Population Pharmacokinetics of Higher-Dose Mizoribine in Healthy Male Volunteers

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Received July 3, 2006; accepted September 7, 2006

The population pharmacokinetic parameters of mizoribine in healthy subjects were estimated using a nonlinear mixed effects model (NONMEM) program. Pharmacokinetic data for population analysis were obtained in the previous study, in which 24 healthy Caucasian male subjects participated in a single-dose (3, 6, 9, 12 mg/kg) study, and 12 subjects participated in a multiple-dose (6, 12 mg/kg/d) study. The mean value of the absorption lag time, absorption rate constant (Ka), and apparent distribution volume (V/F) was estimated to be 0.349 h, 0.869 h⁻¹, and 0.834 l/kg, respectively. Oral clearance (CL/F) was modeled with creatinine clearance (CLcr), and the mean value was estimated to be 1.93 · CLcr l/h. In addition, pharmacokinetic parameters in individual 36 subjects were obtained from population estimates according to Bayes’ theorem. Pharmacokinetic parameters (Ka, V/F, and CL/F) in the single-dose study were almost constant at a dose range of 3—12 mg/kg, and were similar to those in the multiple-dose study. These findings indicated that the pharmacokinetics of mizoribine is well described by a simple one-compartment model with first-order absorption.

Key words Bayesian analysis; mizoribine; nonlinear mixed effect model; population pharmacokinetics

Mizoribine is an orally available immunosuppressive agent, which has been on the market since 1984 in Japan for the prevention of rejection in renal transplantation. In contrast to other immunosuppressive agents (e.g., azathioprine), mizoribine has been shown in animal experiments to lack oncogenicity and has shown clinically a low incidence of severe adverse drug reactions (such as myelosuppression and hepatotoxicity), making it useful in the treatment of long-term immunosuppressive therapy. After oral administration, mizoribine is absorbed rapidly from the gastro-intestinal tract and distributed into living cells according to a concentration gradient between the extracellular and intracellular environment. It is completely eliminated from blood circulation within 24 h, and is excreted in urine (85%), feces (9.7%), and bile (<1%). As elimination rate of mizoribine is highly dependent on renal function, low-dose mizoribine (1 to 3 mg/kg/d) was administered to patients whose renal function did not return soon after transplantation. However, renal function returns much earlier following transplantation than those with 20% fewer acute rejection episodes at 3 months post-transplantation than those with <5 mg/kg/d of mizoribine. Recently, phase 1 single- and multiple-dose studies have been carried out to confirm the safety, tolerability, and pharmacokinetics of higher-dose (up to 12 mg/kg/d) mizoribine. In the phase 1 study, no notable or clinically relevant abnormality was observed in the clinical laboratory values except for transient elevation in serum uric acid at the highest dose level (multiple dose of 12 mg/kg/d). In the present study, to evaluate the pharmacokinetic characteristics of mizoribine in subjects with normal renal function, we estimated the population pharmacokinetic parameters of mizoribine using a nonlinear mixed effects model (NONMEM) program. Pharmacokinetic data for population analysis were obtained in the previous phase 1 study, where 24 healthy Caucasian male subjects participated in a single-dose (3, 6, 9, 12 mg/kg) study, and 12 subjects participated in a multiple-dose (6, 12 mg/kg/d) study. In addition, to assess linearity and constancy in the pharmacokinetics of mizoribine, the pharmacokinetic parameters in individual 36 subjects were obtained from the population estimates according to Bayes’ theorem using the NONMEM post-hoc option. We further evaluated the precision of Bayesian analysis in the sparse sampling protocol by using pharmacokinetic data obtained from 24 subjects in the single-dose study.

