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PHARMACOKINETICS AND DISPOSITION

Prediction of mizoribine pharmacokinetic parameters by serum creatinine in renal transplant recipients

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Abstract

Purpose Mizoribine (MZR) is an immunosuppressive agent with extensive inter-individual differences in pharmacokinetics (PK). Here, we investigated the PK characteristics of MZR in renal transplant recipients and gave equations for prediction of some critical PK parameters.

Methods A total of 40 renal transplant recipients participated in this prospective study and were administered MZR orally twice daily in the range of 1.1–8.9 mg kg^{-1} day^{-1}. Steady-state concentrations of MZR were detected before (0 h) and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h after administration by high-performance liquid chromatography method. Another 38 patients with newly detected trough concentration (C_0) were enrolled to validate the obtained C_0 predictive equation.

Results Significant inter-individual differences in MZR PK parameters were observed. Patients with decreasing creatinine clearance rate (CCr) had significantly decreased terminal elimination rate constant (k_{el}) and apparent total body clearance (Cl/F), while other PK parameters including apparent terminal half-life ($t_{1/2}$), peak time (T_{max}), peak concentration (C_{max}), area under the curve ($AUC_{0\text{-}12h}$), apparent volume of distribution (V/F), and mean residence time (MRT) were significantly increased. Correlation coefficients between $AUC_{0\text{-}12h}$ and C_0/C_{max} were 0.894 and 0.916, respectively (both $p < 0.001$). A serum creatinine (SCr)-based predictive C_0 equation [$C_0 = (2.160 \times SCr - 54.473) \times Dose$] was established and validated by C_0 from another 38 patients. Besides, significant linear correlations between $k_{el}/t_{1/2}$ and CCr were also found ($r^2 = 0.668$ and 0.484, respectively), and equations predicting $k_{el}/t_{1/2}$ were also obtained ($k_{el} = 0.015 + 0.002 \times CCr$, $t_{1/2} = 13.601 - 0.139 \times CCr$).

Conclusions Renal function plays as an essential factor that contributes to great inter-individual MZR PK variation. Both C_0 and C_{max} are suitable for evaluating MZR exposure in the body. SCr could be applied to predict C_0 and $t_{1/2}$ of MZR.

Keywords Mizoribine · Renal transplantation · Pharmacokinetics · Immunosuppression

Introduction

Renal transplantation is the preferred therapy for patients with end-stage renal failure. Triple immunosuppressive regimen including calcineurin inhibitor, antimetabolite, and steroids has been extensively used for the prevention of rejection after renal transplantation. Mizoribine (MZR) is a purine nucleoside synthesis inhibitor isolated from fungal strains in 1974, which specifically inhibits fast-growing lymphocytes and then produces immunosuppressive effects [1]. It was reported that MZR showed almost identical immunosuppressive efficacy with mycophenolic acid (MPA) while had significantly lower incidences of adverse reactions such as diarrhea and infection [2]. MZR has been used as a substitute for MPA in clinical practice in some Asian countries [3].

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MZR is a highly hydrophilic compound that is absorbed rapidly after oral administration. Its serum protein–binding rate in human is relatively low (2.3%) [4]. Naito et al. evaluated the pharmacokinetic (PK) disposition of MZR in renal transplant recipients and demonstrated that the median oral bioavailability of MZR was 44.8% (interquartile range, 37.8–61.5%) [5]. MZR bioavailability was affected by the polymorphisms of *solute carrier family 28 member* 1 (*SLC28A1*) [5, 6]. Besides, a PK study of MZR in 8 healthy Japanese males revealed that the salt intake was expected to improve the MZR bioavailability [7]; moreover, bioavailability and true distribution volume tended to decrease depending on age [8].

The efficacy and safety of MZR were considered to be correlated to serum concentration [9]. It was reported that direct monitoring of the peak concentration (C_{max}) was the reliable method for adjusting the dosage of MZR to obtain target serum concentration [10]. Sonda et al. performed a PK study of MZR, which included 46 renal transplant recipients and indicated a good linear correlation between trough concentration (C_0) and area under the curve (AUC) [11]. MZR did not appear to be hepatically metabolized and most of the oral dose was excreted unchanged in the urine, making the serum concentration greatly dependent on renal function [4, 12]. The reported apparent elimination half-life ($t_{1/2}$) ranged from 2 to 17 h [11–13].

