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RESEARCH ARTICLE

Physiologically based pharmacokinetic (PBPK) modeling of flurbiprofen in different *CYP2C9* genotypes

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Abstract The aim of this study was to establish the physiologically based pharmacokinetic (PBPK) model of flurbiprofen related to *CYP2C9* genetic polymorphism and describe the pharmacokinetics of flurbiprofen in different *CYP2C9* genotypes. PK-Sim® software was used for the model development and validation. A total of 16 clinical pharmacokinetic data for flurbiprofen in different *CYP2C9* genotypes, dose regimens, and age groups were used for the PBPK modeling. Turnover number (k_{cat}) of CYP2C9 values were optimized to capture the observed profiles in different *CYP2C9* genotypes. In the simulation, predicted fraction metabolized by CYP2C9, fraction excreted to urine, bioavailability, and volume of distribution were similar to previously reported values. Predicted plasma concentration-time profiles in different *CYP2C9* genotypes were visually similar to the observed profiles. Predicted AUC_{inf} in *CYP2C9*1/*2*, *CYP2C9*1/*3*, and *CYP2C9*3/*3* genotypes were 1.44-, 2.05-, and 3.67-fold higher than the *CYP2C9*1/*1* genotype. The ranges of fold errors for AUC_{inf}, C_{max}, and $t_{1/2}$ were 0.84–1.00, 0.61–1.22, and 0.74–0.94 in development and 0.59–0.98, 0.52–0.97, and 0.61–1.52 in validation, respectively, which were within the acceptance criterion. Thus, the PBPK model was successfully established and described the pharmacokinetics of flurbiprofen in different *CYP2C9* genotypes, dose regimens, and age groups. The present model could guide the decision-making of tailored drug administration strategy by predicting the pharmacokinetics of flurbiprofen in various clinical scenarios.

Keywords Physiologically based pharmacokinetic (PBPK) model · Flurbiprofen · CYP2C9 · Genetic polymorphism · Pharmacokinetics

Introduction

Flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for symptomatic alleviation of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis (Buchanan and Kassam 1986). Most frequently reported adverse events of flurbiprofen are gastrointestinal related, including abdominal pain, dyspepsia, nausea, diarrhea and constipation (Pfizer 2016). Flurbiprofen is generally marketed as racemates and it has more ulcerogenic potential than its (*S*)-enantiomer (Wechter et al. 1993). Flurbiprofen is rapidly absorbed with maximum plasma concentration observed between 0.5 and 3 h after oral administration and highly bound (> 99%) to plasma albumin (Davies 1995). Flurbiprofen is extensively metabolized via hydroxylation by cytochrome P450 (CYP) 2C9 (Tracy et al. 1996) and glucuronidation by UDP-glucuronosyltransferase (UGT) 2B7 and UGT1A9 (Wang et al. 2011). The metabolites are primarily eliminated in the kidney and an excreted ratio of unchanged flurbiprofen in urine is less than 3% (Pfizer 2016).

Sang-Sup Whang and Chang-Keun Cho have contributed equally to this study.

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CYP2C9, accounting for up to 20% of P450 contents in the total human liver (Shimada et al. 1994), is responsible for the metabolism of approximately 15–20% of drugs that undergo Phase I metabolism (Evans and Relling 1999; Rettie and Jones 2005). *CYP2C9* gene is highly polymorphic with at least 85 allele variants or sub-variants (*CYP2C9*1B* to *CYP2C9*85*) reported (https://www.pharmvar.org/gene/CYP2C9). Of these alleles, *CYP2C9*2* (rs1799853, c.430 C > T, p.Cys144Arg) and *CYP2C9*3* (rs1057910, c.1075 A > C, p.Ile359Leu), the most frequently observed allele variants worldwide (Daly et al. 2017), exhibit the reduction of enzyme activity for the substrate of CYP2C9 in vitro and in vivo (Yasar et al. 2001; Perini et al. 2005; Bae et al. 2011b; Lee et al. 2014). Wang et al. (2015) showed the catalytic activities of *CYP2C9*2* and **3* variants for flurbiprofen in vitro were decreased by 61.4 and 24.3% compared to the wild-type allele, respectively. Several studies reported that genetic polymorphism of *CYP2C9* significantly affected the pharmacokinetics of flurbiprofen in humans (Lee et al. 2003, 2015; Kumar et al. 2008). Clinical Pharmacogenetic Implementation Consortium (CPIC) proposed 50–75% dose reduction for NSAIDs with a short half-life such as celecoxib, flurbiprofen, ibuprofen and lornoxicam in CYP2C9 poor metabolizers (CYP2C9PMs) (Theken et al. 2020).