MATERIALS AND METHODS

Pharmacokinetic Data Serum mizoribine concentration data for population pharmacokinetic analysis were obtained in the previous study. Briefly, 36 healthy Caucasian males, aged 18—45 years old (mean: 25.8) and weighing 54.4—98.2 kg (mean 75.6), took mizoribine in the two trials. Twenty-four subjects participated in the single-dose study; and 12 subjects participated in the multiple-dose study. The single-dose study was enrolled with 4 dose levels (3, 6, 9, 12 mg/kg using 50 mg tablets) of 6 subjects. Blood samples were collected for mizoribine analysis at predose (Hour 0) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 2 predose), 48 (Day 3 predose), 72 h (Day 4 predose), and at the following timepoints on Day 5: predose (Hour 0 of Day 5 or Hour 96 of Day 1), and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdose. The multiple-dose design with 2 dose levels of mizoribine was investigated in 2 groups of 6 subjects. In Dose Group 1, each subject received a once-daily administration of 6 mg/kg mizoribine on Days 1 to 5 (inclusive). Blood samples were collected for mizoribine analysis at predose (Hour 0) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24 (Day 2 predose), 48 (Day 3 predose), 72 h (Day 4 predose), and at the following timepoints on Day 5: predose (Hour 0 of Day 5 or Hour 96 of Day 1), and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdose. In Dose Group 2, each subject received 6 mg/kg/12 h of mizoribine for 7 consecutive days (a total of 13 doses). Blood samples were collected for 7 consecutive days (a total of 13 doses). Blood samples were collected during each study period at predose (Hour 0) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdose.
3, 4, 6, 8, 12 (Day 1, PM predose), 48 (Day 3, AM predose), 72 (Day 4, AM predose), 96 (Day 5, AM predose), 120 h (Day 6, AM predose), and at the following timepoints on Day 7, AM: predose (Hour 0 of Day 7 or Hour 144 of Day 1), and at 0.5, 1, 2, 3, 4, 6, 8, and 12 h postdose. Serum samples were analyzed using a validated HPLC method.5,7

**Estimation of Population Pharmacokinetic Parameters of Mizoribine** Population mean pharmacokinetic parameters and their interindividual variations were estimated using the NONMEM analysis, for which we used the first-order conditional estimation method in the present study.6 The one-compartment model with first-order absorption was parameterized in terms of absorption lag time (ALAG), absorption rate constant (KA), the apparent volume of distribution (V/F), and oral clearance (CL/F) with NONMEM-PREDPP library subroutines, ADVAN2 and TRANS2.6 The absorption lag time in the ith individual (ALAGi) was modeled using the following equation:

\[
ALAG_i = \theta_1
\]

where \( \theta_1 \) is the predicted population mean of the absorption lag time. The absorption rate constant in the ith individual (KAi) was modeled using the following equation:

\[
KA_i = \theta_2 \cdot \exp(\eta_{KA})
\]

where \( \theta_2 \) is the predicted population mean of the absorption rate constant, and \( \eta_{KA} \) is a random variable distributed with a mean of zero and variance of \( \omega_{KA}^2 \). The apparent volume of distribution in the ith individual (VFi) was modeled using the following equation:

\[
V_{Fi} = \theta_3 \cdot WT \cdot \exp(\eta_{VFi})
\]

where \( \theta_3 \) is the predicted population mean of the apparent volume of distribution, and \( \eta_{VFi} \) is a random variable distributed with a mean of zero and variance of \( \omega_{VFi}^2 \). Oral clearance in the ith individual (CLFi) was modeled using the following equation:

\[
CLFi = \theta_4 \cdot CLcr \cdot \exp(\eta_{CLFi})
\]

where \( \theta_4 \) is the predicted population mean of oral clearance, and \( \eta_{CLFi} \) is a random variable distributed with a mean of zero and variance of \( \omega_{CLFi}^2 \). The creatinine clearance (CLcr) value (in l/h) was calculated using the Cockcroft–Gault equation as follows:

\[
CLcr = \frac{140 - AGE}{72 \cdot Scr} \cdot \frac{60}{1000}
\]

where AGE is age, WT is body weight, and Scr is serum creatinine concentration (in mg/dl). Finally, the ith observed serum concentration in the ith subject (Ci) was assumed to be randomly and normally distributed from the predicted value (\( C_i^* \)):

\[
C_i^* = C_i + e_i
\]

where \( e_i \) is a random variable that describes intraindividual variability with a mean of zero and variance of \( \sigma^2 \).

