Effects of cimetidine on ciclosporin population pharmacokinetics and initial dose optimization in aplastic anemia patients

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Abstract

The present study aimed to explore the effects of cimetidine on ciclosporin population pharmacokinetics and initial dose optimization in aplastic anemia patients. Aplastic anemia patients were used to establish a population pharmacokinetic model by the nonlinear mixed effect (NONMEM), and steady-state concentrations of ciclosporin were simulated by Monte Carlo method. With the same weight, the ciclosporin clearance rates were 0.387:1 in patients with or without cimetidine, respectively. In the measured ciclosporin concentrations, compared to aplastic anemia patients without cimetidine, ciclosporin concentrations were higher in patients with cimetidine ($P < 0.01$). Further research found that at the same body weight and same dosage, ciclosporin steady-state concentrations in aplastic anemia patients with cimetidine were indeed higher than those in patients without cimetidine ($P < 0.01$). The initial recommended doses for patients without cimetidine were 7mg/kg splited into two doses for weight of 40-60kg, and 6mg/kg splited into two doses for weight of

60-100kg. The patients with cimetidine were recommended to take 3mg/kg splited into two doses for weight of 40-100kg. It was the first time to explore the effects of cimetidine on ciclosporin population pharmacokinetics and initial dose optimization in aplastic anemia patients. Patients coadministration of cimetidine, may need low ciclosporin dose.

Keywords: cimetidine; ciclosporin; population pharmacokinetics; initial dose optimization; aplastic anemia

1. Introduction

Bone marrow obstacle can result in peripheral blood pancytopenia, which is called aplastic anemia. Serious aplastic anemia can cause risk of fatal, whose mortality is 75%(Li et al., 1972). In resent years, the ciclosporin-based immunosuppressive treatment following aplastic anemia has drastically improved patients(Kitamura et al., 1995; Ni et al., 2013). Ciclosporin is absorbed via the duodenum and the jejunum, metabolized by cytochrome P450 (CYP) 3A4 and CYP3A5 and eliminated mainly by biliary tract(Ni et al., 2013; Yee, 1991). Therefore, the factors that may affect the absorption, distribution, metabolism, and excretion process of ciclosporin are likely to have drug interactions with it.

Cimetidine, a gastric acid reducer, is used to treat the short-term duodenal and gastric ulcers(Pino and Azer, 2020). With the development of proton pump inhibitors, cimetidine is available as an over the counter formulation for the prevention of heartburn or acid indigestion(Pino and Azer, 2020), and often used in aplastic anemia patients. However, cimetidine can inhibit CYP3A(Boralli et al., 2009; Renwick et al., 2002), and whether cimetidine will affect the concentration of ciclosporin and its administration regimen in aplastic anemia patients is not clear. Thus, the present study aimed to explore the effects of cimetidine on ciclosporin population pharmacokinetics and initial dose optimization in aplastic anemia patients.

2. Methods

2.1. Patient information

Chinese aplastic anemia patients between January 2015 and June 2018 from the People's Hospital of Jiangyin, were analyzed. Our research was approved by *the Research Ethics Committee of the People's Hospital of Jiangyin.* Blood concentrations were extracted from therapeutic drug monitoring (TDM) documents. Related clinical data were collected from medical log. The medical information contained gender, age, weight, duration of treatment with ciclosporin, albumin, globulin, alanine transaminase, aspartate transaminase, creatinine, urea, total protein, total bile acid, direct bilirubin, total bilibrubin, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and concomitant drugs (biapenem, cimetidine, clopidogrel, entecavir, estazolam, etamsylate, felodipine, finasteride, glucocorticoid, glutathione, isosorbide mononitrate, lansoprazole, levofloxacin, lidocaine, metoprolol, moxifloxacin, nifedipine, omeprazole, pantoprazole, rabeprazole).

