript{3}).

It has been reported that in patients with severe nephropathy (creatinine clearance rate <20 ml/min), the total clearance (CL\textsubscript{tot}/F) decreases to about 35 ml/min\textsuperscript{4}), but the bioavailability and the distribution volume (Vd/F) of levofloxacin do not differ from those in healthy patients\textsuperscript{5}). It has therefore been recommended that the drug be given to patients with severe nephropathy at a dose of 100 mg at intervals of 48 h or longer. However, there are no data on the peritoneal permeability of levofloxacin in patients receiving peritoneal dialysis, and there is no established schedule for administration of the drug in these patients.

We have administered the drug to patients under CAPD at a dose of 100 mg at intervals of 48 h, but this dosage regime treatment has proved to be clinically ineffective in some patients. This prompted us to investigate the issue further. Here, we attempted to determine the most appropriate administration schedule for levofloxacin in patients receiving CAPD. We measured the concentration of levofloxacin in plasma, peritoneal dialysate and plasma ultrafiltrate to estimate CL\textsubscript{tot}/F, Vd/F and peritoneal clearance (CL\textsubscript{pd}), and examined the significance of the CL\textsubscript{pd} of levofloxacin in relation to oral clearance. We also examined the relationships between CL\textsubscript{pd} and the volume of drainage in peritoneal dialysis, plasma unbound fraction of the drug present, and the depot time, which are factors that could affect CL\textsubscript{pd}. We attempted to determine an optimum administration schedule and dosage for levofloxacin based on the CL\textsubscript{tot}/F and Vd/F obtained.

Methods

1. Patients

All patients were undergoing CAPD and were infected with Gram-negative bacteria at their catheter exit sites. The infections were diagnosed at the St. Marianna University School of Medicine Hospital. Patients with peritonitis and systemic infections were excluded. This study was approved the ethics committee of Meiji Pharmaceutical University, and written informed consent was obtained from each patient. Table 1 shows the clinical background of each patient.

2. Data collection

The clinical data collected included age, gender, body weight, current medical conditions, type of dialysate, inflow and outflow volume of dialysate, urine volume, and dialysate to plasma (D/P) ratio of creatinine concentration 4 h after the beginning of CAPD. Creatinine clearance was calculated according to the method of Bhatla et al\textsuperscript{6}).
Table 1  Clinical Characteristics of Subjects Undergoing CAPD

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>CLcr* (ml/min)</th>
<th>Additional Therapy†</th>
<th>Duration of CAPD (months)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>57</td>
<td>52.3</td>
<td>5.2</td>
<td>e, fl, i, pca, r</td>
<td>96</td>
<td>Chronic glomerulosclerosis</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>61</td>
<td>58.4</td>
<td>5.8</td>
<td>al, de, n, pca, fu</td>
<td>35</td>
<td>Diabetic glomerulosclerosis</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>57</td>
<td>73.0</td>
<td>5.6</td>
<td>al, b, fs, pca, z, t</td>
<td>60</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>50</td>
<td>58.2</td>
<td>5.6</td>
<td>do, pca, sf, isn, fu, en, br</td>
<td>30</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>58</td>
<td>74.5</td>
<td>5.6</td>
<td>am, do, al, pca, fu</td>
<td>26</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>70</td>
<td>68.0</td>
<td>4.8</td>
<td>Al, fu, pca</td>
<td>61</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
</tbody>
</table>

Mean±SD 58.5±6.7  64.1±9.05  5.4±0.36  51±26.6

*: from the equation of Bhatla et al.

3. Drug administration

All patients took 100 mg of levofloxacin three times a day after meal on the first day and 100 mg of levofloxacin once in the morning thereafter from the second day.

