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ORIGINAL ARTICLE

Population pharmacokinetics of mizoribine in pediatric recipients of renal transplantation

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Abstract
Background An immunosuppressive agent, mizoribine, is excreted predominantly in the urine. The aim of this study was to investigate the pharmacokinetic variability of mizoribine in pediatric recipients of renal transplantation.
Methods Pharmacokinetic data for population analysis were collected from 51 recipients (32 males and 19 females) treated with oral administration of mizoribine (0.83–5.56 mg/day/kg). The population pharmacokinetic parameters of mizoribine were estimated using a nonlinear mixed effects model program.
Results The pharmacokinetics of mizoribine in pediatric recipients of renal transplantation was well described by a one-compartment model with first-order absorption. The mean value of the absorption lag time (ALAG) and absorption rate constant (K_A) was estimated to be 0.363 h and 0.554 h^{-1}, respectively. Apparent volume of distribution (*V/F*) was modeled as a function of body weight (WT), and the mean value was estimated to be 1.03 · WT L. Oral clearance (CL/*F*) was modeled as a function of creatinine clearance (CL_{cr}), and the mean value was estimated to be 2.81 · CL_{cr} · 60/1000 L/h. In addition, there was a positive correlation between CL_{cr}-corrected CL/*F* and WT-corrected *V/F* in the pediatric recipients, indicating large interindividual variability in the bioavailability (*F*) of mizoribine.
Conclusion The present findings indicated that the rate of renal excretion and also the extent of intestinal absorption of mizoribine are responsible for the large interindividual pharmacokinetic variability of the drug.

Keywords Mizoribine · Population pharmacokinetics · Bioavailability · Renal transplantation · Pediatric recipients

Introduction

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 [1]. Additional indications for which mizoribine has subsequently been approved are lupus nephritis, rheumatoid arthritis, and nephrotic syndrome [2]. In contrast to other immunosuppressive agents (e.g., azathioprine), mizoribine has been shown to lack oncogenicity in animal experiments, and exhibited a clinically low incidence of severe adverse drug reactions (such as myelosuppression and hepatotoxicity), making it useful in long-term immunosuppression therapy [3]. Although mizoribine is a highly hydrophilic compound, it is absorbed from the gastrointestinal tract following oral administration. In addition, plasma protein binding and metabolism of mizoribine in humans are negligible; therefore, the unchanged drug is

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predominantly excreted into the urine [4]. Indeed, Takada et al. [5] evaluated the pharmacokinetics of mizoribine in renal transplant patients and reported that the elimination rate of mizoribine from serum was dependent on the kidney function.

Population pharmacokinetic analysis of mizoribine in adult recipients of renal transplantation has been performed using a nonlinear mixed effects model (NONMEM) program [6, 7]. The 449 serum mizoribine concentration data obtained from 114 adult recipients were used in the population pharmacokinetic analysis. The mean absorption lag time (ALAG) and absorption rate constant (K_A) were estimated to be 0.581 h and 0.983 h^{-1}, respectively. The apparent volume of distribution (V/F) was modeled as a function of body weight (WT), and the mean value was estimated to be 0.858 · WT L. Oral clearance (CL/F) was modeled as a function of creatinine clearance (CL_{cr}), and the mean value was estimated to be 1.80 · CL_{cr} · 60/1000 L/h. In addition, CL_{cr}-corrected CL/F in the adult recipients was positively correlated with WT-corrected V/F, suggesting that the bioavailability (F) of mizoribine was also responsible for the interindividual pharmacokinetic variability of the drug [6]. However, it is still unknown whether the pharmacokinetic characteristics of mizoribine in pediatric recipients of renal transplantation are similar to those in adult recipients of renal transplantation.

