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Research Article

Do calcineurin inhibitors influence the serum concentrations of mizoribine?

Takahisa Hiramitsu*, Makoto Tsujita, Takayuki Yamamoto, Norihiko Goto, Shunji Narumi, Yoshihiko Watarai, Takaaki Kobayasi

Department of Transplant and Endocrine Surgery, Nagoaya Daini Red Cross Hospital, 466-8650 2-9 Myoken-cho Showa-ku Nagoya Aichi, Japan

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***Correspondence to:**
Takahisa Hiramitsu,
Email: thira@nagoya2.jrc.or.jp

ABSTRACT

Background: Mizoribine (MZR) is an antimetabolite that inhibits inosine-monophosphate dehydrogenase and has been used for preventing rejection in renal transplantation. However, the effect of calcineurin inhibitors (CNIs) on the pharmacokinetics of MZR has not been shown. This study was performed to show the influence of CNIs (tacrolimus [Tac] or cyclosporine [CyA]) on the serum concentration of MZR.
Methods: Thirty-four living-donor renal transplant recipients administered a four-drug immunosuppressive therapy regimen (steroid, CNIs, basiliximab and MZR 6 mg/kg/day) were investigated. 20 recipients were treated with Tac and 14 were with CyA. Serum concentrations of MZR were obtained retrospectively at 464 points and at 243 points for each. Population pharmacokinetic (PPK) analysis was used to make pharmacokinetic models of serum MZR. After statistically evaluating the correlation of the pharmacokinetic models with the actual data, areas under the curves (AUCs) of each CNI were also estimated in these models and statistically evaluated.
Results: The mean values of the PPK parameters (absorption lag time, absorption rate constant [Ka], apparent volume of distribution [V/F] and oral clearance of MZR [CL_{MZR}/F]) were 0.600 hr and 0.643 hr, 1.14/hr and 0.911/hr, 0.732×body weight (WT) (L) and 0.784×WT (L), and 1.64×creatinine clearance (CL_{cr}) (L/hr) and 1.81×CL_{cr} (L/hr), respectively. Moreover, the serum concentrations of MZR at all-time points were estimated with these parameters. The correlation coefficients between the individual actual and estimated serum concentrations of MZR in the Tac group and the CyA group were 0.988 and 0.992, respectively. The average value of the AUCs of MZR corrected by the CL_{cr} in the Tac group, and the CyA group were 0.61±0.21 and 0.55±0.19 (average value±standard deviation) for each (p=0.19).
Conclusion: These findings suggest the pharmacokinetics of MZR were well-described by 1-compartment model with first-order absorption. Moreover, concomitant use of CNIs, e.g., Tac and CyA, may have no significant influence on the pharmacokinetics of MZR.

Keywords: Mizoribine, Calcineurin inhibitors, Population pharmacokinetics

INTRODUCTION

Mizoribine (MZR) is an antimetabolite that inhibits inosine-monophosphate dehydrogenase just like mycophenolate mofetil (MMF), and has been used for preventing rejection in renal transplantation. It has been reported that the pharmacokinetics of mycophenolic acid (MPA), which is the metabolically activated form of MMF, shows large variations among individuals, depending on the concomitant use of a calcineurin inhibitor (CNI), steroid, etc.[1,2] On the other hand, the pharmacokinetics of MZR is known to be influenced strongly by the renal function.[3] But, there are as yet no reports in the literature of clinical investigations of the effect of CNIs on the pharmacokinetics of MZR. These data were evaluated by population pharmacokinetic (PPK) analysis.

METHODS

This study was approved by our Ethics Committee and in accordance with Helsinki Declaration of 1975 (as revised in 1983).

Selection and description of participants

A total of 34 recipients performed living-donor renal transplantation between October 2006 and December 2010 were administered with steroid, CNIs (tacrolimus [Tac] or cyclosporine [CyA]), basiliximab and MZR 6 mg/kg/day. Of these 34 recipients, 20 patients were administrated with Tac 0.2 mg/kg/day and 14 patients were with CyA 8 mg/kg/day.

