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RESEARCH ARTICLE

Physiologically based pharmacokinetic (PBPK) modeling for prediction of celecoxib pharmacokinetics according to *CYP2C9* genetic polymorphism

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Abstract Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) and a representative selective cyclooxygenase (COX)-2 inhibitor, which is commonly prescribed for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, and primary dysmenorrhea. It is mainly metabolized by CYP2C9 and partly by CYP3A4 after oral administration. Many studies reported that *CYP2C9* genetic polymorphism has significant effects on the pharmacokinetics of celecoxib and the occurrence of adverse drug reactions. The aim of this study was to develop a physiologically based pharmacokinetic (PBPK) model of celecoxib according to *CYP2C9* genetic polymorphism for personalized pharmacotherapy. Initially, a clinical pharmacokinetic study was conducted where a single dose (200 mg) of celecoxib was administered to 39 healthy Korean subjects with *CYP2C9*1/*1* or *CYP2C9*1/*3* genotypes to obtain data for PBPK development. Based on the conducted pharmacokinetic study and a previous pharmacokinetic study involving subjects with *CYP2C9*1/*13* and *CYP2C9*3/*3* genotype, PBPK model for celecoxib was developed. A PBPK model for *CYP2C9*1/*1* genotype group was developed and then scaled to other genotype groups (*CYP2C9*1/*3*, *CYP2C9*1/*13* and *CYP2C9*3/*3*). After model development, model validation was performed with comparison of five pharmacokinetic studies. As a result, the developed PBPK model of celecoxib successfully described the pharmacokinetics of each *CYP2C9* genotype group and its predicted values were within the acceptance criterion. Additionally, all the predicted values were within two-fold error range in comparison to the previous pharmacokinetic studies. This study demonstrates the possibility of determining the appropriate dosage of celecoxib for each individual through the PBPK modeling with *CYP2C9* genomic information. This approach could contribute to the reduction of adverse drug reactions of celecoxib and enable precision medicine.

Keywords Celecoxib · CYP2C9 · Dose optimization · PBPK · Genotype · Precision medicine

Introduction

Celecoxib is a representative cyclooxygenase (COX)-2 selective inhibitor and a non-steroidal anti-inflammatory drug (NSAID) commonly prescribed for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, and primary dysmenorrhea (Goldstein et al. 2001; Pfizer Inc. 2016). Like other NSAIDs, celecoxib is highly protein bound (> 97%), especially to albumin (Davies et al. 2000). Celecoxib undergoes hepatic metabolism mainly by methyl-hydroxylation to hydroxy celecoxib and further by oxidation to carboxy celecoxib, and this hepatic metabolism is the main pathway for elimination of celecoxib. CYP2C9 plays a major role in the methyl-hydroxylation of celecoxib and CYP3A4 is also involved in the hydroxylation process, albeit to a lesser extent (Davies et al. 2000; Paulson et al. 2000; Sandberg et al. 2002). CYP2C9 is one of the most important

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metabolizing enzymes for many of the prescribed drugs (Rettie et al. 2005). The human *CYP2C9* gene is highly polymorphic in its promoter and coding regions, and more than 71 variant alleles of *CYP2C9* have been reported (https://www.pharmvar.org/gene/CYP2C9). The allelic variants vary in frequency among different ethnic groups, and *CYP2C9 *2* and **3* are major variant alleles in most ethnic groups. The *CYP2C9*2* and **3* variants have been reported to be significantly prevalent in Caucasians (8.0–19.1% and 3.3–16.2%, respectively). However, *CYP2C9*2* is absent in East Asians (Chinese, Japanese, and Korean), and *CYP2C9*3* and **13* occur at frequencies of 1.0–6.0% and 0.2–1.0%, respectively (Kimura et al. 1998; Bae et al. 2005; Dai et al. 2014; Ding et al. 2015; Kim et al. 2017). *CYP2C9*2*, **3* and **13* alleles are associated with significant reductions in intrinsic clearance of a variety of CYP2C9 substrates compared with *CYP2C9* 1*; however, the degree of these reductions appear to be highly substrate-dependent (Lee et al. 2002).

Although one clinical study indicated that *CYP2C9* genotype does not affect the steady-state systemic exposure (area under the curve, AUC) and elimination rate (Brenner et al. 2003), most of the pharmacogenetic studies for celecoxib have reported that subjects with *CYP2C9*3* or *CYP2C9*13* allele including *CYP2C9*1/*3*, *CYP2C9*1/*13* and *CYP2C9*3/*3* genotype resulted in significantly increased AUC and maximum plasma concentration (C_{max}) compared to subjects with *CYP2C9*1/*1* genotype (extensive metabolizers, EMs) (Tang et al. 2001; Kirchheiner et al. 2003; Stempak et al. 2005; Lundblad et al. 2006; Prieto-Perez et al. 2013; Liu et al. 2015; Kim et al. 2017; Park et al. 2018). Administration of celecoxib is associated with gastrointestinal (GI), cardiovascular, and renal adverse events (Mohammed et al. 1999; Moore et al. 2005; Caldwell et al. 2006; Pfizer Inc. 2016; Kim et al. 2017). Especially, one study demonstrated that subjects with higher AUC and C_{max} resulted in more adverse events than those with lower values (Liu et al. 2015). Furthermore, another study reported that one patient identified as an intermediate metabolizer (IM) of CYP2C9 had gastropathy after taking celecoxib (Gupta et al. 2015).