Physiologically based pharmacokinetic (PBPK) modeling is a mechanistic approach to predict the dispositions of xenobiotics in humans and other animal species (Kuepfer et al. 2016; Zhuang and Lu 2016). It is a valuable tool for tailoring drug administration strategies according to the alteration of physiological characteristics (Abduljalil and Badhan 2020; Verscheijden et al. 2020; Heimbach et al. 2021), drug–drug interactions (Abouir et al. 2021; Ferreira et al. 2021), cigarette consumption (Plowchalk and Rowland Yeo 2012), and genetic polymorphism (Cho et al. 2021a, 2021b; Jung et al. 2021; Kim et al. 2021; Rüdesheim et al. 2022). In the present study, we aimed to develop and validate the PBPK model for flurbiprofen related to the genetic polymorphism of *CYP2C9*.

Materials and methods

Software and data source

PBPK model was developed and validated using PK-Sim® version 10.0 (Bayer AG, Leverkusen, Germany). Plasma concentration-time profiles for model development were digitized with Engauge Digitizer® version 12.1 (https://markummitchell.github.io/engauge-digitizer/) according to the proposed digitization algorithm in Wojtyniak et al. (2020). Pharmacokinetic parameters which were not obtained from the publications were estimated via non-compartmental analysis (NCA) with the BA calc 2007 analysis program (MFDS, Cheongju, Republic of Korea).

A total of 16 clinical pharmacokinetic data for flurbiprofen were collected and used to develop and validate the PBPK model. The data for fifteen subjects with *CYP2C9*1/*1* (n = 5), *CYP2C9*1/*2* (n = 5), and *CYP2C9*1/*3* (n = 5) genotypes from the report of Lee et al. (2003) and for two subjects with *CYP2C9*3/*3* genotype from the report of Kumar et al. (2008) were used to develop the model. Other 12 data were used to validate the developed model. Clinical data from studies without information on the *CYP2C9* genotype were assumed that the all subjects were carrying the *CYP2C9*1/*1* genotype.

Model building

"Middle-out" strategy was used for the model building. Physicochemical properties of the drug were collected from previous publications or drug databases. The specific intestinal and organ permeabilities were calculated in the software (Thelen et al. 2011, 2012). CYP2C9, UGT1A9, and UGT2B7 enzymes were incorporated to describe the metabolism of flurbiprofen. Michaelis–Menten constant (K_m) values for CYP2C9 (Wang et al. 2015) and UGTs (Wang et al. 2011) were obtained from previous studies. CYP2C9 turnover number (k_{cat}) values in different *CYP2C9* genotypes were optimized to capture the observed profiles. The k_{cat} values for UGT1A9 and UGT2B7 were optimized based on clinical pharmacokinetic data for *CYP2C9*3/*3* genotype in Kumar et al. (2008) in which the effects of UGT1A9 or UGT2B7 on the total clearance of flurbiprofen were expected to be sensitive. The reference concentration of CYP2C9 was 3.84 μmol/L (Rodrigues 1999) and UGTs was 1.00 μmol/L, the default value of PK-Sim®. Relative expression values for CYP2C9 and UGTs in each organ were obtained from the reverse transcription-polymerase chain reaction (RT-PCR) data (Nishimura et al. 2003; Nishimura and Naito 2005, 2006). Hepatic plasma clearance was incorporated with considerations of minor enzymatic pathways, those not mediated by CYP2C9, UGT1A9, and UGT2B7. Renal plasma clearance was adjusted to recover the excreted fraction in urine as unchanged form (< 3% of dose, Pfizer 2016). Dissolution time (80% dissolved) was adjusted from the dissolution profiles for marketed tablet of Daravath et al. (2018) and lag time was optimized to capture the observed profiles more accurately. Parameter optimization was performed via the Levenberg-Marquardt algorithm in the PK-Sim® software. Schmitt (2008) and PK-Sim® standard method (Hindmarsh et al. 2021) was used to estimate partition coefficients and cellular permeabilities, respectively.

Sensitivity analysis

Sensitivity analysis was performed in the PK-Sim® software. In the analysis, a total of 241 input parameters were evaluated for the area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) and peak plasma concentration (C_{max}). The sensitivity was calculated as follows

$$S = \frac{\Delta PK}{PK} \div \frac{\Delta p}{p} \tag{1}$$

where S is the sensitivity, PK is the initial values of the pharmacokinetic parameter, ΔPK is the change of the pharmacokinetic parameters from initial values, p is the initial values of the evaluated input parameter, and Δp is the change of evaluated input parameters from initial values, respectively. A sensitivity of + 1.0 indicates that + 10% change of an evaluated input parameter causes + 10% change of the predicted pharmacokinetic parameters.

