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RESEARCH ARTICLE

Physiologically based pharmacokinetic (PBPK) modeling of piroxicam with regard to *CYP2C9* genetic polymorphism

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Abstract Piroxicam is a non-steroidal anti-inflammatory drug used to alleviate symptoms of osteoarthritis and rheumatoid arthritis. *CYP2C9* genetic polymorphism significantly influences the pharmacokinetics of piroxicam. The objective of this study was to develop and validate the piroxicam physiologically based pharmacokinetic (PBPK) model related to *CYP2C9* genetic polymorphism. PK-Sim® version 10.0 was used for the PBPK modeling. The PBPK model was evaluated by predicted and observed plasma concentration–time profiles, fold errors of predicted to observed pharmacokinetic parameters, and a goodness-of-fit plot. The turnover number (k_{cat}) of CYP2C9 was adjusted to capture the pharmacokinetics of piroxicam in different *CYP2C9* genotypes. The population PBPK model overall accurately described and predicted the plasma concentration–time profiles in different *CYP2C9* genotypes. In our simulations, predicted AUC_{inf} in *CYP2C9*1/*2*, *CYP2C9*1/*3*, and *CYP2C9*3/*3* genotypes were 1.83-, 2.07-, and 6.43-fold higher than *CYP2C9*1/*1* genotype, respectively. All fold error values for AUC, C_{max}, and $t_{1/2}$ were included in the acceptance criterion with the ranges of 0.57–1.59, 0.63–1.39, and 0.65–1.51, respectively. The range of fold error values for predicted versus observed plasma concentrations was 0.11–3.13. 93.9% of fold error values were within the two-fold range. Average fold error, absolute average fold error, and root mean square error were 0.93, 1.27, and 0.72, respectively. Our model accurately captured the pharmacokinetic alterations of piroxicam according to *CYP2C9* genetic polymorphism.

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

Introduction

Piroxicam is a non-steroidal anti-inflammatory drug used to alleviate symptoms of osteoarthritis and rheumatoid arthritis (Weintraub et al. 1977; Dessain et al. 1979). Piroxicam reduces the synthesis of prostaglandins via inhibition of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Berg et al. 1999; Blanco et al. 1999). The most common adverse events of piroxicam are nausea, constipation, flatulence, abdominal pain, and diarrhea (Pfizer 2016). The risk of serious cardiovascular adverse events, including myocardial infarction and stroke, and serious gastrointestinal adverse events such as bleeding, ulceration, and perforation are increased by piroxicam (Dean 2019). It should be used for the shortest possible duration at the lowest effective dose (Pfizer 2016).

Piroxicam is primarily metabolized to 5'-hydroxypiroxicam by cytochrome P450 2C9 (CYP2C9) (Brogden et al. 1981). CYP2C9 is involved in the metabolism of various

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clinically used drugs, including glipizide (Kim et al. 2022), losartan (Bae et al. 2011b, 2012), meloxicam (Bae et al. 2011a; Lee et al. 2014), and *S*-enantiomer of warfarin (Rettie et al. 1992). CYP2C9 is genetically polymorphic and approximately 85 allele variants for *CYP2C9* (*CYP2C9*1B* to *CYP2C9*85*) have been identified to date (https://www.pharmvar.org/gene/CYP2C9). Among them, *CYP2C9*2* (rs1799853, c.430C > T, p.Cys144Arg) and **3* (rs1057910, c.1075A > C, p.Ile359Leu) alleles are the most common variants with overall frequency of 9.14% and 6.37% worldwide, respectively (Daly et al. 2017). These allele variants show impaired enzyme activity toward a number of substrates both in vitro and in vivo (Tang et al. 2001; Kirchheiner et al. 2004; Choi et al. 2012; Lee et al. 2015; Wang et al. 2015; Kim et al. 2017). Tracy et al. (2002) demonstrated that the *CYP2C9*3* allele variant reduces enzyme activity for 5'-hydroxylation of piroxicam in vitro. Perini et al. (2005) reported significantly higher exposures and lower clearances for piroxicam in individuals carrying *CYP2C9*2* or *CYP2C9*3* alleles compared to homozygous *CYP2C9*1* allele in vivo. Especially, exposure and half-life ($t_{1/2}$) in the *CYP2C9*3/*3* genotype were increased by 5.31- and 8.75-fold compared to the *CYP2C9*1/*1* genotype, respectively (Perini and Suarez-Kurtz 2006). In vivo studies presented notable differences not only in the pharmacokinetics but also pharmacodynamics of piroxicam according to *CYP2C9* genetic polymorphism (Perini et al. 2005; Perini and Suarez-Kurtz 2006). The drug label for piroxicam recommends the dose reduction in CYP2C9 poor metabolizers (CYP2C9PM) because they may have abnormally high plasma levels (Pfizer 2016). These studies suggest that responses of piroxicam could be varied according to the genetic polymorphism of *CYP2C9*.

