Effect of Hepatic Dysfunction on Oral Cyclosporine Pharmacokinetics in Marrow Transplant Patients

By Gary C. Yee, Michael S. Kennedy, Rainer Storb, and E. Donnall Thomas

The effect of hepatic dysfunction, defined as abnormal serum bilirubin level, on oral cyclosporine (CSP) pharmacokinetics was examined in 28 marrow transplant patients who received CSP for prophylaxis of graft-v-host disease. Serum CSP concentrations were measured by radioimmunoassay. Forty-one concentration–time courses were studied, divided among patients with no (< 1.2 mg/dL), mild (1.2 to 2.0 mg/dL), and moderate (2.0 to 5.0 mg/dL) hepatic dysfunction. CSP elimination, as determined by elimination rate constant and clearance, was delayed in patients with moderate hepatic dysfunction compared to those with no hepatic dysfunction (P < .05). The volume of distribution, lag time for absorption, maximum serum concentration, and time at which the maximum concentration was achieved was not affected by hepatic function. These data indicate that patients with moderate hepatic dysfunction have delayed CSP or CSP metabolite elimination and may be at higher risk for developing CSP-related toxicity.

Cyclosporine (CSP) is a cyclic undecapeptide with immunosuppressive activity. The exact mechanism is unknown, although the drug selectively inhibits T lymphocyte activity. Unlike most immunosuppressive agents, CSP is not myelosuppressive at therapeutic concentrations, which is important in marrow transplant patients. In patients with acute nonlymphocytic leukemia, a randomized comparison of CSP and methotrexate for prophylaxis of graft-v-host disease shows that CSP-treated patients have significantly faster engraftment and shorter hospitalization than methotrexate-treated patients. Severe graft-v-host disease was also less common in the CSP group, but this difference was not statistically significant. A nonrandomized study in aplastic anemia patients shows similar results, although the incidence or severity of graft-v-host disease was not different in the CSP group.

Marrow transplant recipients frequently develop hepatic dysfunction during their posttransplant course. Since CSP is extensively metabolized and subject to biliary elimination, we analyzed our pharmacokinetic data after oral administration to determine the possible effect of hepatic dysfunction on CSP elimination. Our results show that moderate hepatic dysfunction delays CSP or CSP metabolite elimination.

Materials and Methods

Subjects

Twenty-eight patients with leukemia (21) or aplastic anemia (seven) were admitted to the Fred Hutchinson Cancer Research Center for allogeneic marrow transplantation. Forty-one CSP concentration–time courses were studied in these patients after oral administration. The pretransplant chemotherapy and irradiation regimens used to prepare patients for marrow grafting have been described elsewhere. Briefly, patients with aplastic anemia were prepared with high-dose cyclophosphamide (50 mg/kg x 4), while those with leukemia were prepared with high-dose cyclophosphamide (60 mg/kg x 2) and fractionated total body irradiation.

Informed consent was obtained from all donors and recipients. Protocols and consent forms were approved by the Human Subjects Review Committee of the University of Washington or the Fred Hutchinson Cancer Research Center. Only adults (age > 16 years) were included in the analysis; the median age of patients was 28.5 years (range, 17 to 44).

All patients received CSP for prophylaxis of acute graft-v-host disease, beginning at least one day before transplant and continuing until day 180, although doses were gradually tapered after day 50. The oral CSP dose ranged between 5.5 and 7.5 mg/kg in all patients (daily dose 11 to 15 mg/kg/d), administered twice daily as a suspension diluted in milk or juice. All CSP concentration–time courses were analyzed after steady-state was achieved (> two days). All of the courses were studied during the first 30 days after marrow grafting.

Hepatic dysfunction was defined by serum bilirubin levels. CSP courses were divided into three categories of hepatic dysfunction: none (< 1.2 mg/dL), mild (1.2 to 2.0 mg/dL), and moderate (2.0 to 5.0 mg/dL). Similar analyses were performed for serum transaminase and alkaline phosphatase, but these tests of hepatic function did not appear to correlate with CSP pharmacokinetics. Renal function, as measured by serum creatinine, was normal (< 1.5 mg/dL) in all 41 courses.