Model evaluation

The PBPK model was evaluated using visual and numerical methods. Observed plasma concentration-time profiles were visually compared with the predicted profiles by plotting the geometric mean and 5th–95th percentiles for a virtual population ($n = 100$). Demographic data for virtual populations were designated to be similar to those of the observed populations. The demographic data which could not be obtained from previous studies were generated using the implemented algorithm in the PK-Sim® software. Standard deviations for the reference concentration of CYP2C9 and UGTs were assigned as 1.15 and 0.30 μmol/L, respectively, to reflect moderate variability (30% of the mean). The PBPK model were numerically evaluated by comparing the observed and predicted AUC_{inf}, C_{max}, and half-life ($t_{1/2}$) values. A two-fold error range for the pharmacokinetic parameters was used as the evaluation criterion. The PBPK model was acceptable if the fold error (predicted value divided by observed value) is within the 0.5–2 range.

Results

The summary of input parameters for the PBPK model is presented in Table 1. In the simulation shown in Fig. 1, estimated values for the fraction metabolized by CYP2C9 ($f_{m,CYP2C9}$) and fraction excreted to urine of 71.8 and 2.91%, respectively, were very close to the reported values of 71 (Patel et al. 2003; Loisios-Konstantinidis et al. 2020) and < 3%, respectively (Pfizer 2016). Bioavailability and volume of distribution (V_d/F) were estimated as 0.94 and 0.11 L/kg, similar to the reported values of 0.96 and 0.12 L/kg, respectively (Pfizer 2016).

Predicted plasma concentration-time profiles for *CYP2C9* allele variants were visually similar to the observed profiles (Fig. 2). Predicted AUC_{inf} in *CYP2C9*1/*2*, *CYP2C9*1/*3*, and *CYP2C9*3/*3* genotypes were 1.44-, 2.05-, and 3.67-fold higher than *CYP2C9*1/*1* genotype, respectively. Significant differences for predicted C_{max} in different *CYP2C9* genotypes were not identified (5.1–5.8 μg/mL). The ranges of fold errors for AUC_{inf}, C_{max}, and $t_{1/2}$ in development were 0.84–1.00, 0.61–1.22, and 0.74–0.94, respectively, which were within the acceptance criterion (Table 2).

Sensitivity analysis is shown in Fig. 3. Dose had the equally highest impact on both AUC_{inf} and C_{max}. Several physicochemical parameters including lipophilicity and fraction unbound were sensitive to AUC_{inf} and C_{max}. Parameters related to CYP2C9 and UGT2B7 enzymatic pathways such as K_m, k_{cat}, and reference concentration were identified as sensitive but UGT1A9 was not. Renal plasma clearance and pK_a had slight influence on AUC_{inf} and C_{max}, respectively.

A total of 12 clinical data for the validation included 40–150 mg single dose regimen in various age groups (from 6 to 83 years). In validation, the ranges of fold errors for AUC_{inf}, C_{max}, and $t_{1/2}$ were 0.59–0.98, 0.52–0.97, and 0.61–1.52, respectively, which is within the acceptance criterion (Table 2).

Discussion

The activity of the drug metabolizing enzymes and transporters is closely related to the disposition of the drug in the body. Genetic polymorphism of drug metabolizing enzymes and transporters causes the inter-individual variability in drug responses. Various studies to investigate the influences of genetic variants of drug metabolizing enzymes (Choi et al. 2012; Byeon et al. 2015; Bae et al. 2020; Jung et al. 2020a, b; Kim et al. 2022) and transporters (Sai et al. 2010; Choi et al. 2013; Shin et al. 2020) on the pharmacokinetics or pharmacodynamics of clinically used drugs have been reported. As the utilization of the PBPK modeling approach has been rapidly increasing in the last couple of decades (El-Khateeb et al. 2021), access to a tailored drug administration strategy, considering physiological characteristics, genotypes, diseases, and drug interactions of individuals, has been attempted using the PBPK model (Rüdesheim et al. 2020, 2022; Cho et al. 2021a, b; Jung et al. 2021; Kim et al. 2021; Marok et al. 2021).

Majority of NSAIDs including celecoxib, lornoxicam, meloxicam, naproxen, and piroxicam are metabolized by CYP2C9 and the influences of *CYP2C9* allele variants on the pharmacokinetics and pharmacodynamics of NSAIDs