4. Blood sample and dialysate collection

Blood samples were drawn into heparinized tubes before administration on the second day and eighth day, and in the morning of the fifteenth day. The blood samples were centrifuged at 3,000 rpm for 15 min and the plasma was separated and stored at −20°C until analysis. Peritoneal dialysate samples were taken from a Tenckhoff catheter on the morning of the eighth day, and were stored at −20°C until analysis.

5. Assay methods

1) Materials

Levofloxacin and an internal standard (I.S.; DL-8493) were kindly supplied by Daiichi Pharmaceutical Co. (Tokyo, Japan). HPLC-grade tetrahydrofuran was purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). All other chemicals were reagentgrade products obtained commercially.

2) Drug analysis

One hundred microliters of plasma or peritoneal dialysate and 100 µl of internal standard solution (1.0 µg/ml) were mixed in a glass tube. Then 200 µl of tetrahydrofuran was added to the tube, mixed, and sonicated for 30 s. The tube was centrifuged at 3,000 rpm for 15 min at 4°C. One hundred microliters of the supernatant was transferred to another glass tube and diluted with 100 µl of the mobile phase. Then 20 µl of solution was injected into the HPLC system.

Bound and free levofloxacin were separated by ultrafiltration of plasma (Ultrafree-MC, 10,000 NMWL Filter Unit, Millipore, Bedford, MA, USA) at room temperature for 3 min at 7,000 rpm. Twenty microliters of the ultrafiltrate was diluted with 140 µl of the mobile phase and 20 µl of the solution was injected into the HPLC system.

3) HPLC conditions

HPLC analysis was performed according to the method of Okazaki et al. We used a fluorescence detector (RF-550, Shimazu, Kyoto, Japan) and set the excitation wavelength at 259 nm and the emission wavelength at 504 nm.
Analytical separation was accomplished with a Bensil 5C18-C (15 cm × 4.6 mm i.d.). The mobile phase consisted of tetrahydrofuran : 50 mM potassium dihydrophosphate (pH 2.0, adjusted with orthophosphoric acid) : 1 M ammonium acetate (7.5 : 92.5 : 1, v/v). The flow rate was 1.0 ml/min.

4) Peritoneal dialysis clearance

Since the levofloxacin was absorbed as rapidly as 0.5 to 1 h after oral administration (much shorter than the half life of levofloxacin of 28.22 h reported for patients with nephropathy), we examined the time course of change in the plasma drug concentration after oral administration by using a model of bolus administration. The patients were asked exactly when they had taken the drug. Equation 1 was used to describe the drug plasma concentration after a patient had received the drug three times on the first day (Cpt1), and equation 2 was used to describe the drug plasma concentration when the drug was being administered at regular intervals on the eighth day and the fifteenth day (Cpt4n).

\[
Cpt1 = (F \times D/Vd) \times (e^{-kel \times t1} + e^{-kel \times t2} + e^{-kel \times t3}) \quad \text{Equation 1}
\]

\[
Cpt4n = \frac{(F \times D/Vd) \times (1 - e^{-kel \times \tau})}{(1 - e^{-kel \times \tau})} \times e^{-kel \times t4} \quad \text{Equation 2}
\]

In these equations, the t1, t2, and t3 represent the time interval between the time of administration of each of the doses and the time at which the plasma sample (Cpt1) was collected, t4 denotes the time between the time when the patient took the drug last and the time when blood was collected on the nth day and \( \tau \) is the dosage interval of 24 h from the second day on.

The Vd/F and the elimination rate constant (kel) were calculated from the plasma concentrations measured at t1, t2, t3, and t4 using equations 1 and 2.

The CLtot/F was calculated by equation 3.

\[
CLtot/F = kel \times (Vd/F) \quad \text{Equation 3}
\]

Since all patients carried out the peritoneal dialysis all day, CLpd/F of all patients involved the peritoneal clearance.