**Bayesian Analysis** The pharmacokinetic parameters of mizoribine in individual 36 subjects were estimated according to Bayes’ theorem using the NONMEM post-hoc option.9 We examined linearity in the pharmacokinetics of mizoribine in the single-dose (3, 6, 9, 12 mg/kg) study, based on pharmacokinetic parameters in individual subjects. In addition, in order to examine constancy in the disposition of mizoribine, the pharmacokinetic parameters in the single-dose study were compared to those in the multiple-dose (6, 12 mg/kg/d) study. We further evaluated the precision of Bayesian analysis in the sparse sampling protocol by using pharmacokinetic data obtained from 24 subjects in the single-dose study.9 That is, the mean absolute differences (MAD) for KA, CL/F, and V/F between the full and reduced sampling protocols were calculated as follows:

\[
MAD(\%) = \frac{\sum_{i=1}^{24} |P_{full(i)} - P_{reduced(i)}|}{24} \cdot 100
\]

where \( P_{full(i)} \) is the parameter estimate from the full sampling protocol consisting of 9 sampling points (0.5, 1, 2, 3, 4, 6, 8, 12, 24 h postdose) in the ith subject, and \( P_{reduced(i)} \) is the parameter estimate from any reduced sampling protocol in the ith subject.

**Statistical Analysis** Values are expressed as the mean±S.D. Comparisons between the means of multiple groups were made by using one-way analysis of variance (ANOVA). p values of less than 0.05 were considered significantly different.

**RESULTS**

**Population Pharmacokinetic Parameters of Mizoribine** The mean and S.D. values of serum mizoribine concentration following single oral administration at doses of 3, 6, 9, or 12 mg/kg are shown in Fig. 1. The individual observed concentrations of mizoribine following once- and twice-daily administrations at the dose of 6 mg/kg are shown in Figs. 2 and 3, respectively. The population pharmacokinetic parameters were estimated using serum mizoribine concentration data obtained from all 36 subjects. NONMEM provides estimates of the standard error (S.E.) for all parameters, and S.E. can be used to define 95% confidence intervals (CI) for true parameter values: 95% CI=(the estimated parameter value)±1.96·S.E. Table 1 shows the population pharmacokinetic parameters of mizoribine and their 95% CI estimated by NONMEM analysis. The mean values of ALAG and KA were estimated to be 0.349 h and 0.869 l/h, respectively, indicating that mizoribine is very rapidly absorbed after oral administration. The mean value of V/F was estimated to be 0.834·WT1. The mean (±S.D.) CLcr values in 36 subjects were 7.54 (±1.40) l/h. The CL/F value was estimated to be 1.93·CLcr l/h, which suggested that the CL/F value is greater than the renal glomerular filtration rate, and that renal tubular secretion is involved in the elimination pathway. In the present study, we did not introduce interindividual variability in ALAG for simplicity. On the other hand, the \( \omega_{KA}^2, \omega_{VFi}^2, \) and \( \omega_{CLFi}^2 \) values were estimated to be 0.269, 0.354, and 0.332, respectively, which indicated that the interindividual variability of KA, V/F, and CL/F was significant. In addition, Fig. 1 shows concentration-time curves calculated according to population pharmacokinetic parameters following single administration at the 4 dose levels. The predicted serum concentrations of mizoribine were well correlated with the ob-
CLcr-corrected oral clearance (CLcr)
weight-corrected apparent distribution volume (VWT)
repetitive administration. Moreover, the mean values of mizoribine was linear for dose-escalation and stationary for stationary for parameter value of mizoribine absorption.

The pharmacokinetic parameters (Table 2) of Bayesian analysis in these well-designed sampling protocols was fairly good: MAD values were less than 6% in all 12 subjects. These results indicated that the pharmacokinetics of mizoribine was constant for repetitive administration, and that intestinal absorption and renal excretion were not saturated even after multiple doses at up to 12 mg/kg/d.

Sparse Sampling Designs in Bayesian Analysis

In clinical practice, the estimation of pharmacokinetic parameters from only a few measurements is useful to assess drug exposure (AUC or Cmax) in individual subjects, which is possible by Bayesian analysis that takes into account prior information (population mean pharmacokinetic parameters and their interindividual variability). To evaluate the performance of Bayesian analysis in sparse sampling designs, we used data from 24 subjects in the single-dose study. The MAD values of KA, CL/F, and V/F in the reduced sampling protocol are shown in Fig. 4. The objects in the rows and columns are called stars, and the lengths of the radii of each star are MAD values of these parameters estimated from 5, 4, and 3 blood samples, respectively. Expectedly, the predictive performance of Bayesian analysis in these well-designed sampling protocols was fairly good: MAD values were less than 6% in all parameters. Panels (D)—(N) show the performance of Bayesian analysis in relatively poor sampling protocols. The MAD values of KA and/or V/F in panels (D)—(N) were considerably large. In addition, the precise estimation of CL/F is important to predict the AUC value at any given dose. The MAD values of CL/F in panels (D), (H), (I), (J), and (K) were not very large compared with those in panels (E), (F), (G), (L), (M), and (N), suggesting that taking two blood samples at 2—8 h after the dose is generally useful for the precise estimation of CL/F.