A multicenter prospective study had been conducted to evaluate the safety and efficacy of steroid withdrawal in children treated with cyclosporine and mizoribine after renal transplantation [8, 9]. In the present study, we evaluated the pharmacokinetic characteristics of mizoribine in pediatric recipients of renal transplantation. That is, pharmacokinetic data for population analysis were collected from 51 recipients (32 males and 19 females) treated with oral administration of mizoribine (0.83–5.56 mg/day/kg). Pharmacokinetic analysis was performed using a NONMEM program, since population pharmacokinetics based on NONMEM analysis can simultaneously evaluate the mean pharmacokinetic parameters, the covariates affecting the pharmacokinetics of a drug, and also unknown inter- and intraindividual pharmacokinetic variability [6, 7]. We then compared the population pharmacokinetic parameters in the pediatric recipients of renal transplantation with those in adult recipients of renal transplantation.

Methods

Pharmacokinetic data

To estimate the population pharmacokinetic parameters of mizoribine, we collected 54 serum concentration profiles (353 serum concentration data of mizoribine) from 51 pediatric recipients of renal transplantation, which were obtained in the previous study [8, 9]. Table 1 shows their demographic characteristics. The ranges of age, body weight, height, and serum creatinine concentration were 1.7–17.2 years old (mean 10.5 years), 8.8–61.0 kg (mean 29.8 kg), 79.0–159.7 cm (mean 127.7 cm), and 0.2–2.9 mg/dL (mean 0.84 mg/dL), respectively. These recipients were routinely treated with oral administration of mizoribine (Bredinin® Tablet, Asahi Kasei Pharma, Tokyo, Japan) at daily doses of 0.83–5.56 mg/day/kg (mean 2.79 mg/day/kg). In addition, the serum concentration of mizoribine was measured using high performance liquid chromatography [10].

Estimation of population pharmacokinetic parameters of mizoribine in pediatric recipients of renal transplantation

The pharmacokinetics of mizoribine in healthy males, adult recipients of renal transplantation, and pediatric patients with renal diseases are well described by a one-compartment model with first-order absorption [6, 11–13]. Population mean pharmacokinetic parameters and their interindividual variations were estimated with the NONMEM analysis, for which we used the first-order method in the present study [7]. The one-compartment model with first-order absorption was parameterized in terms of ALAG, K_A, V/F, and CL/F with NONMEM-PREDPP library subroutines, ADVAN2 and TRANS2 [7]. ALAG in the ith recipient ($ALAG_i$) was modeled using the following equation:

$$ALAG_i = \theta_1 \quad (1)$$

where θ_1 is the predicted population mean of the absorption lag time (in hours). K_A in the ith recipient (K_{A_i}) was modeled using the following equation:

$$K_{A_i} = \theta_2 \cdot \exp(\eta_{KA_i}) \quad (2)$$

where θ_2 is the predicted population mean of the absorption rate constant (in $hour^{-1}$), and η_{KA_i} is a random variable distributed normally with a mean of zero and variance of

Table 1 Demographic characteristics of patient population

Total number of patients	51
Male/female	32/19
Age (years)	10.5 ± 4.1 (1.7–17.2)
Weight (kg)	29.8 ± 13.7 (8.8–61.0)
Height (cm)	127.7 ± 20.8 (79.0–159.7)
Serum creatinine (mg/dL)	0.84 ± 0.53 (0.2–2.9)
Daily dose (mg/day/kg)	2.79 ± 1.12 (0.83–5.56)

Values are expressed as the mean ± SD (range)

$\omega^2_{K_A}$. *V/F* and CL/*F* in the *i*th recipient (V/F_i and CL/F_i, respectively) were modeled using the following equations:

$$V/F_i = \theta_3 \cdot \mathrm{WT} \cdot \exp(\eta_{V/F_i}) \quad (3)$$

$$\mathrm{CL}/F_i = \theta_4 \cdot \mathrm{CL_{cr}} \cdot \frac{60}{1000} \cdot \exp(\eta_{\mathrm{CL}/F_i}) \quad (4)$$

where WT is the body weight (in kg), and $\theta_3 \cdot \mathrm{WT}$ is the predicted population mean of the apparent volume of distribution (in L). CL_{cr} is the creatinine clearance (in mL/min), and $\theta_4 \cdot CL_{cr} \cdot 60/1000$ is the predicted population mean of oral clearance (in l/h). Random variables, η_{V/F_i} and η_{CL/F_i} were assumed to be distributed normally with means of zero and covariance of $\omega^2_{V/F}$, $\omega_{V/F,CL/F}$, and $\omega^2_{CL/F}$. In addition, the CL_{cr} value (in ml/min) was calculated using the updated Schwartz equation as follows [12, 14]:

$$\mathrm{CL_{cr}} = \frac{0.413 \cdot \mathrm{HT}}{S_{\mathrm{cr}}} \cdot \frac{\mathrm{BSA}}{1.73} \quad (5)$$

where HT, BSA, and S_{cr} are the height (in cm), body surface area (in m^2), and serum creatinine concentration (in mg/dL), respectively. Finally, the *j*th observed serum concentration in the *i*th recipient (C_{ij}) was assumed to be randomly and normally distributed from the predicted value (C^*_{ij}):

$$C_{ij} = C^*_{ij} + \varepsilon_{ij} \quad (6)$$

where ε_{ij} is a random variable that describes intraindividual variability with a mean of zero and variance of σ^2.

Results

Mizoribine concentration profiles in pediatric recipients of renal transplantation

The observed serum concentration of mizoribine, daily doses, and creatinine clearance in six typical recipients of renal transplantation are shown in Fig. 1. The serum concentration of mizoribine was variable among the recipients and seemed to be dependent on renal function. That is, the serum concentrations of mizoribine in the patients with lower CL_{cr} (ID = 5, 9, and 21) were relatively high. On the other hand, although the daily doses (in mg/day/kg) of mizoribine were relatively high, the serum concentration of mizoribine in the recipients with higher CL_{cr} (ID = 16, 28, and 31) were relatively low.

Population pharmacokinetic parameters of mizoribine in pediatric recipients of renal transplantation

Population pharmacokinetic parameters were estimated from 353 serum concentration data of mizoribine in 51 recipients using the NONMEM software. NONMEM also provided estimates of the standard error (SE) for all parameters, and SE was used to define the 95% confidence interval (CI) for true parameter values: 95% CI = (estimated parameter value) $\pm$ 1.96 $\times$ SE [7]. Table 2 shows the population pharmacokinetic parameters of mizoribine and their 95% CI estimated with NONMEM analysis. The mean values of ALAG, K_A, *V/F*, and CL/*F* were estimated to be 0.363 h, 0.554 h^{-1}, $1.03 \cdot \mathrm{WT}$ L, and $2.81 \cdot CL_{cr} \cdot 60/1000$ L/h, respectively. The $\omega^2_{K_A}$, $\omega^2_{V/F}$, $\omega_{V/F,CL/F}$, and $\omega^2_{CL/F}$ values in the recipients were estimated to be 0.739, 0.286, 0.113, and 0.166, respectively. The population mean pharmacokinetic parameters in pediatric recipients of renal transplantation seemed to be more similar to those in pediatric patients with renal disease rather than to those in adult recipients of renal transplantation (Table 2) [6, 12].

Pharmacokinetic parameters in individual pediatric recipients of renal transplantation

The 95% CI of θ_4 (2.48–3.14) was much higher than the value of zero, indicating the statistical significance of θ_4 (Table 2). In order to reconfirm the effect of renal function on the pharmacokinetics of mizoribine, the pharmacokinetic parameters of mizoribine in individual recipients were estimated according to Bayes' theorem using the NONMEM program and its post hoc option [7]. Figure 2 shows the relationship between CL_{cr} and CL/*F* in pediatric recipients of renal transplantation. Although there was a large interindividual variability in CL/*F* at least partly due to the interindividual variability of *F* (see below), CL/*F* seemed to be positively correlated with CL_{cr} among the recipients (Fig. 2).

The 95% CI of $\omega_{V/F,CL/F}$ (0.045–0.185) was also higher than the value of zero, indicating the statistical significance of $\omega_{V/F,CL/F}$ (Table 2). In addition, the coefficient (ρ) of correlation between η_{V/F_i} and η_{CL/F_i} was 0.519, which was calculated as follows: $\rho = \omega_{V/F,CL/F}/(\omega_{V/F} \cdot \omega_{CL/F})$ [7]. We therefore evaluated the relationship between CL_{cr}-corrected CL/*F* and WT-corrected *V/F* in pediatric recipients of renal transplantation (Fig. 3). There was a positive correlation between $(CL/F)/(CL_{cr} \cdot 60/1000)$ and (*V/F*)/WT in the pediatric recipients, indicating that the bioavailability (*F*) of mizoribine is another major factor responsible for the interindividual pharmacokinetic variability of the drug.

