Elimination Kinetics of Quinaprilat and Perindoprilat in Hypertensive Patients with Renal Failure on Haemodialysis

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Objective of the present study was to investigate the elimination kinetics of quinaprilat and perindoprilat, the active metabolites of angiotensin-converting enzyme (ACE) inhibitors quinapril and perindopril, in hypertensive patients with renal failure under haemodialysis to evaluate the appropriate duration of off-dose of these drugs before starting of low-density lipoprotein (LDL) apheresis. The informed consent was received from 12 hypertensive patients with renal failure, who were under haemodialysis (42 to 62 years). The patients received oral administration of quinapril (10 mg) or perindopril (2 mg) once a day for four weeks. First, to evaluate the dialyzability of each metabolite, blood samples were collected before and after haemodialysis one week after the repeated doses. Second, to evaluate the elimination kinetics of quinaprilat or perindoprilat, blood samples were collected at 24, 72, 120, 192 and 240 h after the final administration. Plasma concentrations of quinaprilat and perindoprilat were measured by high-performance liquid chromatography (HPLC) and radioimmunoassay, respectively. Pharmacokinetic parameters were determined by a model-dependent method. Values of haemodialysis clearance (CLHD) and extraction ratio (ER) were 51.5±30.2 ml/min and 0.35±0.21 for quinaprilat and 108.1±5.9 ml/min and 0.75±0.04 for perindoprilat, respectively. The terminal elimination half-lives of quinaprilat and perindoprilat were 60.7±2.1 and 79.9±14.0 h, respectively. The dialyzability of perindoprilat was much higher than that of quinaprilat probably due to low protein binding potency. The present study suggests that hypertensive patients receiving chronic therapy with quinapril or perindopril on haemodialysis should be withdrawn for at least 2 to 3 weeks before LDL apheresis.

Key words angiotensin-converting enzyme inhibitor; quinaprilat; perindoprilat; haemodialysis; elimination kinetics

It is well known that anti-hypertensive drug therapy plays an important role in the prevention of cerebrocardiovascular complications in hypertensive patients receiving haemodialysis. Alternatively, anti-hypertensive drugs are used in patients with congestive heart failure (CHF) caused by excessive fluid retention, those who often receive the life-long haemodialysis. Angiotensin-converting enzyme (ACE) inhibitors are known to be the most appropriate drugs for the prevention and treatment of hypertension and CHF. There are several reports on the pharmacokinetic characteristics of various ACE inhibitors in patients with renal failure receiving haemodialysis, suggesting that the dosage adjustment of ACE inhibitors would be needed since these drugs and their active metabolites are primarily excreted into the urine.

Quinapril and perindopril are nonsulphydryl ACE inhibitor pro-drugs. Their active metabolites, quinaprilat and perindoprilat, possess high affinity for ACE in the artery, heart and renal tissues, and exhibit potent and long-lasting ACE inhibitory effect. Thus, they are widely used for the treatment of hypertension and CHF. After oral administration both drugs are absorbed rapidly from the gastrointestinal tract and extensively hydrolyzed to their active metabolites. Since the active metabolites are primarily excreted into the urine, the elimination kinetics of the active metabolites might be altered in patients with renal failure. However, clinical pharmacokinetic studies of quinapril and quinaprilat in hypertensive patients with renal failure on haemodialysis are limited in Japan.

It is recognized that the abnormality of lipoprotein metabolism characterized as renal failure is one of the risk factors for arteriosclerotic disease and that an elevated level of low-density lipoprotein (LDL)-cholesterol is the most important risk factor for coronary artery disease. LDL apheresis is, therefore, considered to be one of the critical therapies for these diseases. However, there is a fact that LDL apheresis is contraindicated for patients receiving ACE inhibitors. In our hospital, administrations of ACE inhibitors to hypertensive patients on haemodialysis are routinely withdrawn for about four weeks prior to LDL apheresis. However, this duration of off-dose of ACE inhibitors is based on our clinical experiences, but not based on clinical evidence. There is little information currently available on the time required to eliminate completely ACE inhibitors from the body.