2.2. PPK model

Dataset were used to build up model with NONMEM software. PK parameters and inter- and intra-individual variabilities were assessed by FOCE-I method, which was called first-order conditional estimation method with interaction. Thus, the PK parameters mainly included apparent oral clearance (CL/F) and volume of distribution (V/F). The Ka, absorption rate constant, was $1.04h^{-1}$, fixed based on the publication(Fruit et al., 2013). Variabilities of inter-individual were explored by the exponential error model, as Equation 1:

$$C_i = TV(C) \times exp\ (\eta_i) \quad (1)$$

Where C_i is the individual parameter value, TV(C) is typical individual parameter value. η_i is symmetrical distribution, which is zero-mean chance variables with variance term. Variabilities of random residual were described by Equation 2:

$$OBSE = IPCN \times (1+\varepsilon) \quad (2)$$

Where OBSE is the observation, IPCN represents the individual predicted

concentration. ε represents symmetrical distribution, which is zero-mean chance variables with a variance. Equation 3 describes the relation between PK parameters with weight:

$$C_i = C_{std} \times (W_i / W_{std})^{power} \quad (3)$$

C_i represents the ith individual PK parameter, W_i represents the ith individual weight. W_{std} is the standard weight of 70kg. C_{std} represents typical individual parameter, whose weight is W_{std}. Power represents allometric coefficient: 0.75 for the CL/F and 1 for the V/F(Anderson and Holford, 2008). Equation 4 and 5 describe the relation between PK parameters with continuous covariates, categorical covariates, respectively.

$$C_i = T(C) \times (Cov_i / Cov_{median})^{\theta} \quad (4)$$

$$C_i = T(C) \times (1 + \theta \times Cov_i) \quad (5)$$

where C_i was the individual parameter value, T(C) was the typical individual parameter value. θ was the parameter to be estimated and Cov_i was the covariate of the ith individual. Cov_{median} was the population median for the covariate.

Changes in objective function values (OFV) were produced by covariate inclusions and a decrease in OFV >3.84 (P<0.05) was considered into the base model. An increase in OFV >6.64 (P<0.01) was considered into the final model.

2.3. Model validation

The PK parameters of final model were evaluated using bootstrap. Visual inspection of routine diagnostic plots, Histogram and QQ figures, individual plots were used for evaluating the final model. Prediction-corrected visual predictive check (VPC) plots were used for assessing final model predictive performance.

2.4. Monte Carlo simulation

Based on usage cimetidine in combination or not, two parts were included into the Monte Carlo simulation: (I) individualas without cimetidine, and (II) individualas with cimetidine. In every part, 1000 virtual patients were simulated in each of the seven weight groups (40, 50, 60, 70, 80, 90, and 100kg) and for eight dosage

(1mg/kg/day, 2mg/kg/day, 3mg/kg/day, 4mg/kg/day, 5mg/kg/day, 6mg/kg/day, 7mg/kg/day, 8mg/kg/day) splited into two doses. The target concentrations were fixed to 150-350 ng/ml(Marsh et al., 2009; Marsh et al., 2003).

3. Results

3.1. Patient information

A total of 18 aplastic anemia patients were included for the present study, 8 men and 8 women, aged from 16.50-73.35 years old. Demographic data of patients and drug combination were shown in Table 1 and 2.

3.2. Modelling and evaluation

The dataset were fitted by a one-compartment model, which was first order absorption and elimination. Ciclosporin PK parameters, CL/F and V/F, were assessed with NONMEM and the final model was:

$$CL/F = 52.1 \times (weight / 70)^{0.75} \times (1 - cimetidine \times 0.613) \quad (6)$$

$$V/F = 1010 \times (weight / 70) \quad (7)$$

where CL/F was apparent oral clearance, V/F was apparent volume of distribution.

Visual inspection of routine diagnostic plots were demonstrated in Figure 1A. The weighted residual distribution in the final model were exhibited in Figure 1B. Individual plots of all sixteen patients, as shown in Figure 1C, demonstrating acceptable predictability from the perspective of clinical sparse data. The VPC plots of the final model were shown in Figure 1D, indicating most observed drug concentrations were included in 95% prediction intervals from simulation data, and uncovering the final model could predict concentrations very well. Table 3 was parameter estimates of the final model and bootstrap validation, in which median values of the parameter estimate from bootstrap were close to the respective values from the final population model, showing that the estimates for the PK parameters in the final population model were reliable, and the model was accurate.