Discussion

In the present study, we utilized serum concentration data of mizoribine in pediatric recipients of renal transplantation in order to estimate the population pharmacokinetic parameters of the drug using a NONMEM program. The

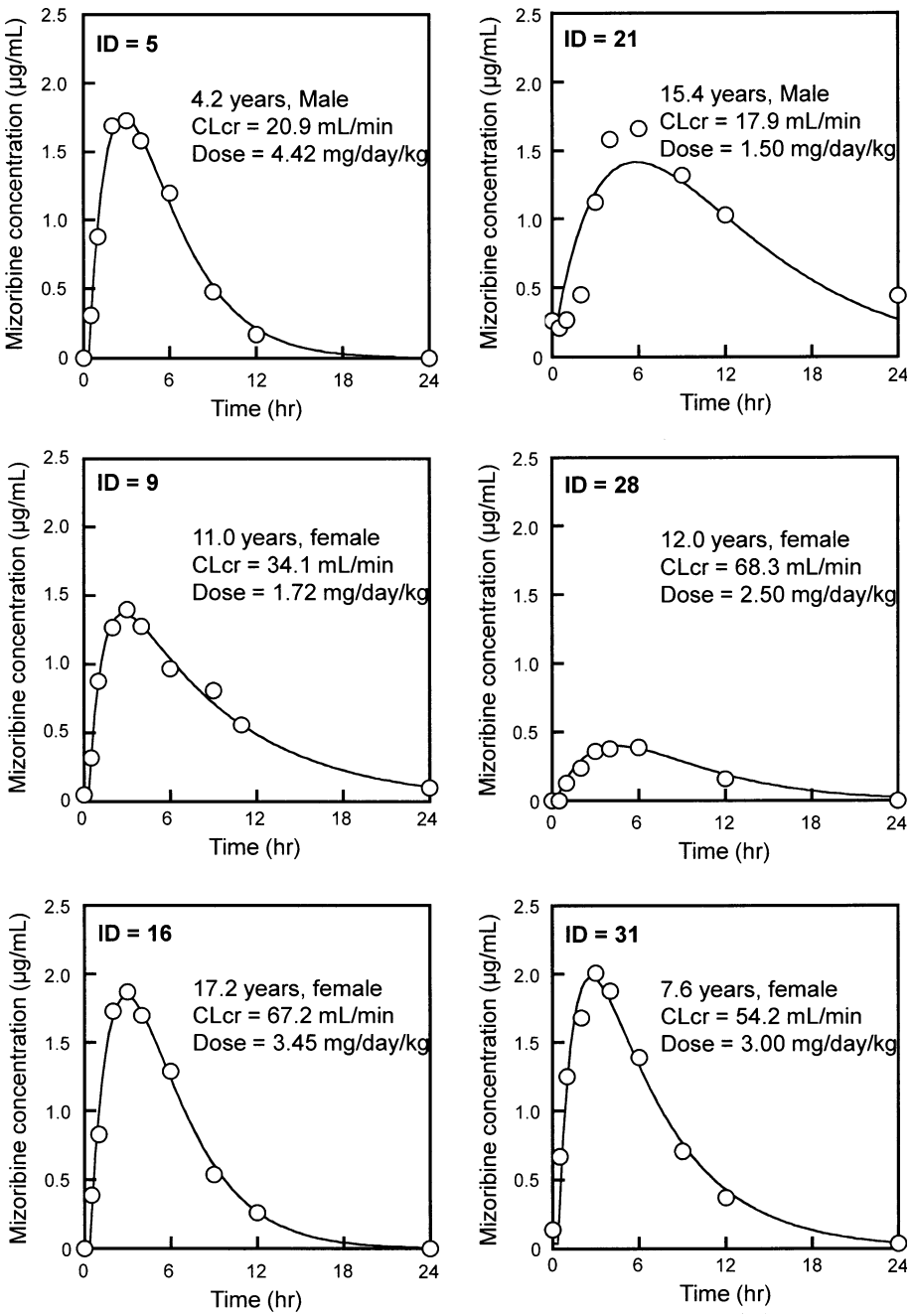

Fig. 1 Mizoribine concentration profiles in typical 6 pediatric recipients of renal transplantation. *Open circles* indicate the observed mizoribine concentration. The pharmacokinetic parameters of mizoribine in individual recipients could be estimated according to Bayes' theorem using the NONMEM program and its post hoc option. *Solid lines* represent the predicted mizoribine concentration

population mean pharmacokinetic parameters in the pediatric recipients of renal transplantation were similar to those in pediatric patients with renal disease rather than to those in adult recipients of renal transplantation (Table 2). We confirmed that renal function is a main factor responsible for the interindividual pharmacokinetic variability of mizoribine (Table 2; Figs. 1, 2). In addition, CL_{cr}-corrected CL/*F* in pediatric recipients was positively correlated with WT-corrected *V/F*, indicating that the bioavailability (*F*) of mizoribine is also responsible for the interindividual pharmacokinetic variability of the drug (Fig. 3).