As part of a program for determining the duration for off-dose of ACE inhibitors prior to start LDL apheresis in hypertensive patients with renal failure on haemodialysis, we attempted to investigate the elimination kinetics of quinaprilat and perindoprilat after chronic administration to hypertensive patients with renal failure on haemodialysis.

MATERIALS AND METHODS

Subjects Twelve male hypertensive patients with chronic renal failure, who require chronic haemodialysis in our hospital, aged 42 years to 62 years (mean 50.3 years), participated in this study (Table 1). Each patient was informed a full explanation of the purpose and procedures and we got a written consent. All patients had normal liver function based on the clinical laboratory data (Table 1).

Patients received haemodialysis for 4 h (9:30 a.m. to 13:30
(HPLC). Briefly, 0.5 ml of 0.25 N HCl and 1 ml of 30 mM 1-
determined by a high-performance liquid chromatography
ersyl®; 2 mg perindopril erbumine per tablet) once a day
androchloride per tablet) or perindopril erbumine tablets (Cov-
quinar tablets (Covarin®; 10 mg quinapril hydro-
mittee of our hospital. Each patient received oral doses of
and the protocol was approved by the Medical Ethics Com-
2
ples obtained by centrifuging blood were kept frozen at
30 °C until analysis.

The study was conducted in our hospital
Clinical Study The study was conducted in our hospital and
the protocol was approved by the Medical Ethics Com-
mittee of our hospital. Each patient received oral doses of
quinapril hydrochloride tablets (Conan®; 2 mg perindopril
hydrochloride per tablet) once a day (8:00 a.m.) for four weeks. The doses of both drugs used in
this study were based on those reported previously.13—15)

One week after the starting of the treatment of quinapril
and perindopril, blood samples were collected before and
after haemodialysis to determine the dialyzability of the ac-
tive metabolites quinaprilat and perindoprilat. Four weeks
after the start of the treatment, the dosing of quinapril and
perindopril was discontinued, and the drugs were switched to
an ACE inhibitor, trandolapril. After the completion of the
treatment with quinapril and perindopril, blood samples were
collected at designated intervals (24, 72, 120, 192, and 240 h
after the completion of administration) for 8 or 10 d until
quinaprilat and perindoprilat were no longer detectable.

Blood samples were taken from the artery at the time of in-
duction of the needle for dialysis. The dose was unchanged
after the completion of administration) for 8 or 10 d until
quinaprilat and perindoprilat were no longer detectable.

Biochemical Analyses Blood samples for clinical labo-
atory tests were taken just before administration of each
drug. Creatinine clearance was calculated using creatinine
concentration in plasma by Cockcroft and Gault equation.17)
The detection limit of this assay was 0.7 ng/ml and
radioimmunoassay according to the method reported previ-
ously.16) The detection limit for quinaprilat was 1.5 ng/ml. Coefficient of varia-
tion at 20 ng/ml was less than 8%. This assay
was performed at the Pharmacokinetics Research Depart-
ment, Research and Development Research Laboratories,
Welfide Corporation (Fukuoka, Japan).

Plasma perindoprilat concentrations were determined by
radioimmunoassay according to the method reported previ-
ously.16) The detection limit of this assay was 0.7 ng/ml and
coefficient of variation was less than 8%.

Table 1. Characteristics of Patients Studied in Clinical Studies of Quinapril and Perindopril