The maximum plasma concentration (Cp0) was calculated from the obtained Vd/F and CLtot/F. The area under the plasma concentration time curve (AUC) during the peritoneal dialysis was calculated as follows:

\[
AUC_{T1-T2} = -Cp0 \int_{T1}^{T2} e^{-kel \times dt} = -\frac{Cp0}{kel} \left[ e^{-kel \times T1} \right]_{T2} \quad \text{Equation 4}
\]

Where T1 and T2 denote the start and completion of the dialysis, respectively, and Cp0 is the maximum plasma concentration of the day when the dialysate was collected which is estimated from Vd/F and CLtot/F of each patient.

The CLpd was calculated from the following equation:

\[
CLpd = Vpd \times Cp0 / AUC_{T1-T2} \quad \text{Equation 5}
\]

Where Vpd is from the volume of peritoneal drainage dialyzed between T1 and T2 and Cp0 denotes the total drug concentration in the drainage.

The plasma unbound fraction (fuB) was determined as follows:

\[
fuB = Cu / Cp \quad \text{Equation 6}
\]

in which Cp and Cu represent the drug concentration in plasma and in the ultrafiltrate, respectively.

5) Statistical analysis

Data were expressed as means±S. D. The correlations between the estimated CLpd and the volume of drainage in the peritoneal
dialysis, fuB, and the depot time were analyzed by Pearson's correlation coefficient (n=6). The minimum level of significance accepted was P<0.05. For statistical analysis, we used the application software Microsoft Excel® (Microsoft Co., WA, USA).

**Results**

There were 6 patients, all of whom had chronic renal insufficiency. The average creatinine clearance was 5.4 ml/min (range 4.8 to 5.8 ml/min). The concentration of levofloxacin determined by HPLC was 3 ng/ml when the detection limit was set at a peak concentration of three times as high as the noise. The calibration curve was set between 0.3 and 3 μg/ml, and a straight line with a favorable correlation coefficient of 0.997 was obtained. The mean diurnal variations in levofloxacin concentration (n=5) were 8.9%, 5.6% and 3.6%, and the mean day-to-day variations (n=11) were 14.7%, 7.1% and 6.8% when the levofloxacin was 0.3 μg/ml, 1.8 μg/ml and 3.0 μg/ml, respectively.

Table 2 shows the CLtot/F, Vd/F, depot time of drainage in the peritoneal dialysate, volume of drainage, CLpd and fuB, in which CLtot/F and Vd/F were calculated from patients' plasma concentrations listed in Table 3.

The mean fuB was 69.7% (range 47.3% to 84.9%), a value slightly higher than the value stated in another report of healthy humans⁹. The mean CLtot/F was 22.6±7.34 ml/min, and the mean Vd/F was 76.3±21.9 L. The CLtot/F was similar to the extrarenal clearance in healthy humans, and the Vd/F was almost identical to that of healthy humans. The mean CLpd was 3.4±0.81 ml/min. Assuming oral bioavailability (F) to be almost 100%, peritoneal clearance of levofloxacin accounted for about 17% of the total body clearance. In some patients the CLpd was almost twice as high as that in other patients. We examined the possible relationship between CLpd and fuB (r=0.08, not significant), the CLpd/fuB and the flow rate of the drainage (obtained by dividing the volume of the drainage by the depot time; r=0.372, not significant), the Vd/F(r=0.245, not significant) and the ratio of creatinine concentration in the drainage to that in the plasma during excretion of the dialysate (r = −0.607, not significant). No significant correlations were found (Fig. 1).

**Discussion**

The estimated CLpd values for levofloxacin were as low as 2.1 to 4.5 ml/min. The CLpd of ceftizoxime (a cefalosporin antibiotic fuB = 70%), cefpodoxime (also a cephalosporin fuB = 80%), and imipenem (a carbapenem antibiotic fuB = 85%) are reported to be 2.7 ml/min¹⁰, 2.3 ml/min¹¹, 4.2 ml/min¹², respectively. Levofloxacin was similar to these values. We examined the possible relationship between fuB and CLpd because only the free form of levofloxacin in plasma may be dialyzed, however we found no definite tendency in the data from the present patients.