Blood Collection

Blood samples (5 to 7 mL) were obtained from indwelling right atrial (Hickman) catheters at 0.5, 1.5, 2, 3, 4, 6, 8, and 11 hours after oral CSP administration. Some patients also had blood drawn immediately preceding the study course. Blood was allowed to clot at room temperature for at least two hours, and serum was removed after centrifugation. Serum samples were either analyzed the next day or frozen at −70 °C until analysis.

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**Assay Procedure**

Serum samples were assayed in duplicate by radioimmunoassay. The procedure was carried out as published. The coefficient of variation at CSP concentrations of 100 and 400 ng/mL is 8.8% and 4.7%, respectively. The minimum detectable concentration is about 20 ng/mL.

**Data Analysis**

CSP concentration–time data were fitted with DRUGMODEL, a nonlinear least-squares regression program available on the PROPHET system. CSP concentrations from the preceding dose, when available, were included in the analysis of concentration vs time data. All CSP concentration data were weighted as the reciprocal of the measured value. For oral CSP, this analysis provided estimates of elimination rate constant ($K_e$), lag time for absorption ($t_{lag}$), maximum serum concentration ($C_{max}$), and time at which $C_{max}$ was achieved ($t_{max}$). Mean serum half-life was calculated by dividing 0.693 by the mean $K_e$. Since patients received different doses, the maximum CSP concentration was also divided by the CSP dose and reported as the $C_{max}/D$ ratio ([ng/mL]/[mg/kg]). Volume of distribution and clearance were also calculated and divided by the fraction of dose absorbed ($V_d/F$ and $C_l/F$).

Pharmacokinetic parameters for patients with normal hepatic function were compared to those with mild or moderate hepatic dysfunction. No statistically significant differences were noted between leukaemia and aplastic anaemia patients. Both parametric and nonparametric statistical methods were used. When the data were normally distributed, the two-sample t-test was used for statistical comparisons. When the data were nonnormally distributed, the Mann-Whitney test was used. A $P$ value of less than .05 was considered statistically significant.

**RESULTS**

Table 1 shows the effect of hepatic dysfunction on CSP pharmacokinetics after oral administration. Mean serum half-life increased in patients with hepatic dysfunction; mean values were 3.5, 5.8, and 8.7 hours in patients with no, mild, or moderate hepatic dysfunction, respectively. The difference in $K_e$ between patients with no hepatic dysfunction and those with moderate hepatic dysfunction was statistically significant ($P < .01$). Patients with moderate hepatic dysfunction also had delayed $C_l/F$ values compared to patients with no hepatic dysfunction (Fig 1) ($P < .05$).

![Fig 1. Cyclosporine $C_l/F$ in patients with no, mild, or moderate hepatic dysfunction. Bars indicate the mean ± SEM (serum bilirubin, mg/dL).](image)

patients with no hepatic dysfunction ($P < .05$). $V_d/F$ did not appear to be altered by changes in hepatic dysfunction. Since there was no significant difference in $C_{max}$ or $C_{max}/D$ ratios between patients with no hepatic dysfunction and those with mild hepatic dysfunction, these groups were combined and compared to patients with moderate hepatic dysfunction. Patients with moderate hepatic dysfunction also had increased $C_{max}$ and $C_{max}/D$ ratios compared to patients with no or mild hepatic dysfunction ($P < .05$).

**DISCUSSION**

Our data show that changes in serum bilirubin correlate with changes in CSP elimination. Serum half-life increased as serum bilirubin increased, with mean values of 3.5, 5.8, and 8.7 hours in patients with no, mild, and moderate hepatic dysfunction, respectively. Since changes in half-life can be caused by changes in volume of distribution, clearance, or both, we also calculated these pharmacokinetic parameters, divided by the estimated fraction absorbed. The decrease in $C_l/F$ without a change in $V_d/F$ in patients with moderate hepatic dysfunction compared to those with no hepatic dysfunction clearly shows that decreased CSP clearance is responsible for the increased half-life (Fig 1). $C_l/F$ in patients with mild hepatic dysfunction was not significantly different than in patients with no hepatic dysfunction, although mean half-life was increased from 3.5 to 5.8 hours. This was probably due to an increase in $V_d/F$ (29.6 v 22.8 L/kg) in patients with mild hepatic dysfunction.