DISCUSSION

Pharmacokinetic data of higher-dose mizoribine were ob-

Table 1. Population Pharmacokinetic Parameters of Mizoribine in Healthy Volunteers

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimates</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \theta_1 ) (h)</td>
<td>0.349</td>
<td>0.325—0.374</td>
</tr>
<tr>
<td>( \theta_2 ) (h(^{-1}))</td>
<td>0.869</td>
<td>0.767—0.971</td>
</tr>
<tr>
<td>( \theta_3 ) (l/kg)</td>
<td>0.834</td>
<td>0.730—0.938</td>
</tr>
<tr>
<td>( \alpha_{ALAG} )</td>
<td>1.93</td>
<td>1.72—2.14</td>
</tr>
<tr>
<td>( \alpha_{CL/F} )</td>
<td>0.269</td>
<td>0.124—0.341</td>
</tr>
<tr>
<td>( \alpha_{V/F} )</td>
<td>0.354</td>
<td>0.257—0.429</td>
</tr>
<tr>
<td>( \alpha_{CL} )</td>
<td>0.332</td>
<td>0.267—0.385</td>
</tr>
<tr>
<td>( \sigma (\mu g/ml) )</td>
<td>0.352</td>
<td>0.263—0.423</td>
</tr>
</tbody>
</table>

erved serum concentration of the drug at any dose tested, which indicated that the pharmacokinetics can be well described by a simple one-compartment model with first-order absorption.

Linearity and Constancy in the Pharmacokinetics of Mizoribine
The pharmacokinetic parameters (KA, V/F, CL/F) in individual 36 subjects were obtained from population estimates according to Bayes’ theorem using the NONMEM post-hoc option. In addition, the pharmacokinetic parameters (\( t_{1/2} \), \( T_{max} \), \( C_{max} \), AUC) in each subject were calculated using the ALAG, KA, V/F, and CL/F values in individual 36 subjects. Table 2 shows the mean values of KA, weight-corrected apparent distribution volume (\( (V/F)/WT \)), CLcr-corrected oral clearance (\( (CL/F)/CLcr \)), \( t_{1/2} \), \( T_{max} \), \( C_{max} \), and AUC in each single- and multiple-dose group. Each parameter value of KA, (V/F)/WT, and (CL/F)/CLcr was not significantly different among 6 groups (\( p>0.05 \) by one-way ANOVA), which indicated that the pharmacokinetics of mizoribine was linear for dose-escalation and stationary for repetitive administration. Moreover, the mean values of \( t_{1/2} \) and \( T_{max} \), which ranged from 2.68 to 3.08 h and from 2.28 to 2.67 h, respectively, did not change with dose escalation in the single-dose study (Table 2). On the other hand, the mean values of calculated \( C_{max} \) increased linearly along with dose escalation, and were 2.65, 5.32, 6.32, and 9.31 \( \mu g/ml \) at doses of 3, 6, 9, and 12 mg/kg, respectively. Similarly, the mean values of calculated AUC\(_{0\rightarrow t_{max}} \) at the 4 dose levels in the single-dose study increased linearly as the dose increased (Table 2). Figures 2 and 3 show the predicted serum mizoribine concentration–time curves in typical subjects. The trough mizoribine concentration was nearly equal to zero at 24 h after the dose of 6 mg/kg (Fig. 2), whereas 0.16—1.86 \( \mu g/ml \) at 12 h after the dose of 6 mg/kg (Fig. 3). The correlation between predicted and observed serum mizoribine concentrations was fairly good in all 12 subjects. These results indicated that the pharmacokinetics of mizoribine was constant for repetitive administration, and that intestinal absorption and renal excretion were not saturated even after multiple doses at up to 12 mg/kg/d.

