Pharmacokinetic Behavior of Cyclosporine A in Liver Dysfunction

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ABSTRACT

The pharmacokinetic behavior of cyclosporine A (CyA), known as a potential immunosuppressive agent to prevent graft rejection in transplantation, was studied in patients with acute hepatitis and primary biliary cirrhosis (PBC). The ratios of blood concentration of total CyA (CyA and its metabolites), CyA, and CyA metabolites to dose/kg body weight, (t-CyA/dose, CyA/dose, and CyA-Met/dose, respectively) were significantly higher in patients with hepatitis than those in renal transplantation. In PBC patients these ratios showed a tendency to be smaller than those in renal transplantation, but were not significant. The ratio of CyA-Met/CyA was higher in the patients with hepatitis and PBC than that in renal transplantation. It was highest in the patients with PBC. The ratio of CyA-Met/CyA was significantly increased with a decrease of liver functions evaluated by serum glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and total serum bilirubin (t-Bil). These results indicate that hepatic function affects the pharmacokinetic behavior of CyA and the increased ratio of CyA-Met/dose could be caused by a possible increased efflux of metabolites into the blood circulation due to impaired bile excretion. These results also indicate the importance of therapeutic drug monitoring (TDM) in the use of CyA with patients with hepatic dysfunction.

Key words: Cyclosporine A, Renal transplantation, Acute hepatitis, Primary biliary cirrhosis

CyA has been used as a potential immunosuppressive agent to prevent graft rejection in transplantation including kidney, liver, lung, pancreas, and bone marrow transplants, and played an important role in the improvement of clinical results in transplantation. Self-immunosensitive diseases like Bechet's syndrome are also indicative for CyA. However, CyA has serious nephrotoxicity, neurotoxicity, and hepatotoxicity as adverse effects. Therefore, monitoring of the blood concentration of CyA is indispensable in its clinical use. Correlations between concentration and immunosuppressive response have been reported in some studies. However, the optimal blood concentration of CyA in clinical use has not yet been established. CyA is reported to be absorbed from the intestine, distributed widely, and then eliminated mainly through the bile and urine. However, intestinal absorption of CyA has been shown to be low and fluctuates according to the individual. Moreover, pharmacokinetic behavior is also affected by individual physiological conditions. Thus, the optimal application of CyA is difficult to determine. Since CyA is one of the drugs which enter the enterohepatic circulation, pharmacokinetic of CyA would be affected by hepatic function. In the present study, we studied the pharmacokinetic behavior of CyA in patients with liver dysfunction, acute hepatitis and PBC.

MATERIALS AND METHODS

TDM

The trough blood concentrations of t-CyA and CyA at the steady state in patients to whom CyA had been orally administered were measured by the FPIA method using polyclonal or monoclonal antiserum, respectively. From April 1991 to May 1994, the blood samples of 18 patients at Hiroshima University Hospital were proffered for TDM of CyA from the Department of Surgery II (Professor and Director, Kiyohiko Dohi, M.D., Ph.D.), the Department of Internal Medicine I (Professor and Director, Goro Kajiyama, M.D., Ph.D.), and the Department of Internal Medicine, Research Institute for Nuclear Medicine and Biology (Professor and Director, Atsushi Kuramoto, M.D., Ph.D.) after receiving the informed consent in accordance with institutional guidelines. The number of patients with renal transplantation without liver dysfunction, with acute hepatitis, and with PBC were 13 (9 males and 4 females,
Table 1. Ratio of blood concentrations/dose of cyclosporine A and clinical data

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<tr>
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<th>Renal Transplantation</th>
<th>Acute hepatitis</th>
<th>PBC</th>
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<td>(Ratio of blood concentrations*)</td>
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<tr>
<td>t-CyA/dose</td>
<td>105.9 ± 99.0</td>
<td>239.5 ± 26.4</td>
<td>84.2 ± 21.9</td>
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<tr>
<td>CyA/dose</td>
<td>44.7 ± 33.1</td>
<td>92.7 ± 18.2</td>
<td>25.1 ± 9.3</td>
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<tr>
<td>Cy-Met/dose</td>
<td>61.2 ± 66.2</td>
<td>146.8 ± 24.2</td>
<td>59.1 ± 12.5</td>
</tr>
<tr>
<td>Cy-Met/t-CyA</td>
<td>0.51 ± 0.12</td>
<td>0.61 ± 0.07</td>
<td>0.71 ± 0.04</td>
</tr>
<tr>
<td>Cy-Met/CyA</td>
<td>1.18 ± 0.3</td>
<td>1.74 ± 0.6</td>
<td>2.72 ± 0.5</td>
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(Clinical data)

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<tr>
<td>GOT (u/l)</td>
<td>22 ± 8</td>
<td>117 ± 66</td>
<td>320 ± 149</td>
</tr>
<tr>
<td>GPT (u/l)</td>
<td>33 ± 14</td>
<td>124 ± 75</td>
<td>282 ± 147</td>
</tr>
<tr>
<td>t-Bil (mg/dl)</td>
<td>0.6 ± 0.2</td>
<td>10.5 ± 3.7</td>
<td>16.1 ± 14.6</td>
</tr>
</tbody>
</table>

*: The abbreviations CyA, Cy-Met, and t-CyA signify cyclosporine A, its metabolites, and CyA plus Cy-Met, respectively. CyA/dose, Cy-Met/dose, and t-CyA/dose signify ratio of their values (ng/ml) to dose (mg)/body weight (kg).