<table>
<thead>
<tr>
<th>Quinapril</th>
<th>Patient</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Body weight (kg)</th>
<th>CLCR (ml/min)</th>
<th>TP (g/dl)</th>
<th>Albumin (g/dl)</th>
<th>AST (U/l)</th>
<th>ALT (U/l)</th>
<th>Co-medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. K.</td>
<td>53</td>
<td>162</td>
<td>45.0</td>
<td>4.6</td>
<td>6.8</td>
<td>4.7</td>
<td>18</td>
<td>8</td>
<td>6</td>
<td>Amlodipine, famotidine</td>
</tr>
<tr>
<td>T. T.</td>
<td>53</td>
<td>164</td>
<td>53.0</td>
<td>6.9</td>
<td>6.0</td>
<td>3.7</td>
<td>14</td>
<td>6</td>
<td>2</td>
<td>Benidipine, digoxin</td>
</tr>
<tr>
<td>M. K.</td>
<td>42</td>
<td>173</td>
<td>55.2</td>
<td>5.6</td>
<td>6.1</td>
<td>4.7</td>
<td>20</td>
<td>23</td>
<td></td>
<td>Benidipine, doxazosin</td>
</tr>
<tr>
<td>K. K.</td>
<td>43</td>
<td>172</td>
<td>70.0</td>
<td>8.2</td>
<td>6.3</td>
<td>4.4</td>
<td>13</td>
<td>5</td>
<td></td>
<td>Amlodipine, doxazosin</td>
</tr>
<tr>
<td>E. I.</td>
<td>48</td>
<td>179</td>
<td>61.0</td>
<td>7.5</td>
<td>5.9</td>
<td>3.6</td>
<td>13</td>
<td>8</td>
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<tr>
<td>M. M.</td>
<td>44</td>
<td>168</td>
<td>47.0</td>
<td>4.7</td>
<td>5.5</td>
<td>4.2</td>
<td>10</td>
<td>6</td>
<td></td>
<td>Benidipine, mexiletine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perindopril</th>
<th>Patient</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Body weight (kg)</th>
<th>CLCR (ml/min)</th>
<th>TP (g/dl)</th>
<th>Albumin (g/dl)</th>
<th>AST (U/l)</th>
<th>ALT (U/l)</th>
<th>Co-medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. K.</td>
<td>55</td>
<td>170</td>
<td>55.0</td>
<td>6.2</td>
<td>5.7</td>
<td>4.2</td>
<td>13</td>
<td>11</td>
<td></td>
<td>Benidipine</td>
</tr>
<tr>
<td>Y. E.</td>
<td>49</td>
<td>166</td>
<td>62.7</td>
<td>6.2</td>
<td>6.8</td>
<td>3.9</td>
<td>9</td>
<td>7</td>
<td></td>
<td>Benidipine, doxazosin</td>
</tr>
<tr>
<td>F. O.</td>
<td>52</td>
<td>181</td>
<td>64.2</td>
<td>6.1</td>
<td>7.0</td>
<td>4.5</td>
<td>16</td>
<td>13</td>
<td></td>
<td>Amlodipine</td>
</tr>
<tr>
<td>E. I.</td>
<td>44</td>
<td>175</td>
<td>55.4</td>
<td>4.5</td>
<td>6.6</td>
<td>4.3</td>
<td>10</td>
<td>12</td>
<td></td>
<td>Amlodipine, famotidine</td>
</tr>
<tr>
<td>Y. O.</td>
<td>62</td>
<td>164</td>
<td>50.6</td>
<td>4.0</td>
<td>6.5</td>
<td>4.2</td>
<td>11</td>
<td>7</td>
<td></td>
<td>Nifedipine</td>
</tr>
<tr>
<td>R. I.</td>
<td>59</td>
<td>156</td>
<td>43.9</td>
<td>7.1</td>
<td>6.5</td>
<td>3.8</td>
<td>16</td>
<td>6</td>
<td></td>
<td>Amlodipine, doxazosin</td>
</tr>
</tbody>
</table>

CLCR, creatinine clearance; TP, total protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase. CLCR was calculated using the method by Cockcroft and Gault (1976).17)
**Statistical Analysis**  All data are expressed as the mean values±S.E. and were analyzed using a two-tailed Student t-test for paired values with a 5% significance level.