3.3. Effects of cimetidine on ciclosporin

Figure 2 showed the CL/F of ciclosporin in aplastic anemia patients. With the same weight, the ciclosporin clearance rates were 0.387:1 in patients with or without cimetidine, respectively. In the measured ciclosporin concentrations, compared to aplastic anemia patients without cimetidine, ciclosporin concentrations were higher in patients with cimetidine ($P < 0.01$). However, ciclosporin concentration differences were not corrected for the effects of dosage and body weight. Therefore, we further simulated the ciclosporin concentrations in different body weight (40-100kg) and different dosage regiments (1-8mg/kg/day), which were shown in Figure 3, and the results showed that at the same body weight and same dosage, ciclosporin steady-state concentrations in aplastic anemia patients with cimetidine were indeed higher than those in patients without cimetidine ($P < 0.01$). These results suggested that cimetidine significantly increased ciclosporin concentrations in aplastic anemia patients, and attention should be paid to the adjustment of ciclosporin dosage to prevent the occurrence of toxicity when the two drugs were combined.

The initial dose simulation for aplastic anemia patients without cimetidine, and patients with cimetidine were shown in Figure 4A and 4B, respectively, and the initial recommended doses for patients without cimetidine were 7mg/kg splited into two doses for weight of 40-60kg, and 6mg/kg splited into two doses for weight of 60-100kg. The patients with cimetidine were recommended to take 3mg/kg splited into two doses for weight of 40-100kg.

4. Disscusion

Aplastic anemia results from abnormal immune response, hematopoietic stem/progenitor cell deficiency and bone marrow stromal cell abnormality, leading to trilineage marrow hypoplasia and pancytopenia of the peripheral blood, whose exact pathological mechanism remains unclear(Li et al., 2021). For the time being, abnormal immune tolerance and damage of hematopoietic stem/progenitor cells by an abnormal immune response are considered as the main pathological mechanism(Li et

al., 2021). In terms of treatment, ciclosporin has been used in the clinical treatment of aplastic anemia as the basic therapy(Kitamura et al., 1995; Ni et al., 2013).

Ciclosporin mainly combines with erythrocytes and lipoproteins, which is metabolized by CYP 3A, after absorption in the duodenum and the jejunum(Yee, 1991). With narrow therapeutic range and inter- and intra-individual variabilities, making ciclosporin individualized treatment necessary for therapy triumph. Clinically, the majority of centres apply ciclosporin trough concentration data to regulate the individual dosage. The main target aims to keep trough concentrations in the predefined therapeutic window. Dose adjustment based on concentration is often executed. However, the strategy is widespreadly used, it remains untoward to confirm an optimal dosage that can realize the target trough concentrations on account of many population characteristics, biological features, and drug combination factors impacting ciclosporin pharmacokinetics(del Mar Fernandez De Gatta et al., 2002).

In addition, cimetidine is often used in aplastic anemia patients, which can inhibit CYP3A(Boralli et al., 2009; Renwick et al., 2002). Whether cimetidine will affect the concentration of ciclosporin and its administration regimen in aplastic anemia patients is not clear. The present study aimed to explore the effects of cimetidine on ciclosporin population pharmacokinetics and initial dose optimization in aplastic anemia patients.

In clinical practice, the combination of population pharmacokinetics and Monte Carlo method can be used to analyze covariate effects inclding drug interaction and optimize the administration schedule(Chen et al., 2020a; Chen et al., 2020b). For example, Yang *et al* reported population pharmacokinetics and dosage optimization of linezolid in critically ill pediatric patients(Yang et al., 2021). Li *et al* reported population pharmacokinetics and dose optimization of ganciclovir in critically ill children(Li et al., 2020b). Zhang *et al* reported population pharmacokinetics and model-based dosing optimization of teicoplanin in pediatric patients(Zhang et al., 2020). Li *et al* reported population pharmacokinetics and dosing optimization of metformin in Chinese patients with type 2 diabetes mellitus(Li et al., 2020a). Wang *et al* reported population pharmacokinetics of the anti-PD-1 antibody camrelizumab in

patients with multiple tumor types and model-informed dosing strategy(Wang et al., 2020). Chen *et al* reported population pharmacokinetics and pharmacogenomics of tacrolimus in Chinese children receiving a liver transplant: initial dose recommendation(Chen et al., 2020c). Khan-Asa *et al* reported impact of albumin and omeprazole on steady-state population pharmacokinetics of voriconazole and development of a voriconazole dosing optimization model in Thai patients with hematologic diseases(Khan-Asa et al., 2020). Therefore, in our study, it was feasible to explore the effects of cimetidine on ciclosporin population pharmacokinetics and initial dose optimization in aplastic anemia patients by combining population pharmacokinetics with the Monte Carlo method.