Fig. 1. Serum Mizoribine Concentrations Following Single Oral Administration ((A): 3 mg/kg, (B): 6 mg/kg, (C): 9 mg/kg, and (D): 12 mg/kg)

Open circles represent the mean observed concentrations, and horizontal bars represent the S.D. values. Solid curves represent the predicted concentration calculated according to the population pharmacokinetic parameters.
tained in the previous study, in which 24 healthy Caucasian male subjects participated in a single-dose (3, 6, 9, 12 mg/kg) study, and 12 subjects participated in a multiple-dose (6, 12 mg/kg/d) study. In the present study, the population pharmacokinetic parameters of mizoribine in healthy subjects were estimated using a NONMEM program (Table 1). The pharmacokinetics of mizoribine was well described by a simple one-compartment model with first-order absorption (Fig. 1). In addition, the pharmacokinetic parameters in individual 36 subjects could be obtained from population estimates according to Bayes’ theorem. The predicted serum concentrations of mizoribine were correlated fairly well with the observed serum concentrations even in the multiple-dose study (Figs. 2, 3). Furthermore, Bayesian analysis seemed useful to estimate the precise parameters from a limited number of blood samples in individual subjects (Fig. 4).

### Table 2: Pharmacokinetic Parameters of Mizoribine Following Single or Multiple Oral Administration

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>$\text{ALAG (h)}$</th>
<th>$\text{KA (h}^{-1})$</th>
<th>$(\text{V/F)WT (l/kg)}$</th>
<th>$(\text{CL/F)CLcr t}_{1/2} (h)$</th>
<th>$\text{T}_{\text{max}} (h)$</th>
<th>$\text{C}_{\text{max}} (\mu g/ml)$</th>
<th>$\text{AUC (mg·h/l)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.349</td>
<td>0.91±0.10</td>
<td>0.76±0.30</td>
<td>2.16±0.46</td>
<td>2.75±0.29</td>
<td>2.31±0.19</td>
<td>2.65±0.72</td>
</tr>
<tr>
<td>6</td>
<td>0.349</td>
<td>0.72±0.12</td>
<td>0.69±0.23</td>
<td>1.72±0.49</td>
<td>2.96±0.52</td>
<td>2.67±0.23</td>
<td>5.32±1.16</td>
</tr>
<tr>
<td>9</td>
<td>0.349</td>
<td>0.91±0.23</td>
<td>1.01±0.36</td>
<td>2.52±0.90</td>
<td>3.08±0.36</td>
<td>2.43±0.35</td>
<td>6.32±2.50</td>
</tr>
<tr>
<td>12</td>
<td>0.349</td>
<td>0.91±0.14</td>
<td>0.81±0.19</td>
<td>2.21±0.71</td>
<td>2.68±0.53</td>
<td>2.28±0.25</td>
<td>9.31±2.27</td>
</tr>
<tr>
<td>6 (mg/kg/24 h)</td>
<td>0.349</td>
<td>0.86±0.14</td>
<td>0.88±0.19</td>
<td>1.87±0.52</td>
<td>3.21±0.77</td>
<td>2.49±0.29</td>
<td>4.41±0.78</td>
</tr>
<tr>
<td>6 (mg/kg/12 h)</td>
<td>0.349</td>
<td>1.04±0.26</td>
<td>1.16±0.46</td>
<td>2.23±0.71</td>
<td>3.64±0.67</td>
<td>2.24±0.28</td>
<td>3.92±1.42</td>
</tr>
</tbody>
</table>

a) Values are expressed as the mean±S.D. (n=6). b) $\text{T}_{\text{max}}$ at steady-state. c) $\text{C}_{\text{max}}$ at steady-state. d) $\text{AUC}_{0-\infty}$. e) $\text{AUC}_{96-120}$. f) $\text{AUC}_{144-156}$.

Fig. 2. Serum Mizoribine Concentrations in 3 Typical Subjects Following Once-Daily Administration at 6 mg/kg

Open circles represent the observed serum mizoribine concentrations. Solid curves represent the time course of serum mizoribine concentration calculated according to pharmacokinetic parameters in individual subjects.

Fig. 3. Serum Mizoribine Concentrations in 3 Typical Subjects Following Twice-Daily Administration at 6 mg/kg

Open circles represent the observed serum mizoribine concentrations. Solid curves represent the time course of serum mizoribine concentration calculated according to pharmacokinetic parameters in individual subjects.