Since the average distribution volume of levofloxacin is as large as 1.23 L/kg, the dialysis velocity of the drug from plasma may be restricted. Thus, we examined the possible relationship between CLpd/fuB and Vd/F. CLpd/fuB values were almost identical regardless of Vd/F (r = 0.245, not significant).

CLpd is determined using a limited volume of Vpd, and is also determined under the condition that the drug level in the plasma and in the dialysate do not attain a state of equilibrium. Therefore, CLpd is presumed to change according to the volume of drainage and the depot time. We examined the possible relationships
### Table 2  Pharmacokinetic Parameters of Levofloxacin in Subjects Undergoing CAPD

<table>
<thead>
<tr>
<th>Patients</th>
<th>Duration time (hr)</th>
<th>Vpd (ml)</th>
<th>fuB (%)</th>
<th>CLtot/F (ml/min)</th>
<th>Vd/F (L)</th>
<th>CLpd (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2,175</td>
<td>81.3</td>
<td>16.7</td>
<td>68.4</td>
<td>4.1</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>2,300</td>
<td>72.9</td>
<td>18.9</td>
<td>83.0</td>
<td>3.4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1,700</td>
<td>78.7</td>
<td>18.5</td>
<td>63.4</td>
<td>2.1</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1,950</td>
<td>71.7</td>
<td>17.6</td>
<td>50.2</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2,100</td>
<td>50.1</td>
<td>31.5</td>
<td>78.8</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>1,800</td>
<td>49.4</td>
<td>32.5</td>
<td>114.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>5.7±1.86</td>
<td>2,004±229.4</td>
<td>67.4±14.09</td>
<td>22.6±7.34</td>
<td>76.3±21.90</td>
<td>3.4±0.83</td>
</tr>
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</table>

### Table 3  Plasma Concentration of Levofloxacin

<table>
<thead>
<tr>
<th>Patients</th>
<th>on second day</th>
<th>on eighth day</th>
<th>on fifteenth day</th>
<th>on twenty-second day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The time*</td>
<td>concentration of LVFX¹</td>
<td>The time*</td>
<td>concentration of LVFX¹</td>
</tr>
<tr>
<td>1</td>
<td>12 h</td>
<td>3.135</td>
<td>7 h</td>
<td>5.619</td>
</tr>
<tr>
<td>2</td>
<td>9 h</td>
<td>2.584</td>
<td>133 h</td>
<td>0.501</td>
</tr>
<tr>
<td>3</td>
<td>3 h</td>
<td>4.022</td>
<td>22 h</td>
<td>3.255</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>—</td>
<td>7 h</td>
<td>4.437</td>
</tr>
<tr>
<td>5</td>
<td>8 h</td>
<td>1.834</td>
<td>24 h</td>
<td>1.710</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>—</td>
<td>16 h</td>
<td>2.628</td>
</tr>
</tbody>
</table>

¹: The time between the time when the patient took the drug last and the time when blood was collected.
²: The plasma concentration of levofloxacin (μg/ml)
The correlations between CLpd and the variables in patients

The minimum level of significance accepted was $P<0.05$.

between the CLpd and the volume of drainage ($r=0.561$, not significant), the depot time ($r=0.466$, not significant) and the flow rate of the drainage ($r=0.778$, not significant) under the conditions employed in this study, but found no significant correlation.

The ratio of the creatinine concentration in the depot to that in the plasma (D/P ratio) 4 h after the start of depot is occasionally used as a parameter of peritoneal permeability in patients. We examined the possible relationship between CLpd and the D/P ratio, but we found no definite relationship between them ($r=0.302$, not significant).

The reasons why we did not find any definite relationship between CLpd and these factors may be that we used estimated values of AUC instead of determined values to estimate CLpd, and that the number of patients was too small considering the variations in CLpd.