RESULTS

The doses of quinapril and perindopril used in this study were tolerated well by all the patients during the therapy, since no side effects were experienced. Figure 1 shows individual plasma concentration data of quinaprilat and perindoprilat before and after haemodialysis. As shown in Fig. 1, haemodialysis significantly decreased the plasma concentrations of quinaprilat and perindoprilat (214±76 to 135±52 ng/ml at \( p<0.05 \) and 69±15 to 17±3 ng/ml at \( p<0.05 \), respectively). The ER of quinaprilat and perindoprilat by haemodialysis was calculated to be 0.35±0.21 and 0.75±0.04, respectively (Table 2). The value of haemodialysis clearance (CL\(_{HD}\)) was calculated to be approximately 51.5±30.2 and 108.1±5.9 ml/min.

Mean semilogarithmic disappearance curves of quinaprilat and perindoprilat from plasma 24 h after the final administration are illustrated in Fig. 2. Concentrations of quinaprilat and perindoprilat in plasma could be detected in all patients through 8 to 10 d after the final administration. The terminal elimination half-lives (\( t_{1/2} \)) of quinaprilat and perindoprilat were 60.7±2.1 and 79.9±14.0 h, respectively (Table 2). No significant difference in the \( t_{1/2} \) value was observed between quinaprilat and perindoprilat.

DISCUSSION

We withdrew routinely ACE inhibitors for about a week before LDL apheresis in patients who had been receiving chronic therapy with ACE inhibitors. However, one-week withdrawal frequently caused anaphylactic symptoms, including hypotension, bradycardia and dyspnea. Thus, we experientially changed the duration of off-dose from one to four weeks since such symptoms were disappeared. In the present study, we therefore compared the elimination kinetics and haemodialyzability of quinaprilat and perindoprilat at steady state after repeated administration of quinapril or perindopril in patients receiving chronic haemodialysis, in whom the duration of off-dose of quinapril or perindopril is needed to determine before LDL apheresis.

The pharmacokinetics and disposition of quinapril and perindopril might be altered by liver function since both drugs are extensively metabolized to their active metabolites, quinaprilat and perindoprilat, in the liver.8,18,19) In this study, these parent drugs might be converted to their active metabolites in all patients participated, similar to patients with normal liver and renal function, since they had normal liver function. It has been reported that the pharmacokinetics of these parent drugs are not influenced by renal failure.8,18,20) Contrary to the parent drugs, the pharmacokinetics of their metabolites would be differentially influenced by renal failure1,4,15,21) since the percentages of urinary recovery of quinaprilat and perindoprilat in normal subjects are different (quinaprilat: approximately 30%; perindoprilat: approximately 15%).8,15)

It is well known that renal failure causes the accumulation of various endogenous and exogenous substances in the body and that haemodialyzability of such substances in plasma is affected by various factors, such as molecular weight, hydrophobicity, protein binding potency and volume of distribution. In the present study, the decreased percentage of the plasma concentration of perindoprilat by haemodialysis, which is represented as ER, was much greater than that of quinaprilat (0.75 vs. 0.35). The value of CL\(_{HD}\) for perindoprilat was also 2-fold greater than that of quinaprilat (110 vs. 50 ml/min). These results suggest that haemodialyzability of perindoprilat is higher than quinaprilat. Quinaprilat has a high hydrophobicity and binds extensively to plasma proteins (97%)18 although the volume of distribution is relatively small (0.31/kg).21) On the other hand, it has been reported that the protein binding of perindopril in patients with renal failure is approximately 75% whereas that of its active metabolite, perindoprilat, is approximately 20%.5,22) On the basis of these findings, the low haemodialyzability of

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**Table 2. Pharmacokinetic Parameters of Quinaprilat and Perindoprilat**

<table>
<thead>
<tr>
<th></th>
<th>Quinaprilat</th>
<th>Perindoprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER (ng/ml)</td>
<td>0.35±0.21</td>
<td>0.75±0.04</td>
</tr>
<tr>
<td>CL(_{HD}) (ml/min)</td>
<td>51.5±30.2</td>
<td>108.1±59.0</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>60.7±2.1</td>
<td>79.9±14.0</td>
</tr>
</tbody>
</table>

Each value represents mean±S.E.M., \( n=6 \). a) Significantly different from quinaprilat \( p<0.05 \).