33.8±11.0, 14 - 58 years old), 3 (1 male and 2 females, 38.3±17.2, 15 - 56 years old), and 2 (2 females, 22 and 31 years old), respectively.

The blood concentration of CyA-Met was estimated from the difference in concentration of CyA and t-CyA.

Clinical data
Clinical data of GOT, GPT, and t-Bil were obtained at the Clinical Laboratory Services, Hiroshima University Hospital (Professor and Director, Masayuki Kambe, M.D., Ph.D.), with an automatic analyzer (Model 7250, Hitachi Co. Ltd., Tokyo Japan).

Statistical analysis
The statistical analysis of the data was made by t-test. A p value of < 0.05 was considered to be statistically significant.

RESULTS
Concentrations (ng/ml) of t-CyA, CyA, and CyA-Met in each patient group were normalized by dose (mg/kg) body weight (kg) and are summarized in Table 1 and Fig. 1. The ratios of blood concentration (ng/ml) to dose (mg/kg body weight), t-CyA/dose, CyA/dose, and CyA-Met/dose, were 239.5±26.4, 92.7±18.2, and 146.8±24.2 (mg/ml), respectively, in acute hepatitis. Those in patients with renal transplantation were 105.9±99.0, 44.7±33.1, and 61.2±66.2, respectively. The ratios in acute hepatitis were significantly lower (p<0.05) than those in renal transplantation. Those in PBC were 84.2±21.9, 25.1±9.3, and 59.1±12.5, respectively. In PBC, these values tended to be smaller than those in renal transplantation, but were not significant.

Fig. 2 illustrates the correlation of the ratio of Met/CyA to clinical data. The correlation coefficients (r) of the ratio to GOT, GPT, and t-Bil, were 0.72, 0.38, and 0.67, respectively, and these values were significant (p<0.001).

DISCUSSION
As shown in Table 1, the clinical values of the patients with renal transplantation such as GOT, GPT, and t-Bil were within the normal range and those of the patients with acute hepatitis or PBC were higher than normal. The normalized value of t-CyA in the patients with acute hepatitis was found to be higher than that in the patients with renal transplantation or with PBC. The patients with PBC showed the lowest value of t-CyA. Because CyA is reported to be absorbed from the intestine with the aid of bile salts<sup>6</sup>, the absorption of CyA from the intestine depends on the
degree of obstruction of the bile flow. Further, the concentration of t-CyA in the blood depends on both the absorbed amount of CyA and the efflux of CyA and CyA-Met into the blood circulation from the liver cells. In the case of acute hepatitis or PBC, the bile flow is obstructed to some extent depending on the condition of the patients. In such patients, the blood level of CyA and CyA-Met would tend to be increased by the excessive efflux from the liver cells. It has been reported that an acute ligation of the bile duct increased the blood CyA concentration by two to sixfold10).

This fact corresponds well with our results from the patients with acute hepatitis. As discussed above, the blood level of CyA will be affected by both the bile formation and the efflux from the liver cells. The obstruction of the bile flow was more severe in the patients with PBC than in the patients with acute hepatitis. In the patients with acute hepatitis, the bile salts were still available for the absorption of CyA. The higher level of t-CyA/dose in the patients with acute hepatitis compared with those in renal transplantation may be explained by a possible obstruction of biliary excretion of CyA and CyA-Met.

Because of the higher level of t-Bil, an almost complete obstruction of the bile flow is expected in patients with PBC. A complete obstruction of the bile flow will cause impairment of the intestinal absorption of CyA, because CyA is absorbed by the intestine with the aid of bile salts. The lower blood of t-CyA/dose in the patients with PBC may be mainly attributable to an impairment of intestinal absorption. The similar values of CyA-Met/CyA in the three patient groups (Table 1) suggest that CyA is still metabolized by the liver in spite of liver dysfunction in the patients with acute hepatitis or PBC.

The value of CyA-Met/CyA correlates with clinical data as shown Fig. 2. These findings suggest that an excessive efflux of CyA and CyA-Met into the blood circulation from the liver is related to the degree of injury of the hepatocytes, which caused the obstruction of bile flow.

In the present study, we demonstrated that the pharmacokinetic behavior of CyA was affected by liver dysfunction, especially obstruction of the bile flow and the efflux of CyA and CyA-Met into the blood circulation from the hepatocytes. These findings strongly support that TDM is indispensable to therapy with CyA especially in patients with liver dysfunction.

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