Physiologically based pharmacokinetic (PBPK) modeling is a mechanistic approach for the prediction of the pharmacokinetics of drugs (Zhuang and Lu 2016; Kim et al. 2018). It is a useful tool to guide dose adjustment in various clinical scenarios such as pediatric populations (Yellepeddi et al. 2019; Verscheijden et al. 2020), pregnancy (Abduljalil and Badhan 2020; Coppola et al. 2021), organ impairments (Suri et al. 2015; Heimbach et al. 2021), and the effects of genetic polymorphisms (Rüdesheim et al. 2020; Cho et al. 2021a; Jung et al. 2021; Xu et al. 2021). Previously, PBPK models for several NSAIDs including celecoxib (Kim et al. 2021), flurbiprofen (Loisios-Konstantinidis et al. 2020), and meloxicam (Cho et al. 2021b) were established in different *CYP2C9* genotypes. However, the piroxicam PBPK model related to *CYP2C9* genetic polymorphism has not been reported. In this study, we developed and validated the PBPK model for piroxicam in the populations carrying the most two common *CYP2C9* allele variants.

Methods

Software and data source

PBPK model of piroxicam was developed and validated using PK-Sim® version 10.0 (Bayer AG, Leverkusen, Germany). Previously published concentration–time profiles 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).

Previous publications were extensively investigated to obtain information on the absorption, distribution, metabolism, and excretion (ADME) process, physicochemical characteristics, and clinical pharmacokinetic data for piroxicam. In this study, we only gathered the clinical studies in which the administration of piroxicam was an oral route. Among the collected clinical pharmacokinetic data, only two articles contain pharmacogenomic data (Perini et al. 2005; Perini and Suarez-Kurtz 2006). The data of the two articles were used for model development and the others were used for model validation. Information on the collected clinical data for the development and validation of the PBPK model is presented in Table 1.

Model building

The "middle-out" strategy was used for the PBPK model building. The physicochemical parameters were obtained from drug databases or previous studies. The specific intestinal and organ permeabilities were calculated in the software (Thelen et al. 2011, 2012; Hindmarsh et al. 2021). Fraction metabolized by CYP2C9 ($f_{m,\ CYP2C9}$) was estimated as 81.1% using the area under the plasma concentration–time curve from 0 to infinity (AUC_{inf}) values in *CYP2C9*1/*1* and *CYP2C9*3/*3* genotypes (Perini and Suarez-Kurtz 2006) based on previously reported methods (Ito et al. 2005; Huang et al. 2017). In the estimation, it was assumed that *CYP2C9*1/*1* and *CYP2C9*3/*3* genotypes are translated into CYP2C9 extensive metabolizer (CYP2C9EM) and CYP2C9PM phenotypes, respectively. The turnover number (k_{cat}) was optimized to capture the estimated $f_{m,\ CYP2C9}$ value and Michaelis–Menten constant (K_m) obtained from Tracy et al. (2002) was used. The reference concentration of CYP2C9 was 3.84 µmol/L (Rodrigues 1999). Relative expression values in each organ were obtained from the reverse transcription-polymerase chain reaction (RT-PCR) data (Nishimura et al. 2003; Nishimura and Naito 2005, 2006). Renal clearance value was determined to capture the profile of cumulative