A multi-center prospective trial had been conducted to evaluate the safety and efficacy of steroid withdrawal in children treated with cyclosporine and mizoribine after renal transplantation [9]. Ninety-four pediatric recipients of renal transplantation were enrolled in this study, and the 13-year patient survival rate and graft survival rate were 94.6 and 83.1%, respectively [9]. The clinical efficacy and adverse reactions of mizoribine are considered to be correlated with the blood concentration of the drug; however, there is no report about the relationship between the efficacy (adverse reactions) and the blood concentration of mizoribine in pediatric patients. On the other hand, there

Table 2 Population pharmacokinetic parameters of mizoribine in pediatric recipients of renal transplantation

	Pediatric recipients		Adult recipients[a]	Pediatric patients with renal disease[b]
No. of patients:	51		114	105
Parameters	Estimates	95% CI	Estimates	Estimates
θ_1 (h)	0.363	0.287–0.439	0.581	0.513
θ_2 (h^{-1})	0.554	0.464–0.644	0.983	0.793
θ_3 (L/kg)	1.03	0.88–1.18	0.858	1.29
θ_4	2.81	2.48–3.14	1.80	2.79
$\omega^2_{K_A}$	0.739	0.286–1.192	1.03	0.513
$\omega^2_{V/F}$	0.286	0.080–0.492	0.259	0.306
$\omega_{V/F,CL/F}$	0.113	0.045–0.185	0.174	0.192
$\omega^2_{CL/F}$	0.166	0.094–0.238	0.169	0.225
σ (μg/mL)	0.0901	0.0720–0.1052	0.212	0.103

[a] Ishida et al. [6]

[b] Ishida et al. [12]

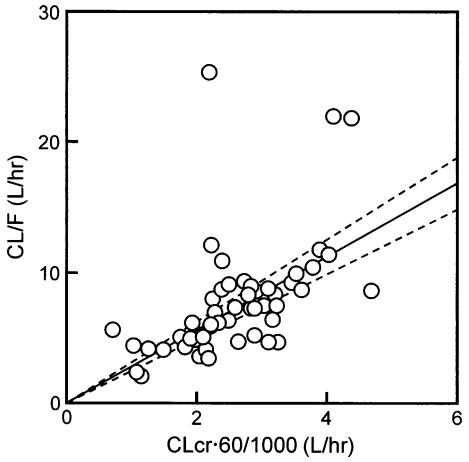

Fig. 2 Relationship between CL_{cr} and CL/*F* in pediatric recipients of renal transplantation. *Solid lines* represent the predicted mizoribine concentration. *Solid line* indicates $CL/F = 2.81 \cdot CL_{cr} \cdot 60/1000$. *Dotted lines* indicate the regression using the border of 95% CI of θ_4