Table 1 Summary of input parameters used in the PBPK model

Parameter	Reference value	Input value	References/Comments
Basic physico-chemistry			
Molecular weight (g/mol)	244.26	244.26	Pubchem
log P	3.57	3.57	DrugBank/ALOGPS
pK_a	4.42	4.42	DrugBank/ALOGPS
Binding protein	Albumin	Albumin	DrugBank
f_u (%)	0.031	0.031	Kumpulainen et al. (2010)
Solubility (mg/mL)	1.25	1.25	Yaşin et al. (2018)
Absorption			
Specific intestinal permeability (cm/min)	–	1.47×10^{-3}	Calculated by PK-Sim®
Distribution			
Specific organ permeability (cm/min)		0.78	Calculated by PK-Sim®
Metabolism			
CYP2C9 K_m (µM)	8.76	8.76	Wang et al. (2015)
CYP2C9 k_{cat} (/min), *CYP2C9*1/*1*	–	74.50	Optimized by PK-Sim®
CYP2C9 k_{cat} (/min), *CYP2C9*1/*2*	–	46.89	Optimized by PK-Sim®
CYP2C9 k_{cat} (/min), *CYP2C9*1/*3*	–	27.98	Optimized by PK-Sim®
CYP2C9 k_{cat} (/min), *CYP2C9*3/*3*	–	3.42	Optimized by PK-Sim®
UGT1A9 K_m (µM)	182.2	182.2	Wang et al. (2011)
UGT1A9 k_{cat} (/min)	–	3.29	Optimized by PK-Sim®
UGT2B7 K_m (µM)	50.21	50.21	Wang et al. (2011)
UGT2B7 k_{cat} (/min)	–	90.76	Optimized by PK-Sim®
Hepatic plasma clearance (mL/h/kg)	–	2.68	Optimized by PK-Sim®
Excretion			
Renal plasma clearance (mL/min/kg)	–	0.22	Pfizer (2016) (<3% of dose)
Formulation			
Dissolution time (min)	30–45	30.18	Daravath et al. (2018)
Lag time (min)	–	25.76	Optimized by PK-Sim®

log P logarithm of octanol/water partition coefficient, pK_a negative logarithm of acid dissociation constant, f_u fraction unbound in plasma, K_m Michaelis–Menten constant, k_{cat} turnover number

have been studied (Perini et al. 2005; Bae et al. 2009, 2011a, b; Choi et al. 2011; Kim et al. 2017). Likewise, significant influences on the pharmacokinetics of flurbiprofen according to *CYP2C9* genetic polymorphism have been identified (Lee et al. 2003, 2015; Kumar et al. 2008). CPIC and drug label recommended dose reduction of flurbiprofen in the CYP2C9PM phenotype (Pfizer 2016; Theken et al. 2020). They suggested that the genetic polymorphism of *CYP2C9* is one of the important factors causing inter-individual variability of the responses of flurbiprofen.

The present PBPK model was developed by leveraging a number of information related to physicochemical and pharmacokinetic (absorption, distribution, metabolism, and excretion [ADME]) characteristics of flurbiprofen. An in vitro study showed the major oxidative pathway in flurbiprofen metabolism was conversion to a 4′-hydroxy metabolite mediated by CYP2C9 (Tracy et al. 1996). Also, UGT2B7 and UGT1A9 predominantly and minorly contributed in the glucuronidation of flurbiprofen, respectively (Mano et al. 2007; Wang et al. 2011). The results of sensitivity analysis demonstrated that the present model sufficiently reflected the contributions of the metabolizing enzymes (Fig. 3). Mano et al. (2007) also reported UGT1A1, UGT1A3, and UGT2B4 exhibit the glucuronidation activity of flurbiprofen. Hepatic plasma clearance was additionally incorporated to consider the contributions of these enzymes. In the initial model, in vitro metabolism data (Wang et al. 2015) was incorporated without any modification and AUC was highly overestimated. Lee et al. (2021) reported that in vitro test tends to underpredict the in vivo clearance and recommended the optimization for metabolism parameters based on in vivo data. Thus,

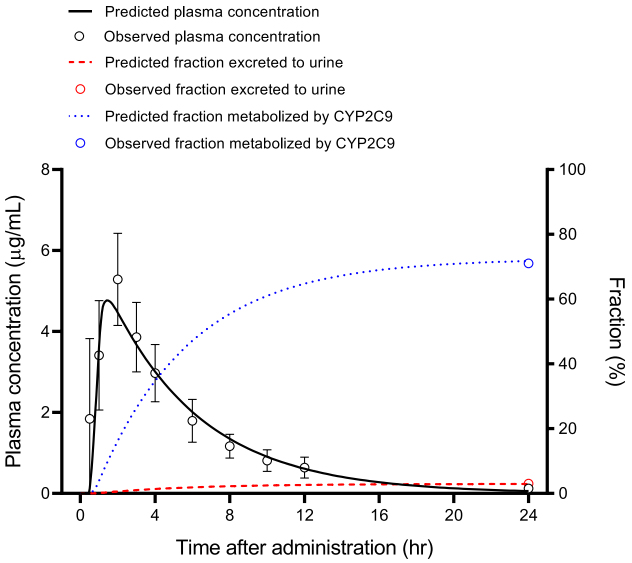


Fig. 1 Predicted and observed profiles of flurbiprofen after 50 mg single oral administration. The black solid, red dashed, and blue dotted lines indicate plasma concentration, fraction excreted to urine, and fraction metabolized by CYP2C9, respectively. Black open circles and error bars indicate the mean and standard deviation of observed plasma concentration, respectively. Red and blue open circles indicate the observed fraction excreted to urine and fraction metabolized by CYP2C9, respectively

CYP2C9 k_{cat} value was optimized to capture the observed profiles. The estimated values including $f_{m,CYP2C9}$, urine excretion, bioavailability, and volume of distribution, were almost similar to previously reported values and this suggests that our model can predict the pharmacokinetics of flurbiprofen.