In our study, we investigated various covariates and finally found the significance: weight and cimetidine were included as significant covariates for CL/F, weight was for V/F. Weight is the main covariate, which is referred to a 70 kg people with allometry by a coefficient of 0.75 for clearance and 1 for volume(Anderson and Holford, 2008). Using these coefficients is verified by fractal geometric concepts and observations from various areas of biology(Anderson and Holford, 2008). Concomitant medication with cimetidine could reduce ciclosporin clearance. The mechanism is that metabolism of ciclosporin occurs in liver via CYP3A(Yee, 1991) and the inhibitory effect of cimetidine on the activity of CYP3A(Boralli et al., 2009; Renwick et al., 2002). Under the same weight, the ciclosporin clearance rates were 0.387:1 in patients with or without cimetidine, respectively. Cimetidine significantly increased ciclosporin concentrations in aplastic anemia patients, and attention should be paid to the adjustment of ciclosporin dosage to prevent the occurrence of toxicity when the two drugs were combined. However, ciclosporin concentration differences were not corrected for the effects of dosage and body weight. Therefore, we further simulated the ciclosporin concentrations in different body weight and different dosage regiments. Finally, we found that at the same body weight and same dosage, ciclosporin steady-state concentrations in aplastic anemia patients with cimetidine were indeed higher than those in patients without cimetidine. Thus, our results indicated that patients coadministration of cimetidine, may need low ciclosporin dose.

Furtherly, according to our simulation results, the initial recommended doses for aplastic anemia patients without cimetidine were 7mg/kg splited into two doses for weight of 40-60kg, and 6mg/kg splited into two doses for weight of 60-100kg. The patients with cimetidine were recommended to take 3mg/kg splited into two doses for weight of 40-100kg.

5. Conclusion

It was the first time to explore the effects of cimetidine on ciclosporin population pharmacokinetics and initial dose optimization in aplastic anemia patients. Patients coadministration of cimetidine, may need low ciclosporin dose.

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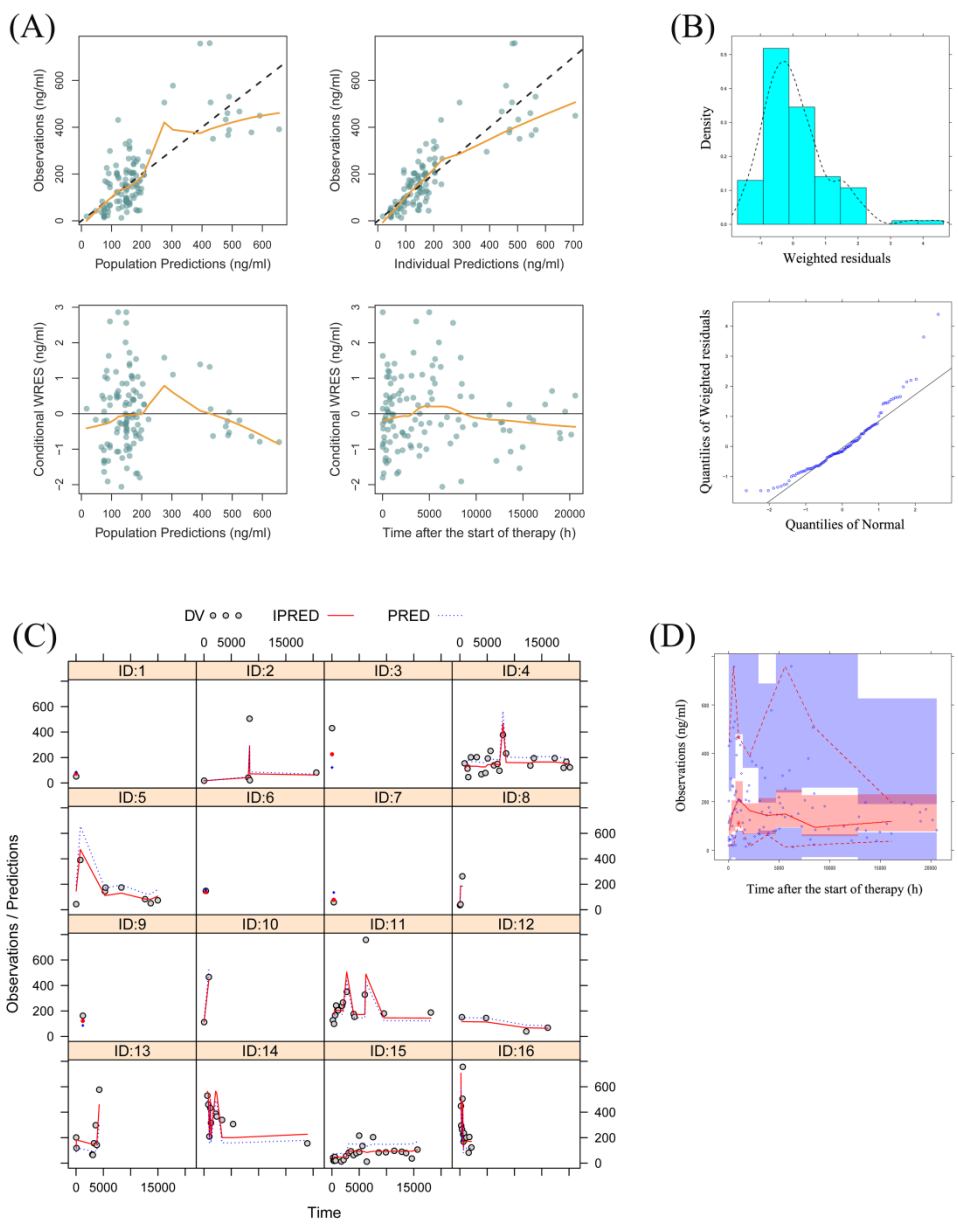