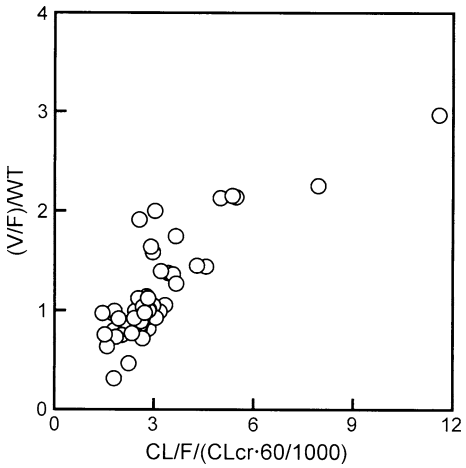

Fig. 3 Relationship between (CL/*F*)/(CL_{cr} · 60/1000) and (*V*/*F*)/WT of mizoribine in pediatric recipients of renal transplantation

are few reports about TDM-based dosage regimens of mizoribine in adult patients with renal transplantation [15, 16]. Sugitani et al. [15] evaluated the blood concentrations and clinical efficacy of mizoribine in 36 renal transplantation patients who were shifted from mycophenolate mofetil to mizoribine. The immunosuppressive effect of mizoribine was observed over a long time without severe adverse reactions in patients whose trough concentrations of mizoribine were to be kept higher than 1 μg/mL [15]. In addition, Sonda et al. [16] investigated the blood concentrations and adverse reactions of mizoribine in 46 renal transplantation patients. Stomatitis was observed in two patients whose trough concentrations of mizoribine were around 4 μg/mL. Thrombocytopenia was observed in one patient at the trough concentration of 6 μg/mL. In addition, one patient had liver dysfunction at the trough mizoribine concentration of 7 μg/mL. The immunosuppressive effect of mizoribine on human mixed-lymphocyte reaction (MLR) was also evaluated, and mizoribine at a concentration range of 0.1–5 μg/mL showed MLR inhibition rates ranging from 36.4 to 62.2%. The authors thought that the therapeutic range of the trough concentration of mizoribine was 0.1–3 μg/mL [16]. However, it is still unclear whether the efficacy and adverse reactions of mizoribine are correlated with other pharmacokinetic parameters of the drug [e.g., area under the time vs. concentration curve (AUC) or the maximum concentration (C_{max}) of mizoribine] in both adult and pediatric patients. The findings in the previous (adult recipients) [6] and present (pediatric recipients)

study will be useful for optimizing the dosage regimen of mizoribine in patients of renal transplantation.

It has been reported that concentrative nucleoside transporters (CNTs) are expressed in intestinal epithelial cells and that CNTs are involved in the intestinal absorption of nucleoside analogs [17, 18]. CNT1 and CNT2 are Na^+-dependent, and the movement of nucleoside regardless of its concentration gradient is coupled to that of the sodium ion [19, 20]. Naito et al. [21] evaluated the effect of the genetic polymorphism of *CNT1* and *CNT2* on the bioavailability of mizoribine in Japanese kidney transplant recipients. The bioavailability of mizoribine in adult patients with *CNT1-G/A* and *-A/A* alleles was significantly lower than that with the *CNT1-G/G* allele. On the other hand, genetic polymorphisms of *CNT2 65C>T* and *225C>T* did not affect the bioavailability of mizoribine in the recipients [21]. In addition, we have recently evaluated the effect of *CNT1 565G>A* polymorphism on the bioavailability of mizoribine in healthy Japanese males [13]. The bioavailability of mizoribine in healthy adult subjects with the *CNT1-A/A* allele was also lower than that in subjects with the *CNT1-G/G* allele [13]. These findings indicated that genetic variability in activity and/or affinity of CNT1 is at least partly responsible for the interindividual variability in the bioavailability of mizoribine in human. Further prospective clinical trials will be needed to clarify the contribution of genetic polymorphisms of CNT1 to the interindividual variability in the bioavailability of mizoribine in pediatric subjects.

In conclusion, the present findings suggested that the rate of renal excretion and also the extent of intestinal absorption (bioavailability) of mizoribine are responsible for the large interindividual pharmacokinetic variability of the drug in not only adult but also pediatric recipients of renal transplantation.

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