Technical information

Blood samples were collected from therapeutic drug monitoring (TDM) study at 0 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 9 hr, 12 hr, after the administration of MZR during the induction period. A total of 464 blood samples and 243 samples were obtained in each group.

Analysis of the serum MZR concentration

The serum MZR concentrations were determined by high-performance liquid chromatography method.[4] In this measuring method, the intra- and inter-day precisions in terms of coefficient of variation were lower than 5.0% and 6.5%, respectively. The accuracy in terms of % relative error ranged from −1.7% to 4.4% (0.25-4.0 μg/mL), detection range was from 0.01 to 10 μg/mL and lower limit of quantitation was 0.01 μg/mL.

Statistical techniques

Significant difference of recipients between two groups was tested by means of Chi-square test and Student's t-test (SSPS software, version 19 [SPSS Chicago, IL, USA]).

The serum MZR concentration-time data were fitted by PPK analysis, with the NONMEM computer program (ADVAN2 TRANS2). The following individual parameters of i^{th} were estimated: absorption lag time $(ALAG)_i$, Ka_i, V/F_i, CL_{MZR}/F_i.

These parameters were defined by following equations.

$ALAG_i = A_1$

$Ka_i = A_2 \times \exp(\eta_{Kai})$

η_{Kai}: random effect variable distributed normally with a mean of zero and variance of n^2_{Ka}.

$V/F_i = \theta_3 \times WT \times \exp(\eta_{V/Fi})$

$CL_{MZR}/F_i = \theta_4 \times CL_{cr} \times 60/1000 \times \exp(\eta_{CL/Fi})$

WT: body weight

CL_{cr}: creatinine clearance

$\eta V/F_i$, $\eta CL/F_i$: random variables distributed normally with means of zero and covariance of $\omega^2_{V/Fi}$, $\omega^2_{V/Fi,\ CL/Fi}$ and $\omega^2_{CL/Fi}$

$\theta_{1,2,3,4}$ are variables for each patient.

$C_{ij} = C_{ij}* + \varepsilon_{ij}$ C_{ij}: j^{th} observed serum concentration in the i^{th} patient, e_{ij}: random effect variable (additive error of the intra-individual variability of serum concentration: defined to disperse according to the normal distribution with a mean of zero and a variance of σ).

These parameters were used to plot the each serum concentration-time curves of i^{th} according to these equations.

$C_i = 1/(V/F_i) \times D_i \times Ka_i/(Ka_i - Ke_i) \times (e^{-Kei \times ea/ALAGi)} - e^{-Kai \times aAGiFons})$

$Ke_i = (CL_{MZR}/F_i)/(V/F_i)$

C_i: serum concentration, F: bioavailability, D_i: dose, Ke_i: elimination rate constant, t: time

To verify the predicted serum MZR concentration from serum concentration-time curves, regression line and correlation coefficient were calculated by SSPS software, version 19 (SPSS Chicago, IL, USA).

Each MZR areas under the curve $(AUC)_i$ of i^{th} was also estimated from this equations.

$AUC_i = Dose/(CL/F_i)$

Significant difference of AUCs between two groups was tested by means of Student's t-test (SSPS software, version 19 [SPSS Chicago, IL, USA]). Tests were considered as significant at $p<0.05$.

RESULTS

Recipients

Recipients' characteristics of two groups are shown in Table 1. There were no significant differences in gender, age, weight, post-transplant serum creatinine level, and dose of MZR.

PPK analysis

The mean values of the PPK parameters for the basic structural model of MZR are shown in Table 2. These parameters (Ka, V/F and CL/F) in both groups were nearly identical to those reported among healthy adults. The mean values of ALAG, Ka, V/F, and CL/F were 0.349 hr, 0.869/hr 0.834969d CL/F were 0.3_{cr}×r.83496 L/hr, respectively in the healthy adults.[5]

Validity of the PPK parameters

The regression lines between the predicted serum MZR concentration based on these parameters and actual serum MZR concentration were plotted on Figure 1. Each correlation coefficient in Tac group and CyA group was 0.988 and 0.992 respectively. These results showed that there was a strong relationship between the estimated serum MZR concentration and actual serum MZR concentration. According to these results, the mean values of the PPK parameters were proved to be valid.

