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Quantitative analysis of elevation of serum creatinine via renal transporter inhibition by trimethoprim in healthy subjects using physiologically-based pharmacokinetic model

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ABSTRACT

Serum creatinine (SCr) levels rise during trimethoprim therapy for infectious diseases. This study aimed to investigate whether the elevation of SCr can be quantitatively explained using a physiologically-based pharmacokinetic (PBPK) model incorporating inhibition by trimethoprim on tubular secretion of creatinine via renal transporters such as organic cation transporter 2 (OCT2), OCT3, multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. Firstly, pharmacokinetic parameters in the PBPK model of trimethoprim were determined to reproduce the blood concentration profile after a single intravenous and oral administration of trimethoprim in healthy subjects. The model was verified with datasets of both cumulative urinary excretions after a single administration and the blood concentration profile after repeated oral administration. The pharmacokinetic model of creatinine consisted of the creatinine synthesis rate, distribution volume, and creatinine clearance (CL_{cre}), including tubular secretion via each transporter. When combining the models for trimethoprim and creatinine, the predicted increments in SCr from baseline were 29.0%, 39.5%, and 25.8% at trimethoprim dosages of 5 mg/kg (b.i.d.), 5 mg/kg (q.i.d.), and 200 mg (b.i.d.), respectively, which were comparable with the observed values. The present model analysis enabled us to quantitatively explain increments in SCr during trimethoprim treatment by its inhibition of renal transporters.

1. Introduction

Creatinine is an endogenous compound primarily produced from creatine in the muscle and is widely used as one of the markers for renal function [1]. Impairment of kidney function is accompanied by a reduction of creatinine clearance (CL_{cre}), and thereby, an elevation of serum creatinine (SCr) concentration. In drug development, an increase in SCr following administration of new investigational drugs found in clinical trials could lead to dose reduction or termination of the clinical development program because of its potential association with acute renal impairment; however, several drugs have been found that cause weak SCr elevation without affecting other markers for renal function. As the underlying mechanism, inhibition of the tubular secretion of creatinine by the drugs, namely, creatinine-drug interactions, has been proposed [2]. Creatinine-drug interactions are liable to lead to the wrong decision to continue clinical trials. It is thus an important issue to understand the mechanism underlying SCr rise during clinical trials.

Creatinine is eliminated in urine through glomerular filtration and renal tubular secretion via drug transporters such as organic anion transporter 2 (OAT2), organic cation transporter 2 (OCT2), OCT3, multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K [3,4]. Of these transporters, drugs that can inhibit MATE1 and MATE2-K at their clinically relevant concentrations particularly cause SCr elevation in clinical settings [3]. Trimethoprim is used for the treatment of various infectious diseases such as urinary tract infections and *Pneumocystis carinii* pneumonia [5]. During

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trimethoprim therapy, SCr has been found to increase up to 18–31% from baseline, with a corresponding decrease in CL_{cre} by 16–22% from baseline without the functional changes in renal function as detected by ^{51}Cr-EDTA or baseline SCr [6–8]. After oral administration, trimethoprim is rapidly and completely absorbed from the gastrointestinal tract and then eliminated in a monophasic manner [9–11]. The fraction of renal excretion as unchanged form is 53–64% of absorbed trimethoprim in healthy subjects [12,13], and the remaining fraction is eliminated by hepatic metabolism. Trimethoprim has been reported to inhibit OCT2, OCT3, MATE1, and MATE2-K based on *in vitro* studies using expression cell systems of these transporters [14–23]. The fact that trimethoprim reduced renal clearance of metformin in healthy volunteers suggests that the inhibition of renal organic cation transporters is clinically relevant [21]. However, to what extent these transporter inhibitions contribute to the change in SCr during trimethoprim therapy remains unknown. The aims of this study were to construct a simple physiologically-based pharmacokinetic (PBPK) model for trimethoprim and creatinine, and to investigate whether the trimethoprim-induced increase in SCr could be quantitatively explained by its inhibitory effects on OCT2, OCT3, MATE1, and MATE2-K.

2. Materials and methods

2.1. Development of the PBPK model for trimethoprim

A schematic structure of the PBPK model for trimethoprim is shown in Fig. 1A. Based on this model, the differential equations can be described as follows:

$$V_b \cdot \frac{dC_b}{dt} = Q_h \cdot \frac{R_B}{K_{p,h}} \cdot C_h - Q_h \cdot C_b - CL_{r,b} \cdot C_b \quad (1)$$

$$V_h \cdot \frac{dC_h}{dt} = Q_h \cdot C_b - Q_h \cdot \frac{R_B}{K_{p,h}} \cdot C_h - f_h CL_{h,int} \cdot C_h + k_a \cdot X_{GI} \quad (2)$$