Table 1 Clinical studies used for the development and validation of the piroxicam PBPK model

References	Administration	Number of Subjects	Prandial	*CYP2C9* Genotype	Proportion of Female (%)	Age (year)	Weight (kg)
Development							
Perini et al. (2005)	Single 20 mg	17	Fasted	**1/*1*	31	N/A	N/A
Perini et al. (2005)	Single 20 mg	9	Fasted	**1/*2*	31	N/A	N/A
Perini et al. (2005)	Single 20 mg	9	Fasted	**1/*3*	31	N/A	N/A
Perini and Suarez-Kurtz (2006)	Single 20 mg	1	N/A	**3/*3*	0	N/A	N/A
Validation – Adult populations							
Al-Shakargi (2012)	Single 20 mg	15	Fasted	N/A	N/A	45 ± 12	77 ± 5
Benveniste et al. (1990)	Single 20 mg	6	Fasted	N/A	0	20–31	N/A
Boudinot and Ibrahim (1988)	Single 20 mg	N/A	N/A	N/A	0	N/A	N/A
Calvo et al. (2016)	Single 20 mg	10	N/A	N/A	70	31.7 ± 9.9	N/A
Campbell et al. (1985)	Single 20 mg	12	Fed	N/A	N/A	18–40	N/A
Dixon et al. (1984)	Single 20 mg	3	Fasted	N/A	0	N/A	N/A
Dixon et al. (1990)	Single 20 mg	18	Fasted	N/A	0	18–36	55–93
Ferry et al. (1990)	Single 20 mg	8	N/A	N/A	38	23 ± 1	N/A
Guentert et al. (1988)	Single 20 mg	8	Fasted	N/A	0	26–36	N/A
Hasan et al. (1997)	Single 20 mg	20	Fasted	N/A	0	19–36	55–90
Helmy and El-Bedaiwy (2014)	Single 20 mg	24	Fasted	N/A	0	16–31	55–95
Hobbs and Twomey (1979)	Single 40 mg	20	Fasted	N/A	0	N/A	N/A
Ishizaki et al. (1979)	Single 30 mg	4	Fasted	N/A	0	21.3 ± 0.5	61.4 ± 2.0
Ishizaki et al. (1979)	Single 60 mg	4	Fasted	N/A	0	21.3 ± 0.5	61.4 ± 2.0
Ishizaki et al. (1979)	Single 30 mg	9	Fed	N/A	0	20.2 ± 0.4	59.0 ± 1.5
Ishizaki et al. (1979)	Single 60 mg	10	Fed	N/A	0	20.2 ± 0.4	59.0 ± 1.5
Jeon et al. (1998)	Single 20 mg	8	Fasted	N/A	38	20–35	45–90
Macek and Vácha (1987)	Single 20 mg	11	N/A	N/A	N/A	N/A	N/A
Palma-Aguirre et al. (2010)	Single 20 mg	28	Fasted	N/A	46	19–35	47.5–81.9
Piscitelli et al. (1998)	Single 20 mg	16	Fasted	N/A	19	22–28	60–90
Rahman et al. (2004)	Single 20 mg	12	Fasted	N/A	0	21–48	62–88
Rasetti-Escargueil and Grangé (2005)	Single 20 mg	16	N/A	N/A	0	21–30	64–84
Richardson et al. (1985)	Single 20 mg	6	Fasted	N/A	100	25.5 ± 2.0	62.8 ± 5.4
Richardson et al. (1985)	Single 20 mg	6	Fasted	N/A	0	23.3 ± 1.0	74.6 ± 1.3
Riedel and Laufen (1983)	Single 20 mg	N/A	N/A	N/A	N/A	N/A	N/A
Rudy et al. (1994)	Single 20 mg	10	Fasted	N/A	80	27 ± 4	69.3 ± 16
Said and Foda (1989)	Single 20 mg	12	Fasted	N/A	0	21–36	N/A
Shahbaz et al. (2018)	Single 20 mg	30	N/A	N/A	0	19–24	N/A
Song et al. (2009)	Single 20 mg	28	Fasted	N/A	21	22.1 ± 3.7	63.8 ± 6.5
Wanwimolruk et al. (1991)	Single 30 mg	18	N/A	N/A	0	18–36	N/A
Blocka et al. (1988)	Multiple 20 mg/day	23	Fed	N/A	61	27–79	N/A
Darragh et al. (1985)	Multiple 20 mg/day	21	Fed	N/A	71	30–59	N/A
Richardson et al. (1987)	Multiple 20 mg/day	6	Fasted	N/A	50	23–33	N/A
Rogers et al. (1981)	Multiple 20 mg/day	8	Fed	N/A	50	26–38	46.5–80
Rudy et al. (1994)	Multiple 20 mg/day	9	Fasted	N/A	80	27 ± 4	69.3 ± 16
Tilstone et al. (1981)	Multiple 20 mg/day	8	Fed	N/A	0	24–36	60–80
Tilstone et al. (1981)	Multiple 20 mg/day	8	Fasted	N/A	0	24–36	60–80
Validation – Pediatric populations							
Dix et al. (2004)	Single 0.4 mg/kg	12	Fasted	N/A	N/A	3–16	N/A
Dix et al. (2004)	Single 1.0 mg/kg	10	Fasted	N/A	N/A	3–16	N/A
Mäkelä et al. (1991)	Multiple 0.4 mg/kg/day	10	N/A	N/A	80	7–16	20–63
Validation – Geriatric populations							
Caldwell (1994)	Single 20 mg	14	Fasted	N/A	73	63 ± 4	N/A