Physiologically based pharmacokinetic (PBPK) modeling is a tool that enables a priori simulation of drug concentration–time profiles through a mechanistic approach to the pharmacokinetics of drug by integrating biological and physiological information at the organism level (Kuepfer et al. 2016). Based on the pharmacokinetic data from a clinical study, PBPK modeling can be applied to simulate the pharmacokinetic profile of different administration protocols and drug-drug interactions (Zhuang and Lu 2016). Due to these characteristics, utilization of PBPK modeling for drug development and discovery has rapidly developed (Jones et al. 2015). Moreover, several studies indicated that PBPK modeling can also be used to apply genetic polymorphism effects on the pharmacokinetics of drugs (Yeo et al. 2013; Vieira et al. 2014; Emoto et al. 2015; Djebli et al. 2015; Duan et al. 2017; Futatsugi et al. 2018; Gong et al. 2018).

In this study, a PBPK model of celecoxib was developed according to *CYP2C9* genetic polymorphism based on reported in vitro metabolic rate data (Tang et al. 2001) with CYP2C9 and CYP3A4 enzymes. The objective of this study was to develop a PBPK model to obtain the optimal dosage of celecoxib related to *CYP2C9* genetic polymorphism.

Methods

Subjects

Twenty-four healthy subjects with *CYP2C9*1/*1* genotype and fifteen subjects with *CYP2C9*1/*3* genotype were recruited for the pharmacokinetic study. Subjects were healthy according to medical history, physical examination, and routine laboratory tests including urine analysis, hematology, and blood chemistry. Their *CYP2C9* genotypes were confirmed by polymerase chain reaction restriction fragment length polymorphism (PCR–RFLP) methods as previously described (Bae et al. 2005).

Study design

All subjects provided informed consent for the study. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Metro hospital (Anyang, Republic of Korea). Pharmacokinetic study of celecoxib was conducted as an open-label, single-phase study. After overnight fasting, participants were administered a single oral dose of 200 mg celecoxib (Celebrex®, Pfizer Korea, Seoul, Republic of Korea). Blood samples were collected in EDTA tubes before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h after administration. Meals were provided at 4, 10, 24, and 30 h after drug administration. Collected blood samples were centrifuged at 3000 rpm for 10 min. Then, the supernatant plasma samples from the EDTA tubes were stored at − 70 °C until needed.

Determination of plasma concentration

HPLC–MS/MS (High Performance Liquid Chromatography-tandem mass spectrometry) analysis of celecoxib and valdecoxib (Internal standard, IS) was determined and validated based on following published method (Kim et al. 2017). HPLC was operated on an Agilent 1200 series HPLC system (Santa Clara, CA, USA) and mass spectrometry was performed by Applied Biosystems SCIEX API 3200 series (Toronto, ON, Canada). Phenomenex Luna phenyl hexyl column (100 × 2.0 mm, 3 µm, Torrance, CA, USA) was

selected for analyte separation. The mobile phase, a mixture of 10 mM ammonium formate (pH 3.5, adjusted with formic acid) with HPLC grade water and acetonitrile (10: 90, v/v) was used for analysis and set to 0.2 mL/min in HPLC system. In quantitative analysis, MRM (Multiple Reaction Monitoring) mode with a dwell time of 250 ms was selected for analyzing celecoxib (m/z 380.2 → 316.1) and IS (m/z 313.3 → 118.0). The calibration curve was linear over the range of 2–1000 ng/mL for celecoxib.

Data and statistical analysis

All pharmacokinetic parameter calculations for celecoxib analysis was based on BA calc 2007 software from MFDS (Ministry of Food and Drugs Safety, Republic of Korea). Maximum plasma concentration values of celecoxib (C_{max}) and the time to reach maximum plasma concentration C_{max} (T_{max}) were experimentally observed values. Area under the curve (AUC: $AUC_{0\text{-}t}$, AUC_{inf}) parameters were assessed based on trapezoidal rule, and t was the last time of measured concentration. $AUC_{0\text{-}t}$ was area under the plasma concentration time curve from time 0 to t and AUC_{inf} was area under the plasma concentration time curve from time 0 to infinite. The clearance was calculated as CL/F = dose/AUC_{inf} and half-life was calculated as $T_{1/2} = \ln 2/k_e$ and k_e was the elimination constant which was derived from terminal data from a concentration–time plot. All of the calculated pharmacokinetic data results were expressed as mean ± SD (standard deviation). After consideration of normality and equal variance, differences in pharmacokinetic parameters between *CYP2C9* genotype groups were evaluated using the student t-test. All results were analyzed by SigmaPlot® version 12 (Systat Software Inc., Chicago, IL, USA). In this study, P values < 0.05 were considered statistically significant.

PBPK model construction and workflow

The PBPK modeling of celecoxib was developed and optimized using the latest PK-Sim® software (Version 7.2, Bayer AG, Wuppertal, Germany). The pharmacokinetic data used for model development was based on the pharmacokinetic information involving subjects with *CYP2C9*1/*1* and *CYP2C9*1/*3* genotypes conducted in this study. Basic information for modeling population group including gender, age, weight, height, and BMI was based on subjects who participated in the pharmacokinetic study. In the case of *CYP2C9*1/*13* (n = 5) and *CYP2C9*3/*3* (n = 2) genotype groups, pharmacokinetic information from a previously published research was applied (Kim et al. 2017).

Basic physico-chemistry data for celecoxib was collected from published literature (Paulson et al. 1999; Baek et al. 2015), PubChem (https://pubchem.ncbi.nlm.nih.gov), and Drug Bank (https://www.drugbank.ca). Adjusted lipophilicity for celecoxib was 3.9 per data provided by Drug Bank. Fraction unbound (f_u) value was 3.5% based on literature (Paulson et al. 1999). ADME properties used in PK-Sim® were adjusted based on a latest human compartmental GI model including fluid secretion and absorption, which was used to simulate the absorption (Thelen et al. 2011, 2012).