Figure 1. Model evaluation.

(A) Goodness-of-fit plots of model. observations *vs.* population predictions, observations *vs.* individual predictions, conditional weighted residuals (WRES) vs. population predictions, conditional WRES vs. time after the start of therapy. (B) Distribution of weighted residuals for model. density *vs.* weighted residuals, and quantiles of weighted residuals *vs.* quantiles of normal. (C) Individual plots. (D) Visual predictive check (VPC) of model. The middle solid line represents the median of the prediction-corrected concentrations. The lower and upper dashed lines are the 2.5th and 97.5th percentiles of the prediction-corrected concentrations.

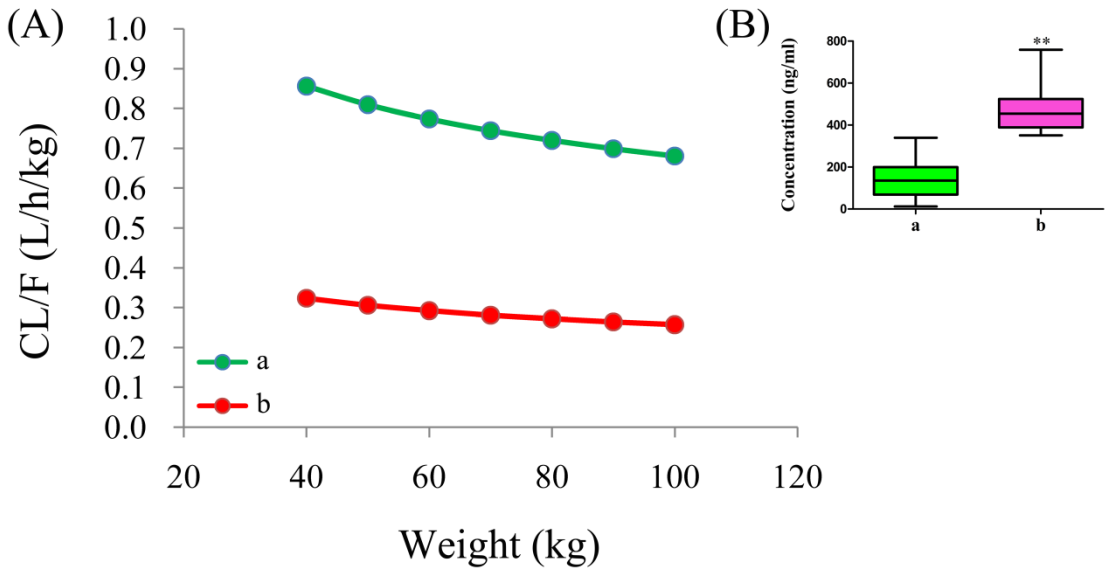

Figure 2. Ciclosporin CL/F and measured concentrations in aplastic anemia patients. (A) Ciclosporin CL/F. (B) Measured ciclosporin concentrations. a, in patients without cimetidine; b, in patients with cimetidine. $^{**}P < 0.01$ *vs.* patients without cimetidine.