Table 1 (continued)

References	Administration	Number of Subjects	Prandial	*CYP2C9* Genotype	Proportion of Female (%)	Age (year)	Weight (kg)
Campbell et al. (1985)	Single 20 mg	12	Fed	N/A	N/A	66–86	N/A
Richardson et al. (1985)	Single 20 mg	7	Fasted	N/A	100	70.6 ± 1.8	59.0 ± 2.6
Richardson et al. (1985)	Single 20 mg	6	Fasted	N/A	0	65.5 ± 1.1	76.8 ± 3.6
Rudy et al. (1994)	Single 20 mg	12	Fasted	N/A	33	73 ± 5	85.3 ± 14
Caldwell (1994)	Multiple 20 mg/day	7	Fasted	N/A	73	63 ± 4	N/A
Darragh et al. (1985)	Multiple 20 mg/day	12	Fed	N/A	71	60–69	N/A
Darragh et al. (1985)	Multiple 20 mg/day	11	Fed	N/A	71	70–80	N/A
Ferry et al. (1990)	Multiple 20 mg/day	43	N/A	N/A	43	69 ± 1	N/A
Rudy et al. (1994)	Multiple 20 mg/day	11	Fasted	N/A	33	73 ± 5	85.3 ± 14

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

N/A not available

excretion as unchanged form in urine within the ranges presented in Ishizaki et al. (1979). Dissolution times (80% dissolved) were adjusted based on dissolution profiles in biorelevant media (Li et al. 2019). Partition coefficients and cellular permeabilities were estimated as Schmitt and PK-Sim® standard methods, respectively (Schmitt 2008; Hindmarsh et al. 2021). k_{cat} values were optimized in different *CYP2C9* genotypes based on the previous pharmacogenetic studies (Perini et al. 2005; Perini and Suarez-Kurtz 2006). Parameter optimization was performed as the Levenberg–Marquardt algorithm in the PK-Sim® software. The PBPK model was developed for the different populations and dose regimens in the development dataset and verified using the validation dataset. Clinical studies without information on *CYP2C9* genotype were assumed that all subjects of the studies were carrying homozygous *CYP2C9*1* allele.