Our model properly captured the pharmacokinetics of flurbiprofen not only for the *CYP2C9*1/*1* genotype but also for genotypes with *CYP2C9* allele variants. The predicted profiles were visually similar to the observed profiles in different *CYP2C9* genotypes (Fig. 2). Also, the range of fold error values for AUC_{inf}, C_{max}, and $t_{1/2}$ in development and validation satisfied the acceptance criterion (Table 2). This suggests that the PBPK model could capture the disposition of flurbiprofen in different dose regimens, demographic characteristics, and genotypes. Although observed C_{max} of *CYP2C9*3/*3* genotype slightly deviated from the predicted range visually, the qualified model can provide reasonable information for the pharmacokinetics of flurbiprofen in different *CYP2C9* genotypes with reduction in the risk of adverse events by administration of the drug.

The present model properly described the pharmacokinetics of flurbiprofen in special populations including the pediatric and geriatric populations. PK-Sim® provides the quantitative data for age-dependent physiological alterations in pediatric and geriatric populations (Edginton et al. 2006; Schlender et al. 2016). It easily enables the prediction of the pharmacokinetics of drugs in various age groups. Thus, we validated the applicability of the model using the clinical data on children (Scaroni et al. 1984) or elderly subjects (Kean et al. 1992) and identified that the PBPK model could be applied to these populations.

Modeling studies to describe the pharmacokinetics of flurbiprofen in humans have been previously identified. Kumpulainen et al. (2010) and Zhang et al. (2018) reported population pharmacokinetic models in healthy children and Chinese patients with postoperative pain, respectively. As these models only applied mathematical methods based on the clinical data to predict the pharmacokinetics of the drug, limitations exist in that physicochemical and physiological characteristics could not be incorporated. Verscheijden et al. (2019) developed a pediatric brain PBPK model to predict the cerebrospinal fluid drug concentrations and flurbiprofen was used as a drug for model validation. However, their model was focused on the pediatric population and the pharmacokinetics of flurbiprofen in the adult population was not presented. Loisios-Konstantinidis et al. (2020) developed the flurbiprofen PBPK model using Simcyp® software to predict the effects of various factors including *CYP2C9* genetic polymorphism, co-administration, and formulation. Although their model can properly describe the pharmacokinetic alterations of flurbiprofen according to *CYP2C9* genetic polymorphism, we developed the flurbiprofen model using PK-Sim® software because there are differences in the description of ADME characteristics between platforms and it can cause discrepant simulation consequences from the equal input parameters. Furthermore, they successfully established the flurbiprofen model in the adult populations. Whether their model could adequately be applied in the pediatric or geriatric populations is uncertain. In the present study, we developed the flurbiprofen model and validated it using the clinical data for a wide range of ages groups including the pediatric and geriatric populations.

The established PBPK model for flurbiprofen has several limitations. Validation was not performed in *CYP2C9*1/*2*