In the present study, we aimed to analyze PK characteristics of MZR in Chinese renal transplant recipients. Besides, some equations predicting PK parameters based on serum creatinine (SCr) were established and validated, which may be useful for further improving MZR efficacy and safety.

Patients and methods

Study design and patients

This study included patients who underwent renal transplantation for the first time at Organ Transplantation Center, the First Affiliated Hospital, Sun Yat-sen University from January 1, 2016 to January 1, 2018. The inclusion criteria were as follows: (1) age between 18 and 60 years old, male or female; (2) primary disease is chronic glomerulonephritis; (3) receiving antithymocyte globulin or anti-CD_{25} monoclonal antibody as immune induction therapy; (4) those whose immunosuppressive therapy was initiated with calcineurin inhibitors (tacrolimus or cyclosporin) and steroids. The following exclusion criteria were implemented: (1) receiving multi-organ transplantation; (2) with concurrent active infection; (3) with history of malignant tumors over 5 years; (4) with other diseases such as mental illness, cardiac dysfunction, or severe gastrointestinal diseases prior to study initiation.

A total of 40 Chinese inpatients post-renal transplantation were selected as subjects for this study. The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University (approved no: 2015118) and informed consent was obtained from each enrolled patient. MZR (Bredinin® Tablet, Asahi Kasei Pharma, Tokyo, Japan) was administered orally twice daily to all the patients in the range of 1.1–8.9 mg kg^{-1} day^{-1} (mean 3.7 mg kg^{-1} day^{-1}).

MZR concentration determination and PK analysis

Blood samples at volume of 2 mL were collected at pre-dose (hour 0) and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h post-dose, respectively. The blood samples were centrifuged at 800*g* for 10 min and the separated serums were frozen at − 20 °C until analysis.

The serum MZR concentration was determined by a validated high-performance liquid chromatographic (HPLC) method published previously [14]. Cytarabine was used as internal standard. The chromatographic separation was performed using a reversed phase C_{18} column. The mobile phase was 10 mM KH_2PO_4 buffer solution (pH 6.3) containing 10 mM perchloric acid, at a flow rate of 1.5 mL/min. An ultraviolet (UV) detector was used for MZR detection, at a measurement wavelength of 280 nm. The linear range was 0.02–10.0 μg mL^{-1} and the lower limit of quantification was 0.02 μg mL^{-1} for MZR in serum.

Statistical analysis

The MZR PK parameters were computed basing on dose-corrected trough concentration (C_0/D) by non-compartmental analysis using Phoenix WinNonlin™ tool (version 7.0, Certara L.P Pharsight, St. Louis, MO, USA). The PK parameters included C_{max}, peak time (T_{max}), $t_{1/2}$, the first-order terminal elimination rate constant (k_{el}), $AUC_{0\text{-}12h}$, apparent total body clearance (Cl/F, calculated as dose/$AUC_{0\text{-}\infty}$), apparent volume of distribution (V/F, calculated as Cl/F/k_{el}), and mean residence time (MRT).

SPSS software (version 21, SPSS/IBM, Armonk, NY) and Prism 6 (GraphPad Software, La Jolla, CA) were used for further analysis. Data were presented as mean ± standard deviation unless noted otherwise. Normality was tested using the Shapiro-Wilk test. A variance inflation factor (VIF) of > 10 was considered indicative of multi-collinearity. The value of Durbin-Waston of ≈ 2

suggests residual independent. The non-parametric spearman's correlation coefficient was used to test for significant correlation between AUC and C_0/C_{max}. Regression analysis was performed between MZR PK parameters and clinical variables, using stepwise regression method. Correlations between actual C_0 and predicted C_0 were evaluated using the Spearman rank test. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Clinical details of enrolled patients were summarized in Table 1. The ranges of age, body weight, SCr, and creatinine clearance rate (CCr) were 20–62 years old (mean 34 years old), 35.0–95.0 kg (mean 55.4 kg), 84–398 μmol L^{-1} (mean 157 μmol L^{-1}), and 12.8–92.8 mL min^{-1} (mean 50.9 mL min^{-1}), respectively. CCr was calculated by the Cockcroft-Gault formula from body weight, age, sex, and SCr. Of these patients, 36 patients were on a tacrolimus-based triple immunosuppressive regimen and 4 patients were on a cyclosporin-based regimen.