Since the bioavailability of levofloxacin is almost 100%, CLpd accounts for an average of 16.6±7.18% (range 9.2% to 25.6%) of the total body clearance. In those patients whose CLpd accounts for 20% or more of the total body clearance, it seems necessary to base the design of the administration schedule for levofloxacin on the rate of removal of the drug by CAPD.

Figure 2 shows the estimated time course of the plasma concentration of levofloxacin, together with that of the same patient when the drug was administered at a dose of 100 mg at intervals of 48 h. Those concentrations were calculated from CLtot/F and Vd/F of each patient using Microsoft Excel® (Microsoft Co.). The MIC50 for *P. aeruginosa* is also shown. There are no reports on the post-antibiotic effect of levofloxacin against *P. aeruginosa*. The plasma concentration of the drug13, therefore, should be kept at a level higher than the MIC50, and it seems that the administration schedule of levofloxacin should be designed mainly to keep the minimum concentration properly adjusted, rather than to maintain the AUC. Therefore, it is necessary to keep the minimum plasma concentration of levofloxacin at the steady state at 2 μg/ml, in accordance with the MIC50 for *P. aeruginosa*. In the present

![Fig. 1](image1)

The correlations between CLpd and the variables in patients

The minimum level of significance accepted was $P<0.05$.
study the mean minimum plasma concentration in the steady state after 100 mg of levofloxacin was administered at intervals of 24 h was 2.7 μg/ml (range 1.6 to 3.5 μg/ml). The mean minimum plasma concentration of the free form was 1.88 μg/ml (range 0.8 to 2.8 μg/ml), and it appeared that an effective plasma concentration was maintained in many patients. Eventually, all patients but one (No. 2) were treated successfully within the study period. The one exception patient (No. 2) refused levofloxacin after the first day of this study and thus he was excluded from the study.

However, if levofloxacin is administered at a dose of 100 mg at intervals of 48 h, the plasma concentration would likely be under the MIC₅₀ for a significant period (Fig. 2). Based on the estimated blood concentrations, this result suggests that with a 48 h regimen it is not possible to keep the plasma concentration high enough to obtain an appropriate antibacterial effect. In the case of other drugs, Taber et al reported that ciprofloxacin at 500 mg/day, which was one-half of the typical dose for patients with normal renal function, showed a plasma concentration sufficient for the treatment of exit-site infection caused by *P. aeruginosa* in CAPD patients[14]. This dosage reduction (one-half) of ciprofloxacin is comparable to that of levofloxacin (one-third) in our study, suggesting that levofloxacin at 100 mg/day is preferable to the conventional dose of 100 mg/2 days since the physiochemical and pharmacokinetic profiles of ciprofloxacin are similar to those of levofloxacin.

In conclusion, CLpd accounts for an average of 16.6±7.18% of the total body clearance of levofloxacin. In patients whose CLpd accounts for 20% or more of the total body clearance, it would be wise to design the administration schedule of levofloxacin based on the rate of removal of the drug by CAPD. We examined the factors that may affect the CLpd of levofloxacin, but we found no definite trends, pos-

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Fig. 2 The plasma concentration of levofloxacin

The solid curves are the estimated time course of the plasma concentration of levofloxacin and the closed circles are the measurements of the plasma concentration of levofloxacin. The dot curves are the estimated plasma concentrations under the assumption that the drug is administered to the same patient at a dose of 100 mg at intervals of 48 h. The MIC₅₀ for *P. aeruginosa* is 1.56 μg/ml.

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sibly because the number of patients evaluated was too small and the variation in the range of factors examined was also small.

Further studies on larger numbers of patients are necessary. However, the values for the pharmacokinetic parameters and peritoneal dialysis clearance obtained in our study suggest that levofloxacin should be administered at a dose of 300 mg a day on the first day, and then at a dose of 100 mg at intervals of 24 h.

References