Fig. 4. Mean Absolute Difference (MAD) of Parameter Estimates between Full and Reduced Sampling Protocols

Each axis represents the percent of MAD of $\text{KA}$, $\text{CL/F}$, and $\text{V/F}$.
cules and require transporters to enter cells.\textsuperscript{9} Recently, Patil et al. reported the presence of two Na\textsuperscript{+}-dependent concentrative nucleoside transporters (CNT1/N2 and CNT2/N1) on the brush border membrane in the human intestine.\textsuperscript{10} The CNT1/N2 transporter is pyrimidine-nucleoside preferring, and thymidine serves as a model substrate. In contrast, the CNT2/N1 transporter is generally purine-nucleoside preferring, and inosine, guanosine, and formycin B serve as model substrates. Ribavirin is a broad-spectrum antiviral drug structurally related to guanosine, and is actively transported across the brush border membrane of the jejunum via the CNT2/N1 transporter with high affinity.\textsuperscript{10} Pharmacokinetic studies of oral ribavirin in adult subjects have demonstrated a lack of proportionality in the peak plasma concentrations achieved on increasing the dose from 600 to 2400 mg, suggesting saturable absorption of the drug.\textsuperscript{11} Since the chemical structure of mizoribine is similar to that of inosine and guanosine, mizoribine as well as ribavirin may be transported via CNT2/N1 in the intestine.\textsuperscript{12} In the present study, however, the mean values of calculated $C_{\text{max}}$ increased linearly along with dose escalation (Fig. 1). The individual $KA$ values were nearly constant at all dose levels in the single-dose and multiple-dose studies (Table 2). These results suggested that the intestinal absorption of mizoribine was not saturated at 12 mg/kg/d or approximately 900 mg/d.

In the previous study, the mean percentage of urinary recovery of mizoribine was 78\% following single oral administration at 12 mg/kg, suggesting that oral bioavailability ($F$) is high, and that most of the oral dose is excreted predominantly in urine.\textsuperscript{5} Mizoribine is water-soluble, and plasma protein binding in human is low; therefore, it is conceivable that mizoribine is filtrated at the renal glomerulus.\textsuperscript{13} In the present study, $CL/F$ was modeled as a function of $CLcr$ (Eq. 4), and the population mean $CL/F$ value was estimated as 1.93 $\cdot$ $CLcr$ (Table 1). This finding suggested that the renal excretion mechanisms of mizoribine were glomerular filtration and also tubular secretion, although the specific transporters in the proximal tubule of the kidney for mizoribine secretion have not been identified yet. In the present study, the mean $t_{1/2}$ and ($CL/F$/$WT$ values were almost constant in each dose group of the single- and multiple-dose studies (Table 2). These results suggested that the renal elimination was not saturable at any dose tested.

Target enzymes of mizoribine are inosine 5\'-monophosphate dehydrogenase and guanosine-monophosphate synthetase.\textsuperscript{12} Mizoribine was originally isolated as a substance having weak antimicrobial activity against Candida albicans, and was subsequently found to inhibit both humoral and cellular immunity by selectively inhibiting the proliferation of lymphocytes via the inhibition of de novo purine biosynthesis.\textsuperscript{14} The drug has been used for the prevention of rejection in renal transplantation and also for the treatment of lupus nephritis, rheumatoid arthritis, and nephrotic syndrome.\textsuperscript{1,15,16} However, the relationship between the therapeutic effect and serum concentration of mizoribine is unclear, and the optimal dose of the drug for autoimmune diseases as well as organ transplantation is still unknown.\textsuperscript{15} Because the serum mizoribine concentration can be easily measured by an HPLC method, monitoring the serum mizoribine concentra-

In conclusion, to evaluate the pharmacokinetic characteristics of mizoribine in subjects with normal renal function, we estimated the population pharmacokinetic parameters of mizoribine using a NONMEM program. The mean values of $ALAG$, $KA$, $V/F$, and $CL/F$ were estimated to be 0.349 h, 0.869 h\textsuperscript{-1}, 0.834 l/kg, and 1.93 $\cdot$ $CLcr$ l/h, respectively, which indicated that orally administered mizoribine is rapidly absorbed from the intestine, distributed into the tissue, and excreted in urine via glomerular filtration and tubular secretion. In addition, Bayesian analysis, which utilizes population pharmacokinetic parameters as prior information, might be useful to assess drug exposure in individual subjects. These findings may provide new information concerning immunosuppressive therapy with higher-dose mizoribine.

Acknowledgements This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Sciences (JSPS).

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