Poulin and Theil method was used to calculate the organ-plasma partition coefficients. In this method, lipophilicity (log P), pKa, and f_u were the main input parameters for calculation of partition coefficients (Poulin and Theil 2000; Poulin et al. 2001; Kuepfer et al. 2016).

For metabolism, metabolic enzymes were primarily considered for the description of celecoxib metabolism. When considering the metabolic pathway of celecoxib, both CYP2C9 and CYP3A4 activities were applied to the model development. Input values for in vitro metabolic rate in the presence of recombinant sub-enzymes were determined according to a previously published study (Tang et al. 2001). In addition, in vitro metabolic rate constant for recombinant CYP2C9 used for the initial model development was applied to the *CYP2C9*1/*1* genotype group. Modified in vitro metabolic rate values for other genotype groups (*CYP2C9*1/*3*, *CYP2C9*1/*13,* and *CYP2C9*3/*3*) were applied in sequence.

In the case of excretion, celecoxib is mainly eliminated by the hepatic metabolism (Davies et al. 2000). Therefore, kidney excretion was partially applied by optimizing plasma clearance for kidney and f_u. Protein gene expression data used in the PBPK modeling was derived from published RT-PCR assay data (Nishimura et al. 2003; Nishimura et al. 2005; Nishimura et al. 2006). Additionally, solubility, kidney plasma clearance and 80% dissolution time were optimized by adjusting parameter identification tool in PK-Sim® version 7.2 for better goodness of fit. The optimization was performed using the Levenberg–Marquardt algorithm of the parameter identification tool in PK-Sim® software.

After generation of the PBPK model for *CYP2C9*1/*1*, simulation for the *CYP2C9*1/*3*, *CYP2C9*1/*13*, and *CYP2C9*3/*3* genotype groups were generated by adjusting the biometric data and in vitro metabolic rate of recombinant CYP2C9 for each genotype.

In this study, a model acceptance criterion based on the variance of observed PK data (C_{max}, $AUC_{0\text{-}48}$, and AUC_{inf}) was applied to evaluate the suitability of the developed PBPK model for celecoxib. Acceptance criterion for modeling was calculated by a previously reported method

(Abduljalil et al. 2014). Equation 1 and Eq. 2 were used to calculate the model assessment as follows:

$$U_b = \exp\left[\ln\left(\bar{x}\right) + 4.26\frac{\sqrt{\ln\left[\left(\frac{CV\%}{100}\right)^2 + 1\right]}}{\sqrt{N}}\right] \quad (1)$$

$$L_b = \exp\left[\ln\left(\bar{x}\right) - 4.26\frac{\sqrt{\ln\left[\left(\frac{CV\%}{100}\right)^2 + 1\right]}}{\sqrt{N}}\right] \quad (2)$$

where $\bar{x}$ is the mean value of the pharmacokinetic values from this study; *CV%* is the coefficient variation of the pharmacokinetic values from this study; *N* is the number of subjects; U_b is the upper limit of boundary; L_b is the lower limit of boundary.

In this study, the model acceptance range was calculated by converting the C_{max}, $AUC_{0\text{-}48}$, and AUC_{inf} values from each *CYP2C9* genotype group obtained from the pharmacokinetic study into U_b and L_b values, respectively. Thereby, all the predicted pharmacokinetic values in the model development were used as an index to determine the suitability of the comparison with observed pharmacokinetic values.

Validation of the PBPK model

PBPK model validation was performed by comparing the predicted values with observed values from the pharmacokinetic studies. In this study, comparison between predicted value and observed value was evaluated by two-fold error which is widely used for acceptable prediction in PBPK model evaluation (Jones et al. 2012; Guo et al. 2015; Rasool et al. 2017; Park et al. 2017). Two-fold error was calculated using Eq. 3:

$$0.5 \leq \text{Ratio score} = \text{Predicted value} / \text{Observed value} \leq 2 \quad (3)$$

Celecoxib pharmacokinetic studies used for comparison in the validation process consisted of different ethnic groups including Asian (China, Korea) and Caucasian (Spain, Sweden, USA) population. These studies also included available celecoxib single/multiple pharmacokinetic data with genotype groups including *CYP2C9*1/*1*, *CYP2C9*1/*3*, and *CYP2C9*3/*3* (Tang et al. 2001; Lundblad et al. 2006; Prieto-Perez et al. 2013; Liu et al. 2015; Park et al. 2018). Demographic data of these pharmacokinetic studies used for validation are summarized in Table 3.

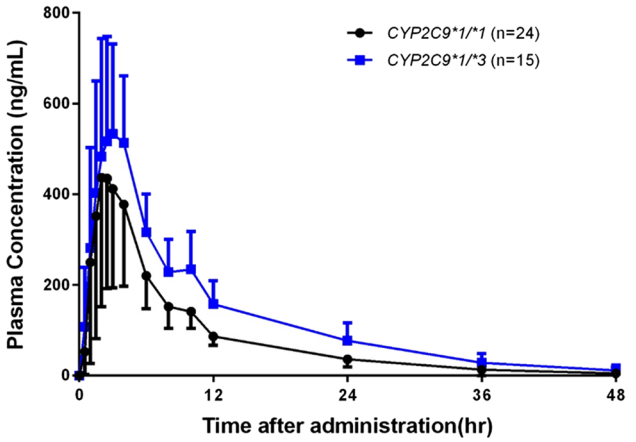

Fig. 1 Mean plasma concentration–time profile of celecoxib after administration of single 200 mg oral dose of celecoxib in *CYP2C9*1/*1* and *CYP2C9*1/*3* genotype groups