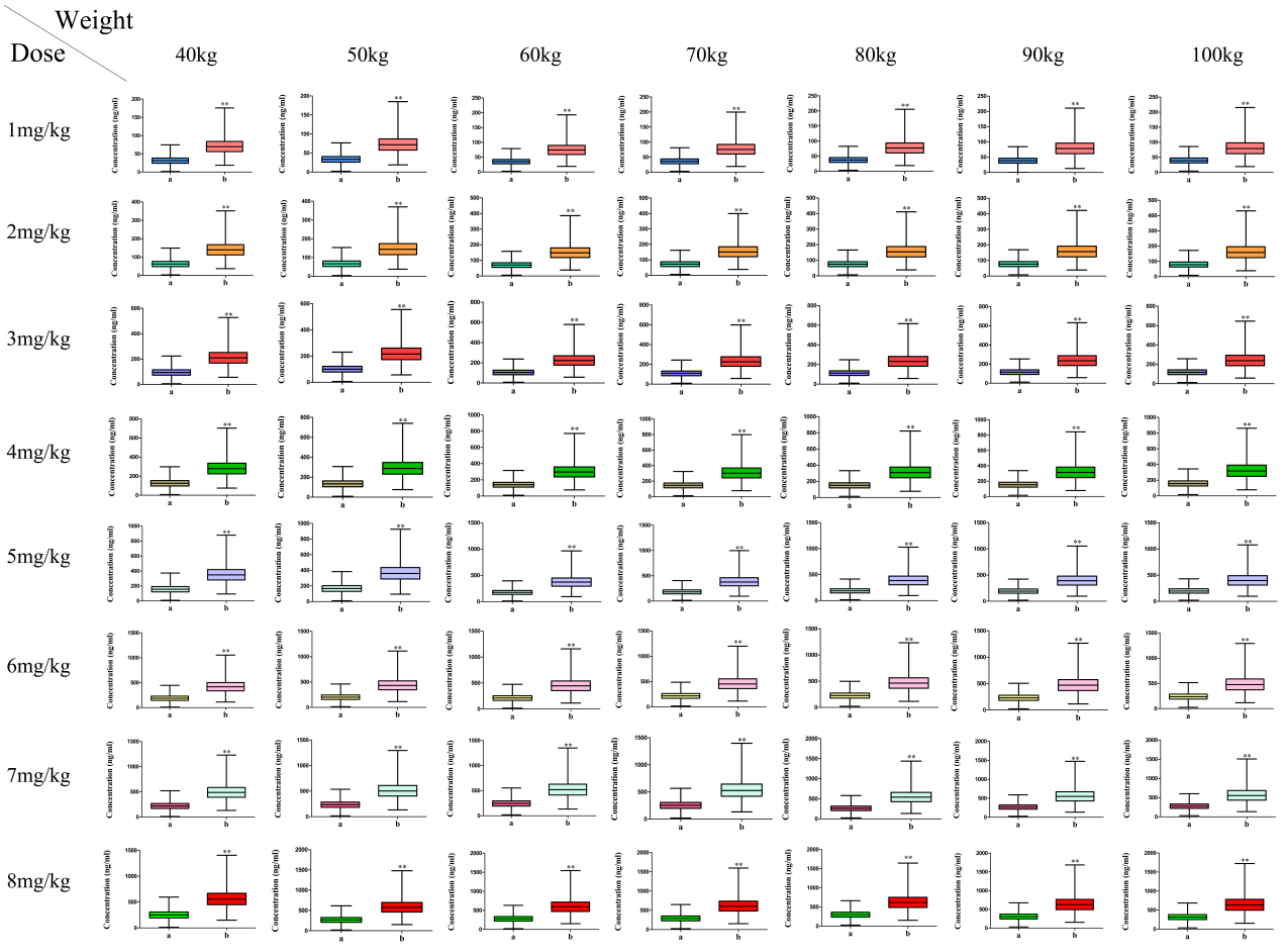

Figure 3. Effects of cimetidine on ciclosporin concentrations at different body weight and dosage.