Although no single test of hepatic function is a specific marker for drug metabolism, serum bilirubin correlated most accurately with CSP elimination. Other common tests of hepatic function, such as serum transaminase or alkaline phosphatase, did not appear to be helpful. $C_l/F$ was not significantly different for patients with abnormal alkaline phosphatase values ($n = 13$) compared to those with normal alkaline

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**Table 1. Effect of Hepatic Dysfunction on Oral Cyclosporine Pharmacokinetics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>None ($n = 29$)</th>
<th>Mild ($n = 9$)</th>
<th>Moderate ($n = 7$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_e$ (h$^{-1}$)</td>
<td>0.20 ± 0.06</td>
<td>0.12 ± 0.03</td>
<td>0.08 ± 0.02†</td>
</tr>
<tr>
<td>$C_l/F$ (mL/min/kg)</td>
<td>62.80 ± 6.00</td>
<td>50.20 ± 11.10</td>
<td>29.60 ± 7.10†</td>
</tr>
<tr>
<td>$V_d/F$ (L/kg)</td>
<td>22.80 ± 3.10</td>
<td>29.60 ± 17.80</td>
<td>21.20 ± 6.10</td>
</tr>
<tr>
<td>$Cl/F$ (mL/min/1.73m²)</td>
<td>1.30 ± 0.10</td>
<td>1.60 ± 0.30</td>
<td>1.70 ± 0.50</td>
</tr>
<tr>
<td>$C_{max}$ (mg/mL)</td>
<td>383.00 ± 69.00</td>
<td>376.00 ± 85.00</td>
<td>776.00 ± 223.00‡</td>
</tr>
<tr>
<td>$C_{max}/D$ (mg/mL)</td>
<td>61.30 ± 10.40</td>
<td>62.20 ± 14.30</td>
<td>129.40 ± 36.50‡</td>
</tr>
<tr>
<td>$t_{lag}$ (h)</td>
<td>3.80 ± 0.20</td>
<td>4.40 ± 0.40</td>
<td>3.90 ± 0.40</td>
</tr>
</tbody>
</table>

*As determined by elevated serum bilirubin levels: none (<1.2 mg/dL), mild (1.2 to 2.0 mg/dL), moderate (2.0 to 5.0 mg/dL).
†$P < .05$ when compared to patients with no hepatic dysfunction.
‡$P < .05$ when compared to patients with either no or mild hepatic dysfunction.
phosphatase values (n = 28) (47.2 \pm 49.7 \text{mL/min/kg}). Similarly, patients with elevated serum transaminase (n = 11) did not eliminate CSP differently than those with normal serum transaminase (n = 30) (50.6 \pm 41.1 \text{mL/min/kg}).

Hepatic dysfunction occurs in many marrow recipients during the postgrafting period. The etiology is often unclear, but the most likely causes during the first 30 days posttransplant are early acute graft-versus-host disease or toxicity from the preparative regimen. Hepatic dysfunction is known to delay elimination of some drugs that are extensively metabolized. Pharmacokinetic studies show that CSP is extensively metabolized and subject to biliary elimination. Less than 1% of an administered dose is excreted unchanged in the urine. No pharmacokinetic studies of CSP in patients with hepatic dysfunction have been reported.

Marrow transplantation is now being performed not only for leukemia and aplastic anemia, but also for non-Hodgkin's lymphoma and a variety of nonmalignant hematologic diseases, such as Fanconi's anemia, thalassemia, and Wiskott-Aldrich syndrome. The recent approval of CSP by the US Food and Drug Administration will probably lead to increased use for "nonapproved" indications, such as marrow transplantation. Although wide interpatient variability in CSP pharmacokinetics precludes any definite dosing recommendations, we suggest that clinicians monitor CSP concentrations in all marrow graft recipients and be aware of the potential for accumulation of CSP or CSP metabolites, with its resulting risk of nephrotoxicity, in patients with hepatic dysfunction.

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REFERENCES

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