Table 1 Pharmacokinetic parameters of celecoxib after 200 mg oral dose of celecoxib in two different *CYP2C9* genotype groups

Parameter	*CYP2C9*1/*1*	*CYP2C9*1/*3*	*P* value
C_{max} [ng/mL]	480.0 ± 270.2	640.2 ± 269.3	0.032
$AUC_{0\text{-}48}$ [ng·hr/mL]	3656.4 ± 980.8	6458.6 ± 1115.0	< 0.0001
$AUC_{0\text{-}\infty}$ [ng·hr/mL]	3781.4 ± 973.5	6646.9 ± 1103.1	< 0.0001
CL/F [L/hr/kg]	55.7 ± 11.4	31.0 ± 12.4	< 0.0001
$t_{1/2}$ [hr]	7.8 ± 3.1	8.4 ± 3.0	0.580
t_{max} [hr]	2.7 ± 1.3	3.4 ± 1.3	0.175

Data are expressed as mean ± SD

Results

Clinical pharmacokinetic study

During the pharmacokinetic study, no unexpected adverse symptoms and/or signs related to celecoxib administration were observed in any of the 39 subjects. There were no significant differences in demographic characteristics between the *CYP2C9*1/*1* group and the *CYP2C9*1/*3* group. The pharmacokinetic parameters and plasma concentration–time profile of celecoxib in each genotype group are shown in Fig. 1 and Table 1.

Among the pharmacokinetic parameters, C_{max}, $AUC_{0\text{-}48}$, AUC_{inf}, and CL/F were significantly different between the two genotype groups. Compared with the *CYP2C9*1/*1* group, the *CYP2C9*1/*3* group had 1.3 fold higher C_{max}, 1.8 fold higher $AUC_{0\text{-}48}$, 1.8 fold higher AUC_{inf}, 1.8 lower CL/F, while $T_{1/2}$ and T_{max} were not significantly different between the two genotype groups.

PBPK model construction for celecoxib

Based on the conducted pharmacokinetic study and a previously reported study (Kim et al. 2017), the PBPK model for celecoxib was developed. Predefined physico-chemical parameters and ADME properties used in the PBPK model development are shown in Table 2. Data set for model development included *CYP2C9*1/*1, CYP2C9*1/*3, CYP2C9*1/*13*, and *CYP2C9*3/*3* genotype groups.

At first, the PBPK model for celecoxib with regards to the *CYP2C9*1/*1* genotype was developed. Initial simulation reflected celecoxib elimination only by metabolism of CYP enzymes including CYP2C9 and CYP3A4. This study assumed that celecoxib was eliminated mainly by hepatic metabolism with little urine excretion of unchanged celecoxib according to Davies et al. (2000).

Thereby, urine excretion was applied to kidney plasma clearance, and parameter identification tool in PK-Sim® software was utilized to perform optimization. Investigated dissolution rate of celecoxib capsule over 1–2 h, which was determined using the paddle method (described in the Korea Pharamacopeia), was 80% or more. Thus, dissolution rate was optimized within 1–2 h and was determined to be 90 min (Baek et al. 2015).

After optimization, predicted values of C_{max}, $AUC_{0\text{-}48}$, and AUC_{inf}, in the *CYP2C9*1/*1* genotype group met the predefined acceptance criterion range (Table 3) and demonstrated more optimal goodness of fit (Fig. 2).

Table 2 Physico-chemical parameters and ADME properties used for PBPK model development of celecoxib in the different *CYP2C9* genotype groups

Parameter	Reference value	Input value	References/Comment
Basic physico-chemistry			
Molecular weight	381.4 g/mol	381.4 g/mol	PubChem
Lipophilicity (logP)	3.9	3.9	Drug bank
Fraction unbound (f_u)	1.8–3.7%	3.5%	Paulson et al. (1999)
pK_a	10.7	10.7	Drug bank
Solubility	3.9–19.1 mg/mL	7.2 mg/mL	LC Laboratories Inc. (2018)
Absorption			
Specific intestinal permeability		$3.07E^{-4}$ cm/min	Calculated by PK-Sim®
Distribution			
Specific organ permeability		0.07 cm/min	Calculated by PK-Sim®
Metabolism			
*CYP2C9*1/*1*			
In vitro V_{max}	8.9 µmol/min/ µmol CYP	8.9 µmol/min/µmol CYP	Tang et al. (2001)
K_m	3.3 µM	3.3 µM	
*CYP2C9*1/*3*			
In vitro V_{max}	3.1 µmol/min/ µmol CYP	3.1 µmol/min/µmol CYP	Tang et al. (2001)
K_m	2.6 µM	2.6 µM	
*CYP2C9*1/*13*			
In vitro V_{max}	–	4.13 µmol/min/µmol CYP	Optimized by PK-Sim®
K_m	–	2.15 µM	
*CYP2C9*3/*3*			
In vitro V_{max}	3.1 µmol/min/ µmol	3.1 µmol/min/µmol CYP	Tang et al. (2001)
K_m	2.6 µM	2.6 µM	
CYP3A4			
In vitro V_{max}	1.4 µmol/min/ µmol	1.4 µmol/min/µmol CYP	Tang et al. (2001)
K_m	18.0 µM	18.0 µM	
CYP2C9 abundance in liver tissue		3.84 µmol/L	PK-Sim® default value
CYP3A4 abundance in liver tissue		4.32 µmol/L	PK-Sim® default value
Excretion			
Kidney plasma clearance		$2.20E^{-3}$ L/h/kg	Optimized by PK-Sim®
Formulation			
80% dissolution time	< 120 min	90 min	Baek et al. (2015)

Table 3 Demographic data and the observed and predicted pharmacokinetics of celecoxib with acceptance criterion range for model development by each *CYP2C9* genotype