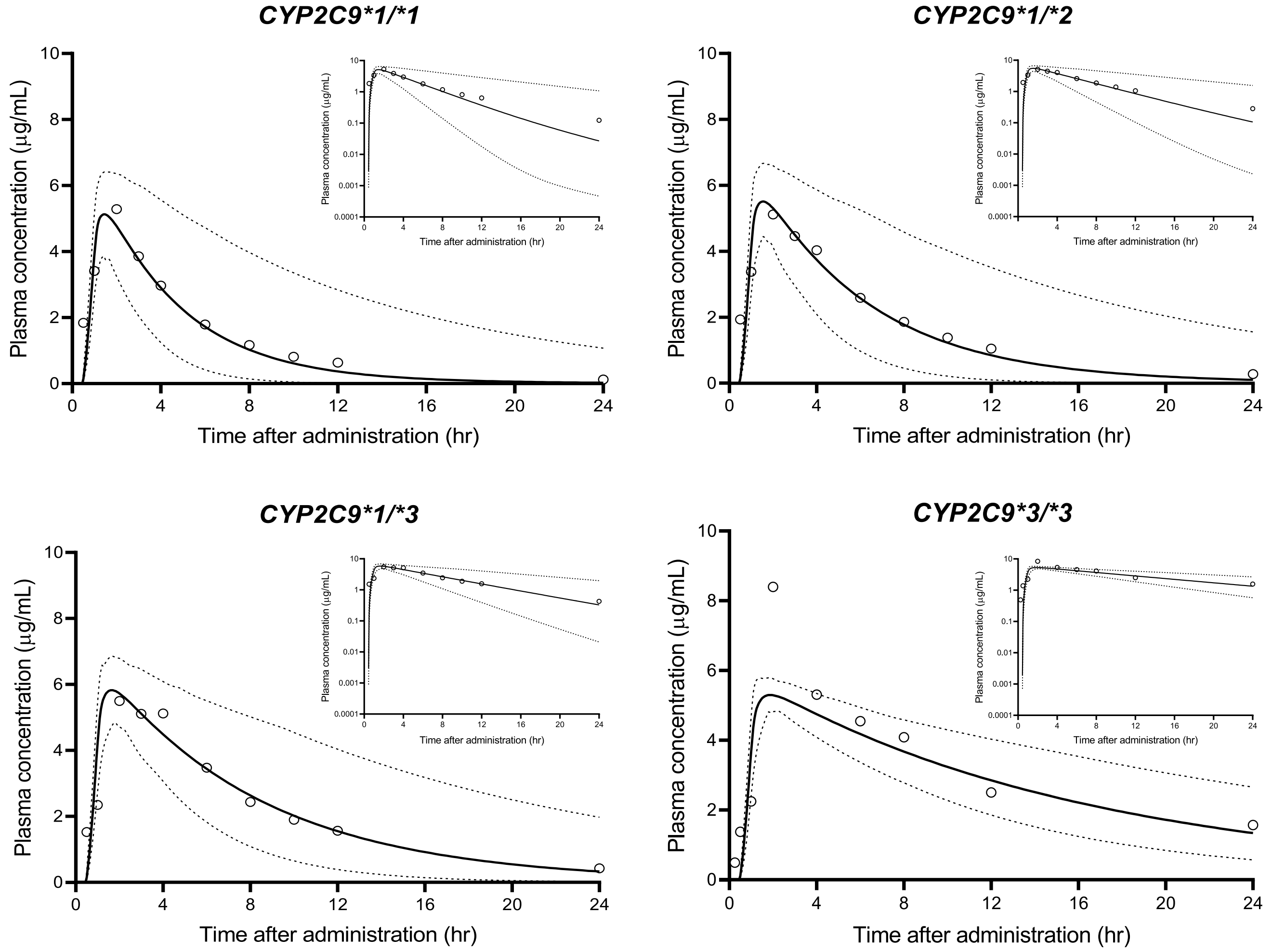


Fig. 2 Predicted and observed plasma concentration–time profiles of flurbiprofen in different *CYP2C9* genotypes. Solid and dashed lines indicate geometric mean and 5th–95th percentile, respectively. Open circles indicate the mean of observed plasma concentrations. Profiles are expressed using linear and semi-logarithmic scales

and *CYP2C9*3/*3* genotypes due to the lack of pharmacogenetic studies for these genotypes. To our knowledge, only one clinical pharmacokinetic data for each of the *CYP2C9*1/*2* (Lee et al. 2003) and *CYP2C9*3/*3* genotypes (Kumar et al. 2008) were identified to date, and these were used in the development. Furthermore, we did not consider the physiological alterations in the patients with arthritis. In our study, we developed the PBPK model using the pharmacogenetic studies for healthy subjects and validated the model by using equal parameters in healthy subjects and patients with arthritis. Further research for the physiological differences between healthy and patient populations may improve the model. It would be better to apply the present model under the consideration of these potential limitations.

In conclusion, the flurbiprofen PBPK model in different *CYP2C9* genotypes was successfully established. The present model could guide the decision-making of tailored drug