MZR pharmacokinetics

Figure 1 showed serum MZR concentration-time curve in all of the 40 recipients. Extensive inter-individual differences in PK parameters including k_{el}, $t_{1/2}$, T_{max}, C_{max}, $AUC_{0\text{-}12h}$, V/F, Cl/F, and MRT were observed, as shown in Table 2. Because renal excretion represents the main elimination pathway of MZR and function of renal graft varied a lot post-transplantation, recipients were subsequently divided into four groups according to CCr. We found that patients with decreased CCr led to decreased k_{el} and Cl/F and increased $t_{1/2}$, T_{max}, C_{max}, $AUC_{0\text{-}12h}$, V/F, and MRT.

Correlation coefficient of $AUC_{0\text{-}12h}$ and C_0 was 0.894 ($p < 0.001$), as demonstrated in Fig. 2a. Besides, there was also a strong correlation between $AUC_{0\text{-}12h}$ and C_{max} ($r_s = 0.916$, $p < 0.001$, Fig. 2b). These data indicate that C_0 and C_{max} were both suitable for evaluating MZR exposure in the body and further applied as monitoring parameters.

Modeling and validation of C_0 prediction equation

For further predicting MZR C_0 by clinical variables, we continued to explore correlation between and C_0/D and SCr, and a regression equation with significant linear correlation was modeled, $C_0/D = 2.160 \times SCr - 54.473$ ($r^2 = 0.400$, $p < 0.001$, Fig. 2c). And a predictive equation of C_0 was deduced: $C_0 = (2.160 \times SCr - 54.473) \times D$. As of note, we also performed multiple linear regression analysis using alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), albumin (ALB), and hematocrit (Ht) as variables, but extremely low correlation coefficients were found ($p > 0.05$).

To validate the efficacy of MZR C_0 predictive equation, we further enrolled another new 38 patients that fitted the inclusion and exclusion criteria and calculated predicted C_0 according to the equation. The routinely detected C_0 were utilized as actual C_0. Figure 2d showed that there was correlation between predicted C_0 and actual C_0 ($r_s = 0.393$, $p < 0.05$).

Correlations between elimination parameters and renal function

k_{el} and $t_{1/2}$ are two critical PK parameters that frequently used for evaluating time to achieve steady concentration in the body and be eliminated from the body. Figure 2e demonstrated that linear correlation was observed between k_{el} and CCr. The regression equation was described by $k_{el} = 0.015 + 0.002 \times CCr$ ($r^2 = 0.668$,

Table 1 Clinical details of 40 inpatients

Clinical characteristics	Mean value (range)
Gender (F/M)	29/11
Age (years)	34 (20–62)
Body weight (kg)	55.4 ± 10.8 (35.0–95.0)
Post-renal transplant day	243 (5–1700)
Based calcineurin inhibitor (tacrolimus/cyclosporin)	36/4
MZR dosage (mg kg^{-1} day^{-1})	3.7 (1.1–8.9)
Serum creatinine (μmol L^{-1})	157 (84–398)
Creatinine clearance rate (mL min^{-1})	50.9 ± 20.4 (12.8–92.8)
C_0/D (ng kg mL^{-1} mg^{-1})	284.1 ± 226.8 (51.0–1000.2)