Genotype	Age [yr]	BMI [kg/m^2]	Height [cm]	Weight [kg]		C_{max} [ng/mL]	$AUC_{0\text{-}48}$ [ng·hr/mL]	AUC_{inf} [ng·hr/mL]
*CYP2C9*1/*1* (n = 24)	19–29	17.2–26.8	162–193	51–100	Observed (mean ± SD)	480.0 ± 270.2	3656.4 ± 980.8	3781.4 ± 973.5
					Predicted	464.8	4307.0	4533.7
					Acceptance range	304.2–757.5	2907.4–4598.3	3033.8–4713.3
*CYP2C9*1/*3* (n = 15)	19–27	21.0–25.5	164–190	59–80	Observed (mean ± SD)	640.2 ± 269.3	6458.6 ± 1115.0	6646.9 ± 1103.1
					Predicted	750.8	7220.4	7954.4
					Acceptance range	481.7–850.8	5364.4–7775.9	5473.6–8071.6
*CYP2C9*1/*13* (n = 5)	21–29	18.2–24.8	164–183	49–82	Observed (mean ± SD)	553.8 ± 273.5	5461.6 ± 1168.6	5565.2 ± 1161.2
					Predicted	564.4	6737.1	7469.1
					Acceptance range	310.2–988.8	3649.8–8172.9	3755.6–8246.7
*CYP2C9*3/*3* (n = 2)	26–27	21.6–24.5	169–180	70	Observed (mean ± SD)	825.0 ± 75.0	25,736.8 ± 4309.6	27,351.1 ± 5432.7
					Predicted	930.7	26,376.9	29,610.1
					Acceptance range	627.7–1084.3	15,595.8–42,471.9	15,123.0–49,466.7

Compared with the reported volume of distribution at steady state (V_{ss}) value following oral administration (approximately 400 L) for celecoxib (Pfizer Inc. 2016), predicted V_{ss} of oral administration from this study was 467.5 L. Absolute bioavailability information for celecoxib is not known because of low solubility in aqueous media (Pfizer Inc. 2016). In our prediction, the oral bioavailability was 76% and the predicted V_{ss} of intravenous drug administration was 354.0 L.

Then, the developed model was scaled to *CYP2C9*1/*3, CYP2C9*1/*13,* and *CYP2C9*3/*3* genotype groups by modifying biometric data and value of in vitro metabolic rate of recombinant CYP2C9 (Table 2).

As a result, the predicted pharmacokinetic data of *CYP2C9*1/*3*, *CYP2C9*1/*13*, and *CYP2C9*3/*3* genotype groups also met the acceptance criterion range (Table 3, Fig. 3).

Sensitivity analysis

A sensitivity analysis was conducted to confirm which input parameters had significant impact on the pharmacokinetic simulation of celecoxib. Sensitivity analysis was performed in PK-Sim® and target pharmacokinetic parameters were AUC and C_{max}. The sensitivity ratio of input parameters are represented in Fig. 4.

Among the input parameters for model development, lipophilicity (log P) showed the highest sensitivity ratio in all target pharmacokinetic parameters. The f_u, celecoxib dose, and solubility were significantly sensitive to AUC and C_{max}. In vitro V_{max} and K_m, which represent the enzyme activity of CYP2C9, also showed to be significantly sensitive to AUC and C_{max}.

Model validation

After the model development, model validation was conducted by comparison of data from previous celecoxib pharmacokinetic studies, which assessed the role of *CYP2C9* polymorphism. Model validation was performed by comparing the observed and predicted values of the PK parameters (AUC and C_{max}) of each study.

Each simulation for validation was performed considering the respective ethnic group, biometric data and the *CYP2C9* genotype. As a result, all the predicted pharmacokinetic values of each study laid within the two-fold error range and the results are shown in Table 4.

Discussion

Most drug metabolizing enzymes and transporters are genetically polymorphic, and these genetic polymorphisms influence pharmacokinetics and pharmacodynamics of drugs to varying degrees (Byeon et al. 2019; Bae et al. 2020; Jung et al. 2020; Shin et al. 2020). Drug interactions also have

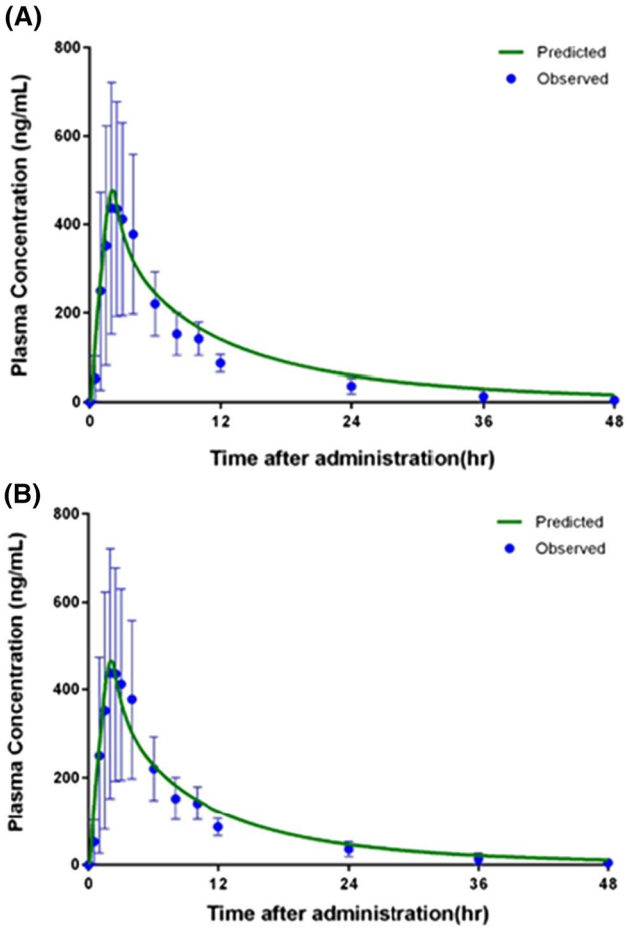

Fig. 2 The observed and predicted celecoxib pharmacokinetic profile in *CYP2C9*1/*1* genotype group: (A) predicted pharmacokinetic profile by initial input values which represent the physico-chemical and ADME properties of celecoxib, (B) predicted pharmacokinetic profile by applying optimized kidney plasma clearance