AUCs of MZR

Average values of AUCs adjusted by CL_{cr} are shown in Figure 2. Adjusted average values of AUCs for Tac group and CyA group were 0.61±0.21 and 0.55±0.19 (average value±standard deviation) respectively, and there was no significant difference (p=0.19).

Table 1: Recipients' characteristics.

	Tac group	CyA group	
Number of recipients	20	14	
Measurement point (total)	464	243	
Male/Female	7/13	4/10	n.s.
Age (years)	47.55±13.46	42.2±14.68	n.s.
Weight (kg)	55.90±14.24	56.65±12.59	n.s.
Serum creatinine (mg/dL)	1.32±0 52	1.32±0 37	n.s.
Mean treatment dose of MZR (mg/day)	348.71±76.15	342.42±63.89	n.s.

Tac: Tacrolimus, CyA: Cyclosporine, MZR: Mizoribine.

DISCUSSION

MZR is an antimetabolite that inhibits inosine-monophosphate dehydrogenase just like MMF. It is widely used in kidney transplantation as an antimetabolite combined with steroids, CNI and basiliximab in Japan.

The efficacy and safety of MZR compared with MMF had already been reported. Acute rejection rate of MZR is almost the same as that of MMF when administered with CyA and

Table 2: PPK parameters.

Tac	CyATac	CyA
Number of patients	20	14
Measurement points	464	243
ALAG (hr)	0.600	0.643
Ka (hr^{-1})	1.14	0.911
V/F (L)	0.732×WT	0.784×WT
CL_{MZR}/F (L/hr)	1.64×CL_{cr}	1.81×CL_{cr}
ω_{ALAG}	Not determined	Not determined
ω_{Ka}	0.562	0.821
$\omega_{V/F}$	0.393	0.533
$\omega_{CL/F}$	0.344	0.345
$\omega_{V/F, CL/F}$	0.888	0.875
σ (μg/ml)	0.256	0.18

Tac: Tacrolimus, CyA: Cyclosporine, PPK: Population pharmacokinetic, ALAG: Absorption lag time, MZR: Mizoribine, CLcr: Creatinine clearance.