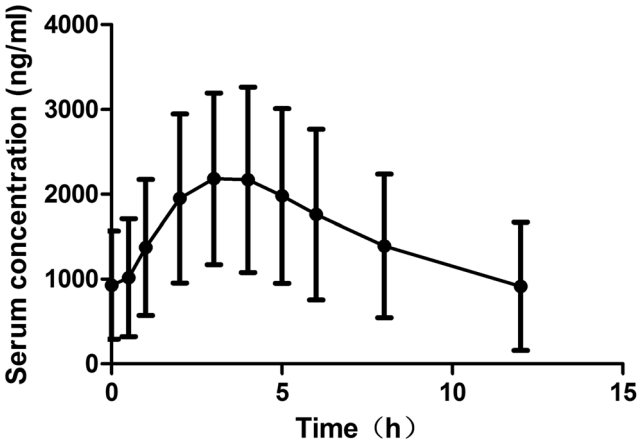

Fig. 1 The serum MZR concentration-time curve in renal transplant recipients. Data was presented as mean ± standard deviation ($n = 40$)

$p < 0.001$). Meanwhile, another regression equation was also obtained: $t_{1/2} = 13.601–0.139 \times \mathrm{CCr}$ ($r^2 = 0.484$, $p < 0.001$, Fig. 2f).

Discussion

In the present study, marked inter-individual MZR PK variability was found in patients with renal transplantation. Further grouping by CCr revealed that MZR in patients with decreased CCr exhibited decreased k_{el} and Cl/F, while other PK parameters including $t_{1/2}$, T_{max}, C_{max}, $AUC_{0\text{-}12h}$, V/F, and MRT were increased. There were linear correlations between $AUC_{0\text{-}12h}$ and C_0/C_{max}, $k_{el}/t_{1/2}$, and CCr. SCr-based equation predicting C_0 was modeled and verified, also equations predicting k_{el} and $t_{1/2}$ were built.

PK characteristics of MZR has been explored in Japanese population with various kidney diseases including child-onset glomerulonephritis [15], lupus nephritis [16], and renal transplantation [11, 13, 17]. All of these PK studies demonstrated that there were wide inter-individual PK variations of MZR, which was consistent with our data. Unlike other immunosuppressive agents such as tacrolimus and mycophenolic acid, MZR is predominately excreted from kidney in an unchanged form [13]. In our study, when renal function was classified by CCr into four grades, we observed significant decreased k_{el} and Cl/F along with unrecovered renal function, and correspondingly, other PK parameters were upregulated. Our data confirmed that renal function may represent a major factor impacting MZR exposure in vivo.

The inconsistency between MZR dose and concentration has been proved in several studies [10, 18, 19], indicating a dose-adjustment strategy guided by therapeutic drug monitoring (TDM). AUC is a surrogate marker for MZR exposure in vivo, but multiple blood sample collection limits its application. We found close relationship between $AUC_{0\text{-}12h}$ and C_0/C_{max}, indicating that both C_0 and C_{max} can be used to estimate AUC and further applied in MZR TDM. As of note, time to achieve C_{max} varies between individuals, which was demonstrated in our study that T_{max} value decreased with transplant kidney function recovery, therefore, there is uncertainty of determining time to achieve C_{max}, especially in patients at early stage post-transplantation. Taking all into consideration, C_0 may be the preferred choice in MZR exposure estimation. Actually, most of the studies clearly pointed out that the target therapeutic range of MZR C_0 value should be 0.5–3 μg mL^{-1} [11, 12, 20, 21].

Drug concentration in vivo is under regulation of various physiological and pathological conditions. Thus, we further analyzed the correlation between MZR C_0 and some clinical variables and found nonlinear correlations between C_0 and ALB /ALT/AST/Tbili, which is consistent with the fact that MZR has low plasma protein–binding rate and is not metabolized by liver enzymes. Ht level was also observed with no linear correlation with C_0, indicating low proportion of MZR in erythrocytes. SCr is one of the essential variables that can reflect renal function, and our data demonstrated SCr was well correlated with MZR C_0. Thus, an equation enrolling SCr was established to predict C_0/D and validated by C_0/D from newly 38 patients. Further, there was a correlation between predicted C_0 and actual C_0 ($r_s = 0.393$, $p < 0.05$). Further enlargement of the sample size will be needed to optimize the equation, so as to provide a basis for clinical timely prediction of MZR C_0.