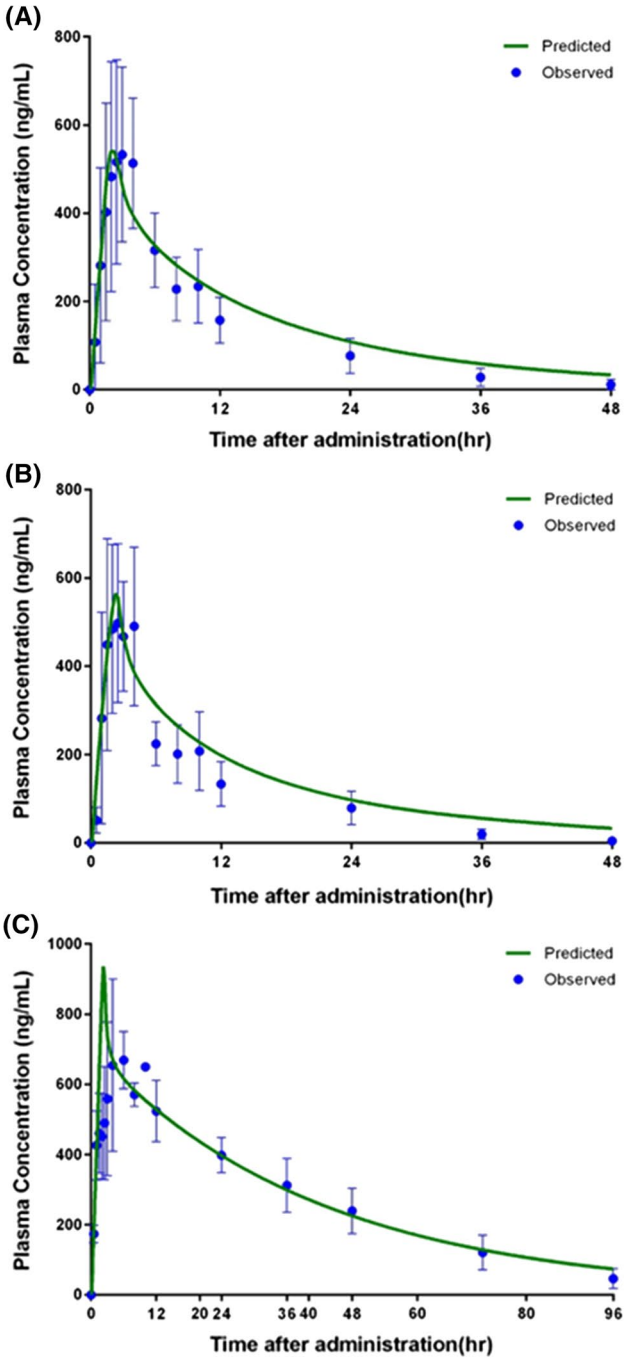

Fig. 3 The observed and predicted celecoxib pharmacokinetic profile in (**A**) *CYP2C9*1/*3*, (**B**) *CYP2C9*1/*13*, and (**C**) *CYP2C9*3/*3* genotype groups

a significant effect on drug action (Lee et al. 2019). PBPK modeling may enable an optimized drug administration strategy for each individual patient by reflecting all of the characteristics such as the patient's physical characteristics, genetic polymorphisms of drug metabolizing enzymes and transporters, drug interactions, diseases, etc. (Duan et al. 2017; Kim et al. 2018).

Through this study, a celecoxib PBPK model was developed based on the genetic polymorphism of *CYP2C9*. Celecoxib is primarily metabolized by CYP2C9 and partly by CYP3A4 after oral administration. CYP2C9 is most abundantly expressed in the CYP2C subfamily, accounting for approximately 20% of total hepatic cytochrome P450 protein (Daly et al. 2017).

Most of NSAIDs including diclofenac, ibuprofen, lornoxicam, tenoxicam, and meloxicam are metabolized by CYP2C9, and the genetic polymorphism of *CYP2C9* has been reported to affect the metabolism of these drugs (Vianna et al. 2004; Choi et al. 2011; Lee et al. 2014; Zhang et al. 2014; Krasniqi et al. 2016; Daly et al. 2017).

Likewise, most clinical studies, including the present one, have reported that *CYP2C9* genetic polymorphism significantly affects the metabolism of celecoxib (Tang et al. 2001; Kirchheiner et al. 2003; Stempak et al. 2005; Prieto-Perez et al. 2013; Liu et al. 2015; Kim et al. 2017; Park et al.