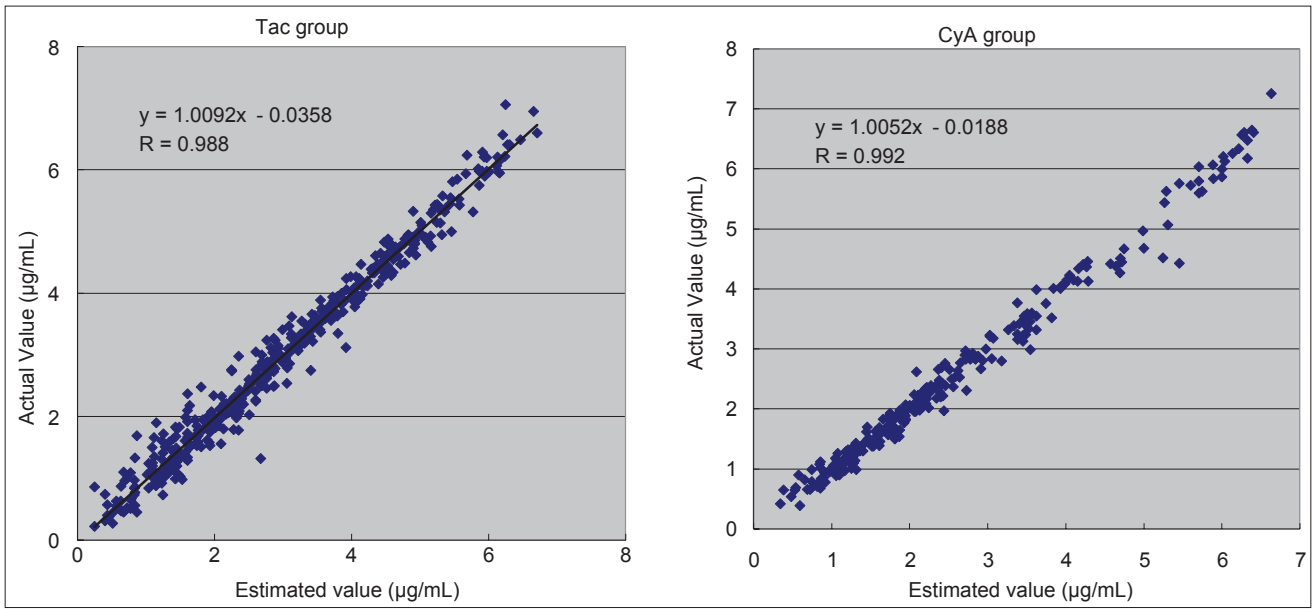

Figure 1: Estimation accuracy from the parameters calculated in the Population pharmacokinetic analysis (all time points).

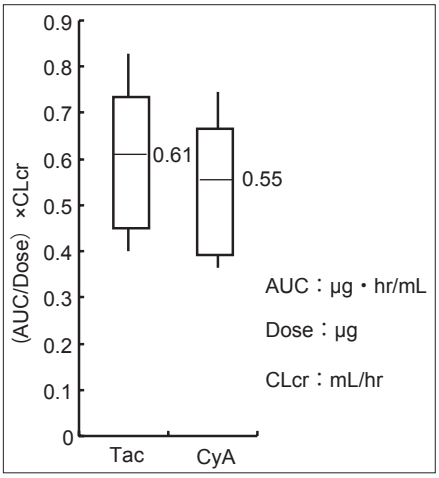

Figure 2: The effects of concomitant calcineurin inhibitors on the areas under the curve of mizoribine.

Tac. Cytomegalovirus disease rate of MZR is significantly lower than that of MMF. However, the serum uric acid is significantly elevated.[6-9]

Compared with lipophilic Tac, CyA and MMF, which are metabolized in the liver, MZR is hydrophilic and excreted from kidney. Pharmacokinetics of MZR is quite different from concomitant CNIs and no drug interaction between these are proven in this study. Hence, the dose monitoring is easier in MZR than in MMF when used with CyA and steroid, because of the precise predictability of the serum concentration by C0 (trough level) or AUC. But, the elimination of MZR is affected by the renal function. So, it is important to measure the C0 in case of increase in serum creatinine level to maintain the appropriate serum MZR concentration.[10]

So far, there are few reports on the concomitant administration with Tac. It has been reported that the pharmacokinetics of MPA shows large variations among individuals, depending on the concomitant use of CNIs, steroid, etc.[1,2] However, the results of our study suggests that pharmacokinetics of MZR (absorption, distribution and excretion) is unlikely affected by the types of CNIs concomitantly administered, and that it is unnecessary to change the administration dose of MZR and the target range of serum MZR concentration according to the types of CNIs. Moreover, serum concentration of MZR can be controlled easily only by monitoring C0 in both Tac group and CyA group.

In this study, TDM was performed in each patient. But, PPK analysis enables us to reduce the frequency of blood sampling per patient, to perform blood samplings at different points by each patient. Statistical processing of data obtained from the blood samplings allows us quantitatively to demonstrate the extent of individual differences among the recipients and their causative factors. A population is a set of a certain element, which is assumed as a base in statistical estimation. It is used to observe samples randomly collected from it, and to estimate a population from the results conversely.

In conclusion, the results of this study illustrates that concomitant CNI use exerts little influence on the serum concentration of MZR.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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