Another PK parameter frequently used in clinical practice is $t_{1/2}$, which can determine the time of achieving steady state and when the drug is eliminated. Therefore, we continued to analyze clinical variables determining $t_{1/2}$ and also found only renal function contributed to variance of $t_{1/2}$. Likewise, a $t_{1/2}$ prediction equation was established. For renal transplant recipients with recovering graft function, it may especially help to decide when to perform MZR C_0 detection. However, this equation also needs to be validated by further inclusion cases.

Renal function represents as an essential factor affecting eliminating process of MZR PK, but other studies have also proved that there was considerably large range of MZR bioavailability [8, 10, 22]. Bioavailability is mainly determined by absorption and metabolism steps, gene polymorphisms of nucleoside transporters such as *SLC28A1* were reported to play roles in the differences of MZR bioavailability

Table 2 The PK parameters of MZR in renal transplant recipients

Pharmacokinetic parameters mean ± SD (range)	General	Groups			
		CCr ≤ 30 mL min^{-1} ($n = 8$)	30 < CCr ≤ 50 mL min^{-1} ($n = 12$)	50 < CCr ≤ 70 mL min^{-1} ($n = 13$)	CCr > 70 mL min^{-1} ($n = 7$)
k_{el} (h^{-1})	0.1379 ± 0.0602 (0.0340–0.2470)	0.0650 ± 0.0182	0.1162 ± 0.0387	0.1718 ± 0.0458	0.1957 ± 0.0423
$t_{1/2}$ (h)	6.52 ± 4.09 (2.81–20.37)	11.57 ± 3.95	7.16 ± 4.17	4.33 ± 1.25	3.72 ± 0.96
T_{max} (h)	3.35 ± 0.89 (2–5)	4.0 ± 0.9	3.5 ± 0.9	3.2 ± 0.7	2.6 ± 0.5
C_{max} (ng mL^{-1})	2305 ± 1064 (793–4926)	3134.74 ± 1452.17	2470.91 ± 934.41	1974.82 ± 758.81	1682.90 ± 696.88
$AUC_{0\text{-}12h}$ (ng h mL^{-1})	18743 ± 10383 (4612–48040)	29216 ± 13201	20587 ± 8285	14725 ± 6771	11072 ± 4820
V/F (mL)	50348 ± 29523 (17951–151884)	69220 ± 45492	51896 ± 32242	43692 ± 16038	38488 ± 9544
Cl/F (mL h^{-1})	6298.6 ± 3339.6 (1561.2–15446.0)	4583.8 ± 4192.9	5464.0 ± 3434.4	7370.9 ± 2547.0	7697.9 ± 2700.6
MRT (h)	11.15 ± 6.08 (5.44–32.16)	18.65 ± 6.18	11.88 ± 6.20	8.22 ± 1.92	6.78 ± 1.09