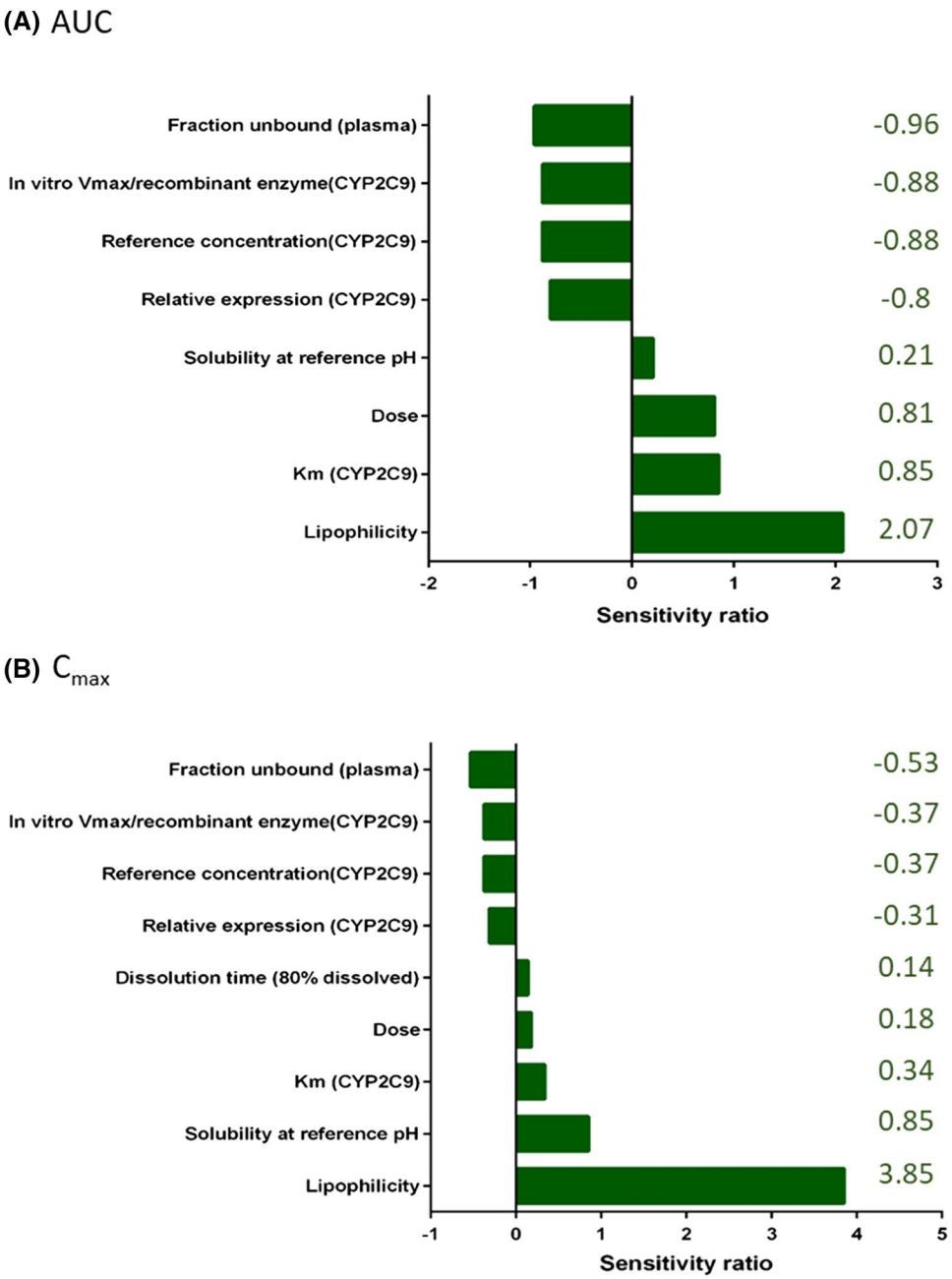

Fig. 4 Sensitivity ratio of input parameters for celecoxib on the AUC (**A**) and C_{max} (**B**)

2018). Besides, in our clinical study, $AUC_{0\text{-}48}$, AUC_{inf}, C_{max} and CL/F parameters were significantly different between *CYP2C9*1/*1* and *CYP2C9*1/*3* genotype groups.

Thus, PBPK model for celecoxib in this study was developed with regards to the genetic polymorphism of the *CYP2C9* enzyme. The workflow of this study was to utilize our clinical pharmacokinetic data for model development, and to validate the model with comparison studies. In the development of the PBPK model, input values for physicochemical parameter and ADME properties of celecoxib were adapted from previously reported studies, and these were calculated and optimized by PK-Sim® software.

Input values of in vitro metabolic rate of recombinant CYP2C9 (in vitro V_{max} and K_m) for *CYP2C9*1/*1*, *CYP2C9*1/*3*, and *CYP2C9*3/*3* genotype were adapted from the literature (Tang et al. 2001). In case of the *CYP2C9*1/*13* group, values were optimized by PK-Sim® based on the pharmacokinetic data by Kim et al. (2017) as in vitro metabolic rate data for *CYP2C9*1/*13* genotype group was not available otherwise. Through the change of these input parameter values, we intended to demonstrate pharmacokinetic differences between four genotype groups. As expected, sensitivity analysis indicated that in vitro V_{max} (CYP2C9) and K_m (CYP2C9) parameter differences

Table 4 Demographic data (range of age, BMI, weight) and ratio scores from observed and predicted mean pharmacokinetic values (AUC, C_{max}) of comparison studies after single and multiple oral administration of 200 mg celecoxib for each *CYP2C9* genotype