a, in patients without cimetidine; b, in patients with cimetidine. $^{**}P < 0.01$ *vs.* patients without cimetidine

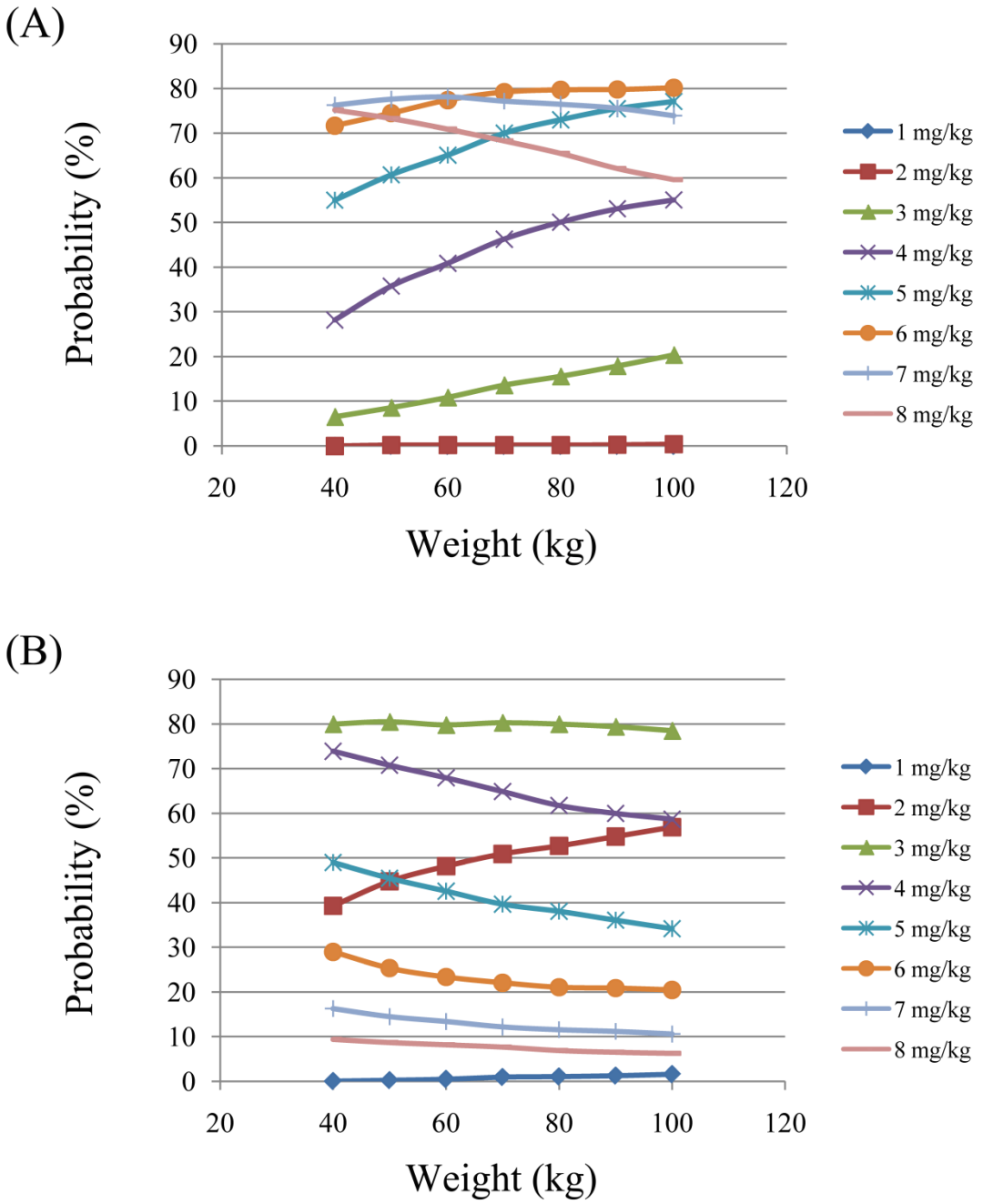

Figure 4. Probability to achieve the ciclosporin target concentrations in aplastic anemia patients.