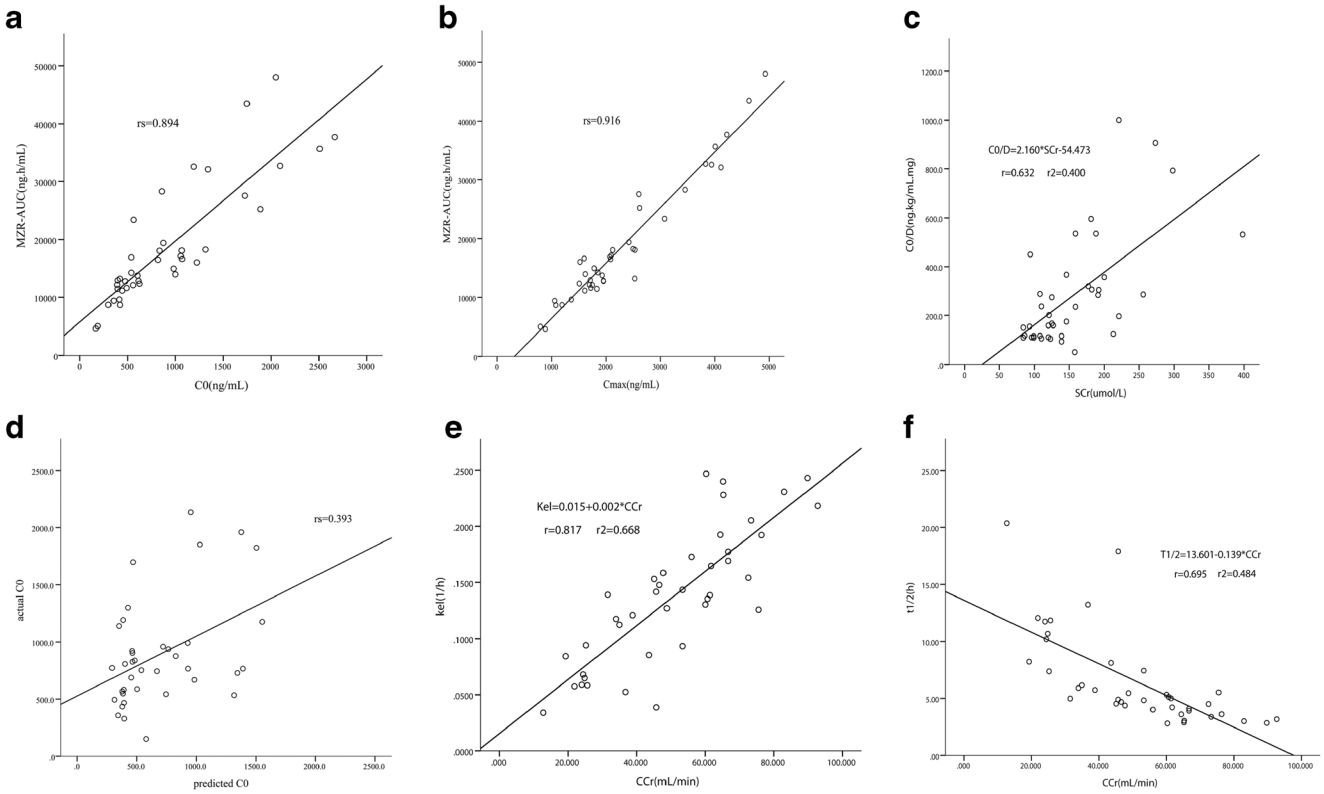

Fig. 2 Correlation analyses of some MZR PK parameters and renal function in renal transplant recipients. **a**, **b** Correlations analyses between $AUC_{0\text{-}12h}$ and C_0 and C_{max} ($r_s = 0.894$ and 0.916, $p < 0.001$),**c** Correlation analysis between C_0/D and SCr, and a regression equation was obtained: $C_0/D = 2.160 \times SCr - 54.473$ ($r = 0.632$, $r^2 = 0.400$, $p < 0.001$). **d** Correlation analysis between predicted C_0 and actual C_0 ($r_s = 0.393$, $p < 0.05$). **f** Correlation analysis between k_{el} and CCr, and the regression equation was described by $k_{el} = 0.015 + 0.002 \times CCr$ ($r = 0.817$, $r^2 = 0.668$, $p < 0.001$). **d** Correlation analysis between $t_{1/2}$ and CCr, a regression equation was obtained $t_{1/2} = 13.601–0.139 \times CCr$ ($r^2 = 0.484$, $p < 0.001$)

[5–7]. Therefore, the analysis of genetic polymorphism is also needed in the further studies, and the proposed predicting equations may be improved by enrolling gene data.

As we know, this is the first PK study of MZR in Chinese renal transplant recipients, and we proposed that renal function plays as an essential factor that contributes to great inter-individual PK differences of MZR. Both C_0/C_{max} are suitable for evaluating MZR exposure in the body. SCr could be applied to predict C_0 and $t_{1/2}$.

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Compliance with ethical standards

This study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University (approved no: 2015118) and informed consent was obtained from each enrolled patient

Conflict of interest The authors declare that they have no conflict of interest.

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