Table 2 Results for the development and validation of the PBPK model

References [Administration]	Age group	Number of subjects	Genotype	Demographic characteristics of populations			Parameters	Mean observed	Mean predicted	Fold error
				Proportion of female (%)	Age (year)	Weight (kg)				
Development										
Lee et al. (2003) [Single 50 mg]	Adult	5	*CYP2C9*1/*1*	53	24 ± 5	79 ± 18	AUC$_{inf}$ (μg·h/mL)	29.4	24.8	0.84
							C$_{max}$ (μg/mL)	5.3*	5.1	0.96
							$t_{1/2}$ (h)	4.9	3.7	0.76
Lee et al. (2003) [Single 50 mg]	Adult	5	*CYP2C9*1/*2*	53	24 ± 5	79 ± 18	AUC$_{inf}$ (μg·h/mL)	40.3	35.8	0.89
							C$_{max}$ (μg/mL)	4.5*	5.5	1.22
							$t_{1/2}$ (h)	5.8	4.3	0.74
Lee et al. (2003) [Single 50 mg]	Adult	5	*CYP2C9*1/*3*	53	24 ± 5	79 ± 18	AUC$_{inf}$ (μg·h/mL)	51.1	50.9	1.00
							C$_{max}$ (μg/mL)	5.5*	5.8	1.05
							$t_{1/2}$ (h)	6.1	5.5	0.90
Kumar et al. (2008) [Single 50 mg]	Adult	2	*CYP2C9*3/*3*	0	25–29	77–85	AUC$_{inf}$ (μg·h/mL)	102.4$^{\$}$	91.1	0.89
							C$_{max}$ (μg/mL)	8.7$^{\$}$	5.3	0.61
							$t_{1/2}$ (h)	11.8$^{\$}$	11.1	0.94
Validation—adult population										
Lee et al. (2015) [Single 40 mg]	Adult	12	*CYP2C9*1/*1*	0	23.1 ± 2.4	65.1 ± 7.1	AUC$_{inf}$ (μg·h/mL)	29.3	20.8	0.71
							C$_{max}$ (μg/mL)	7.5	4.2	0.56
							$t_{1/2}$ (h)	3.2	2.9	0.91
Lee et al. (2015) [Single 40 mg]	Adult	8	*CYP2C9*1/*3*	0	22.0 ± 2.7	64.6 ± 7.1	AUC$_{inf}$ (μg·h/mL)	47.6	35.0	0.74
							C$_{max}$ (μg/mL)	8.9	4.6	0.52
							$t_{1/2}$ (h)	4.3	4.5	1.05
Kumar et al. (2008) [Single 50 mg]	Adult	11	*CYP2C9*1/*1*	64	19–36	51–108	AUC$_{inf}$ (μg·h/mL)	30.8	24.6	0.80
							C$_{max}$ (μg/mL)	7.6	5.6	0.74
							$t_{1/2}$ (h)	4.8	3.8	0.79
Kumar et al. (2008) [Single 50 mg]	Adult	8	*CYP2C9*1/*3*	63	19–28	49–84	AUC$_{inf}$ (μg·h/mL)	53.7	52.5	0.98
							C$_{max}$ (μg/mL)	8.9	5.7	0.64
							$t_{1/2}$ (h)	7.2	5.8	0.81
Kean et al. (1992) [Single 100 mg]	Adult	12	N/A	58	50.1 ± 6.4	72.6 ± 15.5	AUC$_{inf}$ (μg·h/mL)	58.3	48.5	0.83
							C$_{max}$ (μg/mL)	11.7	9.9	0.85
							$t_{1/2}$ (h)	6.2	3.8	0.61
Liu et al. (2009) [Single 150 mg]	Adult	20	N/A	0	19–28	56–78	AUC$_{inf}$ (μg·h/mL)	129.8	84.4	0.65
							C$_{max}$ (μg/mL)	21.2	16.4	0.77
							$t_{1/2}$ (h)	4.4	3.9	0.89
Qayyum et al. (2013) [Single 100 mg]	Adult	22	N/A	0	20–38	50–94	AUC$_{inf}$ (μg·h/mL)	62.2	46.5	0.75
							C$_{max}$ (μg/mL)	12.0	10.8	0.90
							$t_{1/2}$ (h)	4.3*	3.7	0.86

Table 2 (continued)

References [Administration]	Age group	Number of subjects	Genotype	Demographic characteristics of populations			Parameters	Mean observed	Mean predicted	Fold error
				Proportion of female (%)	Age (year)	Weight (kg)				
Volak et al. (2013) [Single 100 mg]	Adult	8	N/A	13	24–52	61–93	AUC_{inf} (µg·h/mL)	75.4	45.4	0.60
							C_{max} (µg/mL)	12.3	9.0	0.73
							$t_{1/2}$ (h)	4.2	3.8	0.90
Hanley et al. (2012) [Single 100 mg]	Adult	12	N/A	16	24–55	N/A	AUC_{inf} (µg·h/mL)	69.5	41.0	0.59
							C_{max} (µg/mL)	11.3	8.8	0.78
							$t_{1/2}$ (h)	4.2	3.7	0.88
Validation—special population										
Scaroni et al. (1984) [Single 50 mg]	Pediatric	4	N/A	50	6–8	18.6 ± 3.6	AUC_{inf} (µg·h/mL)	72.4	64.7	0.89
							C_{max} (µg/mL)	20	13.1	0.66
							$t_{1/2}$ (h)	2.7	4.1	1.52
Scaroni et al. (1984) [Single 75 mg]	Pediatric	4	N/A	50	12	33.9 ± 1.7	AUC_{inf} (µg·h/mL)	72.9	54.2	0.74
							C_{max} (µg/mL)	15.5	12.4	0.80
							$t_{1/2}$ (h)	3.1	3.8	1.23
Kean et al. (1992) [Single 100 mg]	Geriatric	13	N/A	84	73.1 ± 5.6	56.1 ± 10.3	AUC_{inf} (µg·h/mL)	69.6	66.9	0.96
							C_{max} (µg/mL)	12.7	12.3	0.97
							$t_{1/2}$ (h)	5.6	4.0	0.71