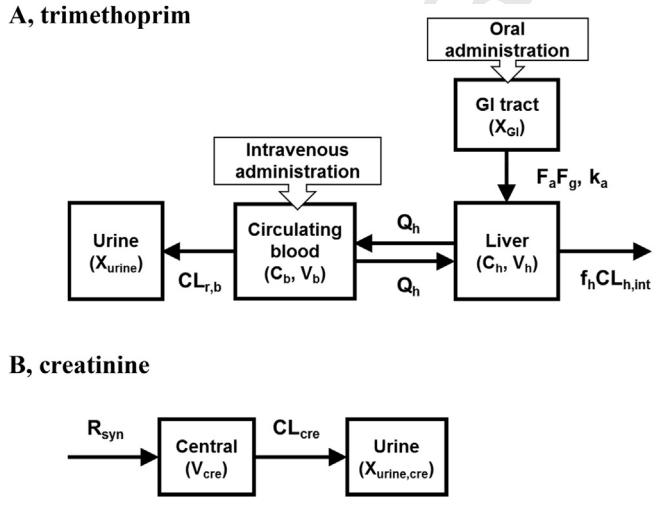

Fig. 1. Simple PBPK model for trimethoprim (A) and creatinine (B). CL_{cre}, creatinine clearance; $CL_{h,int}$, intrinsic hepatic clearance; $CL_{r,b}$, renal clearance; F_aF_g, fraction absorbed multiplied by intestinal availability; f_h, hepatic protein unbound fraction; k_a, absorption rate constant; Q_h, hepatic blood flow rate; R_{syn}, synthesis rate of creatinine; V_b, distribution volume; V_{cre}, distribution volume of creatinine; V_h, liver volume; X_{GI}, amount in the gastrointestinal tract; X_{urine}, amount in the urine.

$$\frac{dX_{GI}}{dt} = -\frac{k_a}{F_aF_g} \cdot X_{GI} \quad (3)$$

$$\frac{dX_{urine}}{dt} = CL_{r,b} \cdot C_b \quad (4)$$

where C_b and C_h represent concentrations in the blood and liver, respectively, $CL_{h,int}$ and $CL_{r,b}$ represent hepatic intrinsic clearance and renal clearance, respectively, F_aF_g represents the fraction absorbed multiplied by intestinal availability, f_h represents the unbound fraction in the liver, k_a represents the absorption rate constant, $K_{p,h}$ represents the liver-to-plasma concentration ratio, Q_h represents hepatic blood flow, R_B represents the blood-to-plasma concentration ratio, V_b and V_h represent distribution volume and the liver volume, respectively, and X_{GI} and X_{urine} represent amounts in the gastrointestinal tract and urine, respectively. The subscript b after each parameter shows the blood-based clearance. The physiological and pharmacokinetic parameters of trimethoprim [24–27] used to construct the PBPK model are shown in Table 1.

The F_aF_g value was assumed to be unity because the estimated value exceeded 1 using Eq. (5) with pharmacokinetic parameters after intravenous and oral administrations:

$$F_aF_g = \frac{F}{F_h} = F \cdot \frac{Q_h}{Q_h - (CL_{tot,b} - CL_{r,b})} \quad (5)$$

where F represents the bioavailability, F_h represents the hepatic availability, and $CL_{tot,b}$ represents the total body clearance, which was calculated as the geometric mean value from two reports [12,13]. V_b, k_a, and $f_hCL_{h,int}$ were optimized by simultaneously fitting Eqs. (1)–(4) to observed blood concentration–time profiles after both intravenous and oral administration of trimethoprim. Concentration profiles were collected from three and six reports of intravenous [12,13,28] and oral [10,11,29–32] administration, respectively, and the geometric mean values were calculated after dose-normalization (Fig. S1). For use as the initial value in the fitting analysis, $CL_{h,int}$ was calculated based on Eq. (6):

$$CL_{h,int} = \frac{CL_{h,b}}{F_h} = F \cdot \frac{Q_h}{Q_h - (CL_{tot,b} - CL_{r,b})} \quad (6)$$

where $CL_{h,b}$ represents the hepatic clearance.

Minimization was performed using Phoenix WinNonlin 6.3 (Pharsight Corporation as part of Certara, Cary, NC) with Gauss–Newton with Levenberg and Hartley minimization algorithms. The weight for the parameter optimization was set at 1/y. The fitting was assessed by the weighted sum of squared residuals (WSSR), as shown in Eq. (7):

$$WSSR = \sum_{i=1}^{n} \frac{(y_i - y_i')^2}{y_i} \quad (7)$$

y_i: ith observed value, y_i': ith predicted value.

2.2. Verification of the PBPK model of trimethoprim

The cumulative urinary excretion of trimethoprim was simulated by the model with renal clearance based on intravenous administration, and compared to the observed time profiles in clinical studies in which trimethoprim was administered intravenously [13] as well as orally [32]. The model was also verified in terms of whether the plasma concentration–time profiles after

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