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**Fig. 1.** Individual Plasma Concentrations of Quinaprilat and Perindoprilat before and after Haemodialysis

**Fig. 2.** Mean Semilogarithmic Data of Disappearance of Quinaprilat and Perindoprilat from Plasma after the Final Administration

Symbols: ○, perindoprilat; ●, quinaprilat. Each plot represents mean±S.E. (\( n=6 \)).
quinaprilat may be due to its hydrophobic property and high protein binding potency.

Owen and Brecher\textsuperscript{25} have encouraged that patients receiving ACE inhibitors should withhold them for at least 24 h prior to therapeutic plasma exchange. Their data appear to be useful for the patients without receiving haemodialysis as an index for therapeutic regimens of only ACE inhibitors that have relatively shorter terminal elimination half-life (t_{1/2}). However, quinaprilat in patients with haemodialysis is quite exceptional. London and colleagues\textsuperscript{13} have previously reported that the time required for concentration of quinaprilat below the detection limit was 100 h. However, in the present study, quinaprilat in plasma of patients with haemodialysis was detectable up to 192 h. Further analysis revealed that the t_{1/2} value of quinaprilat was approximately 60 h in the present study. The dosing and the other unknown elimination pathways such as metabolism and biliary excretion are likely to be important for t_{1/2} of quinaprilat. Wolter and Fritschka\textsuperscript{21} reported that the mean t_{1/2} values of quinaprilat in patients on haemodialysis is approximately 30 h. Another investigators have reported that the value is approximately 18 h for patients on haemodialysis.\textsuperscript{9} These values are smaller than that observed in this study. Although the precise reason for the difference between their data and ours is yet unknown, the discrepancy might be due to difference in the study conditions between the present study (multiple doses) and their studies (single dose). In this study, the estimated time required to eliminate quinaprilat completely from the body would be more than 9 d. Considering that about 7-fold of the t_{1/2} value of drug is needed to exclude completely drug from the body, we can propose that quinapril should be withheld for at least 2 to 3 weeks before LDL apheresis.

Verpooten \textit{et al.} have reported that the t_{1/2} value of perindoprilat in hypertensive patients with renal failure increased to 6-fold of that in patients with normal renal function (5 to 30 h) and that in patients with renal failure on haemodialysis was approximately 31 h, suggesting that the elimination of perindoprilat is influenced by renal failure, but not by haemodialysis.\textsuperscript{4} In the present study, the t_{1/2} value of perindoprilat was approximately 80 h, which is 2.5-fold longer than that has been reported previously.\textsuperscript{4} It is also considered to be able to exclude the effect of trandolapril used in this study on the elimination of quinapril and perindopril since trandolapril, an active metabolite of trandolapril, is mainly metabolized in the liver (data from Chugai Pharmaceutical Company, Tokyo, Japan). Thus, the differences in protocols and races (Japanese vs. Bergian) between their results and ours would be one of the reasons of the discrepancy although the precise reasons are yet unknown.

In consistent with previous report by Guérin and coworkers,\textsuperscript{20} the haemodialyzability of perindoprilat was relatively higher than other ACE inhibitors such as enalaprilat and lisinopril (approximately 60%).\textsuperscript{3} However, the value of CL_{HD} of perindopril observed in this study (108 ml/min) was larger than those observed in the previous studies (62 to 72 ml/min).\textsuperscript{4,22} The discrepancy of the CL_{HD} between our study and their studies may be caused by differences in haemodialyzer and/or membrane although the reasons should be investigated.

On the basis of the present data, the elimination half-life of perindoprilat is similar to that of quinaprilat although the haemodialyzability of perindoprilat is higher than that of quinaprilat. The present findings suggest that quinapril and perindopril should be withheld for at least 2 to 3 weeks before LDL apheresis, providing further information about clinical safety use of quinapril and perindopril for LDL apheresis. Further large scale analysis would be necessary since it is still difficult to standardize the duration of off-dose for haemodialysis patients receiving ACE inhibitors due to small number of patients and/or large interindividual variations in their elimination kinetics.

\textbf{REFERENCES}