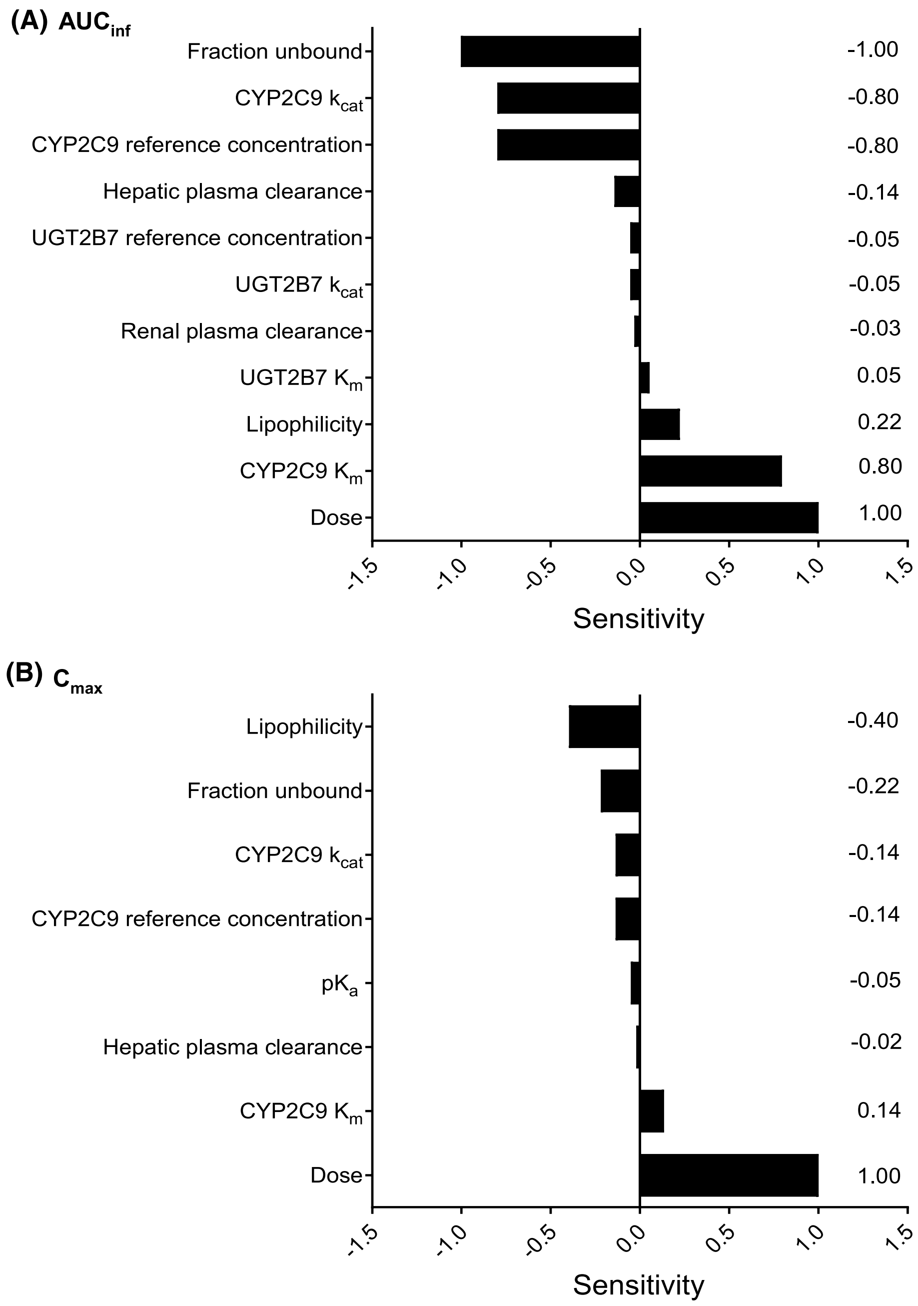
Demographic data are expressed as mean ± standard deviation or range (min–max)

N/A not available

*Calculated by non-compartmental analysis

$^{\$}$Average values of two individuals

Fig. 3 Results of sensitivity analysis toward AUC_{inf} (**A**) and C_{max} (**B**). *x-axis* and *y-axis* indicate sensitivity values and lists of sensitive parameters, respectively



administration strategy by predicting the pharmacokinetics of flurbiprofen in various clinical scenarios.

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Declarations

Conflict of interest The authors declare no competing interest for this work.

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