(A) in patients without cimetidine. (B) in patients with cimetidine.

Table 1. Demographic data of patients

Characteristic	Mean ± SD	Median (range)
Gender (men/women)	8/8	/
Age (years)	49.19 ± 16.14	52.31 (16.50-73.35)
Weight (kg)	61.35 ± 16.59	54.00 (40.90-100.00)
Duration of treatment with ciclosporin (days)	205.54 ± 226.66	129.00 (2.00-859.00)
Albumin (g/L)	38.11 ± 5.66	38.10 (19.00-52.80)
Globulin (g/L)	24.83 ± 5.72	23.80 (14.00-39.40)
Alanine transaminase (IU/L)	25.84 ± 23.88	17.70 (3.80-132.30)
Aspartate transaminase (IU/L)	20.97 ± 10.81	18.40 (6.70-81.00)
Creatinine (μmol/L)	223.32 ± 289.87	79.65 (23.20-972.40)
Urea (mmol/L)	10.66 ± 7.28	8.02 (2.66-33.97)
Total protein (g/L)	62.92 ± 6.45	64.50 (48.90-77.40)
Total bile acid (μmol/L)	3.49 ± 2.02	3.40 (1.10-11.40)
Direct bilirubin (μmol/L)	7.59 ± 5.94	5.60 (1.70-30.80)
Total bilibrubin (μmol/L)	16.17 ± 11.91	13.10 (2.80-77.50)
Hematocrit (%)	18.46 ± 5.66	17.90 (7.50-37.00)
Hemoglobin (g/L)	63.56 ± 18.69	61.00 (27.00-123.00)
Mean corpuscular hemoglobin (pg)	31.97 ± 4.83	31.40 (27.90-76.50)
Mean corpuscular hemoglobin concentration (g/L)	344.49 ± 20.22	346.00 (211.00-423.00)

Table 2. Drug combination

Drug	Category	N	Drug	Category	N
Biapenem	0	13	Isosorbide mononitrate	0	15
	1	3		1	1
Cimetidine	0	7	Lansoprazole	0	15
	1	9		1	1
Clopidogrel	0	15	Levofloxacin	0	14
	1	1		1	2
Entecavir	0	15	Lidocaine	0	14
	1	1		1	2
Estazolam	0	12	Metoprolol	0	15
	1	4		1	1
Etamsylate	0	12	Moxifloxacin	0	14
	1	4		1	2
Felodipine	0	15	Nifedipine	0	14
	1	1		1	2
Finasteride	0	15	Omeprazole	0	13
	1	1		1	3
Glucocorticoid	0	3	Pantoprazole	0	10
	1	13		1	6
Glutathione	0	6	Rabeprazole	0	15
	1	10		1	1

Abbreviations were as follows: category, 0 : without drug, 1: with drug; N: number of patients.

Table 3. Parameter estimates of final model and bootstrap validation

Parameter	Estimate	SE (%)	Bootstrap		Bias (%)
			Median	95% Confidence interval	
CL/F (L/h)	52.1	20.0	50.3	[30.0, 73.0]	-3.455
V/F (L)	1010	51.6	1060	[265, 3420]	4.950
Ka (h^{-1})	1.04 (fixed)	--	--	--	--
$\theta_{cimetidine}$	-0.613	9.4	-0.598	[-0.762, -0.465]	-2.447
$\omega_{CL/F}$	0.289	39.3	0.249	[0.003, 0.472]	-13.841
$\omega_{V/F}$	0.602	42.1	0.215	[0.003, 1.311]	-64.369
σ_1	0.442	10.0	0.431	[0.349, 0.515]	2.489

95% confidential interval was displayed as the 2.5th, 97.5th percentile of bootstrap estimates. CL/F, apparent oral clearance (L/h); V/F, apparent volume of distribution (L); Ka, absorption rate constant (h^{-1}); $\theta_{cimetidine}$ was the coefficient of the cimetidine; $\omega_{CL/F}$, inter-individual variability of CL/F; $\omega_{V/F}$, inter-individual variability of V/F; σ_1, residual variability, proportional error; Bias , prediction error, Bias = (Median-Estimate) / Estimate×100%.