Comparison study [Dose]	Demographic data		Parameter	*CYP2C9*1/*1*			*CYP2C9*1/*3*			*CYP2C9*3/*3*		
				Observed	Predicted	Ratio Score	Observed	Predicted	Ratio Score	Observed	Predicted	Ratio Score
(A) Single administration												
Tang et al. (2001) [200 mg]	Age [yr]	20–47	AUC [ng·hr/mL]	5100.0	4124.9	0.81	11,150.0	5792.8	0.52	11,220	9346.5	0.83
	BMI [kg/m^2]	–										
	Height [cm]	–	C_{max} [ng/mL]	Not given	371.6	–	Not given	387.5	–	Not given	719.4	–
	Weight [kg]	56–84										
Prieto-Perez et al. (2013) [200 mg]	Age [yr]	20–32	AUC [ng·hr/mL]	7178.4	4914.1	0.68	14,068.0	10,841.2	0.77	55,105.3	28,996.5	0.53
	BMI [kg/m^2]	21–24										
	Height [cm]	–	C_{max} [ng/mL]	698.3	454.6	0.65	1066.3	657.2	0.62	1256.3	989	0.79
	Weight [kg]	53–72										
Liu et al. (2015) [200 mg]	Age [yr]	18–40	$AUC_{0\text{-}48}$ [ng·hr/mL]	4007.0	4675.8	1.17	7553.0	7037.9	0.93	–	–	–
	BMI [kg/m^2]	19–24										
	Height [cm]	–	C_{max} [ng/mL]	523.8	475.7	0.91	792.4	578.8	0.73	–	–	–
	Weight [kg]	50–83										
(B) Multiple administration												
Lundblad et al. (2006) [200 mg/day, 7 days]	Age [yr]	18–55	$AUC_{0\text{-}24}$ [ng·hr/mL]	6866.4	4372.7	0.64	6482.8	8320.5	1.28	–	–	–
	BMI [kg/m^2]	–										
	Height [cm]	–	C_{max} [ng/mL]	761.6	623.5	0.82	723.5	845.8	1.17	–	–	–
	Weight [kg]	–										
Park et al. (2018) [200 mg/day, 4 days]	Age [yr]	20–45	$AUC_{0\text{-}48}$ [ng·hr/mL]	4847.9	4366.4	0.90	9832.6	10,702.1	1.09	47,677.9	24,369.4	0.51
	BMI [kg/m^2]	18–27										
	Height [cm]	169.6–179.6	C_{max} [ng/mL]	737.0	547.2	0.74	1278.2	985.6	0.77	2940.2	1566.1	0.53
	Weight [kg]	62.8–80.8										

between four genotype groups had a significant impact on the pharmacokinetics of celecoxib.

The evaluation criteria for model development and validation were separated into model acceptance criterion (99.998% confidence interval) and two-fold error. Model acceptance criterion used to evaluate model development was based on a previously presented literature (Abduljalil et al. 2014). According to Abduljalil et al. (2014), the presented model acceptance criterion has a 99.998% confidence interval, which can more accurately reflect all the inter-individual variabilities of observed pharmacokinetic values than the two-fold error criterion. The ranges of the proposed criterion were 1.58-, 1.33-, 1.79-, and 1.81-fold for *CYP2C9*1/*1, CYP2C9*1/*3, CYP2C9*1/*13,* and *CYP2C9*3/*3* genotype groups, respectively. Moreover, all the predicted pharmacokinetic parameters for model development met the two-fold error range, as well as proposed model acceptance criterion.

There are eight studies that have reported *CYP2C9* genetic polymorphism affecting the pharmacokinetics of celecoxib (Tang et al. 2001; Kirchheiner et al. 2003; Stempak et al. 2005; Lundblad et al. 2006; Prieto-Perez et al. 2013; Liu et al. 2015; Kim et al. 2017; Park et al. 2018). Among them, five pharmacokinetic studies were selected for comparison in the validation process. Kirchheiner et al. (2003) and Stempak et al. (2005) were excluded because biometric information for the subject group was not specified. Kim et al. (2017) was also excluded due to the use of pharmacokinetic data from the *CYP2C9*1/*13* and *CYP2C9*3/*3* genotype groups for model development.

In this model validation, predicted target pharmacokinetic values including AUC and C_{max} for Korean (Park et al. 2018), Chinese (Liu et al. 2015), and Caucasian population (Tang et al. 2001; Lundblad et al. 2006; Prieto-Pérez et al. 2013) studies met the two-fold error criterion. These results indicated that the PBPK model for celecoxib according to *CYP2C9* genetic polymorphism has successfully described the pharmacokinetics of celecoxib after single or multiple oral administration.

Of note, the observed pharmacokinetic values between East Asian population (Chinese and Korean) and Caucasian population were significantly different. These results had a considerable impact on the validation for model development of celecoxib. The ratio scores (between observed and predicted pharmacokinetic values) in the Korean and Chinese population simulation through this model were within 0.67–0.94, and 0.72–1.18, respectively. In the Caucasian population, however, the ratio scores (between observed and predicted pharmacokinetic values) were within 0.54–0.88, which was significantly lower compared to Asian population ($P < 0.01$) (Table 4).

Shu et al. (2001) suggested that CYP2C9 abundance was not significantly related to ethnicity. However, this study strongly suggests that there is a limitation in simulating with same CYP2C9 enzyme abundance (3.84 μM in liver tissue) to all races. Despite these limitations, this model can be useful in determining optimal dosage considering the patient's demographic data (age, height, weight, and BMI) and *CYP2C9* genotype. Additionally, this model may also be applied to construct a drug-drug interaction model with celecoxib and CYP2C9 inhibitor or inducer.

In conclusion, a PBPK model for celecoxib with regard to *CYP2C9* genetic polymorphism was developed, which predicted the pharmacokinetics of celecoxib, considering demographic data of subjects, physico-chemical parameters, ADME properties, and *CYP2C9* genotype. Although further development is required, this PBPK model is the first attempt to demonstrate in silico prediction of celecoxib pharmacokinetics that reflects the pharmacogenetic effects. These results will be beneficial in prescribing the appropriate dosage of celecoxib considering inter-individual differences.

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Declarations

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

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