Sensitivity analysis

Sensitivity analysis was performed in the PK-Sim® software. In the analysis, a total of 861 parameters were assessed for AUC_{inf} and maximum plasma concentration (C_{max}). The sensitivity was calculated by the following Eq. 1.

$$S = \frac{\Delta PK}{PK} \div \frac{\Delta p}{p} \quad (1)$$

where *S* is the sensitivity, *PK* is the initial values of the pharmacokinetic parameter, Δ*PK* is the change of the pharmacokinetic parameters from initial values, *p* is the initial values of the assessed input parameter, and Δp is the change of assessed input parameters from initial values, respectively. A sensitivity of + 1.0 indicates that + 10% change of an assessed 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 graphically compared with the predicted profiles by plotting the geometric mean and 5th to 95th percentiles for a virtual population (n = 100). Demographic ranges for virtual populations were adjusted to be similar to those of the observed population. If the age and proportion of female (%) range had not been obtained from the clinical studies, it was assumed as 19 to 65 years and 50%, respectively. Others were generated via the implemented algorithm in the PK-Sim® software. The standard deviation for the reference concentration of CYP2C9 was assigned as 1.15 µmol/L to reflect moderate variability (30% of the mean). The PBPK model was numerically evaluated by comparing observed and predicted AUC, C_{max}, and $t_{1/2}$ values. A two-fold error range was used as the acceptance criterion for the model. In other words, the PBPK model could be justified if the fold error (predicted value divided into observed value) is within the 0.5–2 range. Geometric mean values for virtual populations were used as predicted values and reported values in clinical studies or estimated values based on the NCA were used as observed values. Lastly, the overall performance of the PBPK model was evaluated via a goodness-of-fit plot for the predicted versus observed plasma concentrations. Average fold error (AFE), absolute average fold error (AAFE), and root mean square error (RMSE) were used to evaluate the prediction accuracy and precision, respectively. AFE, AAFE, and RMSE were calculated according to Eqs. (2–4).

$$AFE = 10^{\frac{1}{N}\sum \log\left(\frac{\text{Predicted}}{\text{Observed}}\right)} \quad (2)$$

Table 2 Summary of input parameters used in the piroxicam PBPK model

Parameters	Reference value	Input value	References/Comments
Basic Physico-chemistry			
Molecular Weight (g/mol)	331.346	331.346	DrugBank
Log P	3.06	3.06	DrugBank
pK_a	4.76 (Acidic) 3.79 (Basic)	4.76 (Acidic) 3.79 (Basic)	DrugBank
Binding protein	Albumin	Albumin	Trnavská and Trnavský 1984
f_u (%)	0.38–2.72	0.37	Blocka et al. 1988
Solubility at pH 6.5 [Fasted] (μg/mL)	341.97	341.97	Li et al. 2019
Solubility at pH 5.0 [Fed] (μg/mL)	56.91	56.91	Li et al. 2019
Absorption			
Specific intestinal permeability (cm/min)	–	8.35E-5	Calculated by PK-Sim®
Distribution			
Specific organ permeability (cm/min)	–	0.02	Calculated by PK-Sim®
Metabolism			
CYP2C9 K_m (μM)	30.5	30.5	Tracy et al. 2002
CYP2C9 k_{cat} (/min), *CYP2C9*1/*1*	–	1.87	Optimized by PK-Sim®
CYP2C9 k_{cat} (/min), *CYP2C9*1/*2*	–	0.88	Optimized by PK-Sim®
CYP2C9 k_{cat} (/min), *CYP2C9*1/*3*	–	0.74	Optimized by PK-Sim®
CYP2C9 k_{cat} (/min), *CYP2C9*3/*3*	–	0.05	Optimized by PK-Sim®
Excretion			
Renal clearance (mL/hr/kg)	0.26–0.29	0.28	Ishizaki et al. 1979
Formulation			
Dissolution time [Fasted] (min)	–	60	Li et al. 2019
Dissolution time [Fed] (min)	–	120	Li et al. 2019

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

$$\mathrm{AAFE} = 10^{\frac{1}{N}\sum\left|\log\left(\frac{\text{Predicted}}{\text{Observed}}\right)\right|} \tag{3}$$

$$\mathrm{RMSE} = \sqrt{\frac{\sum(\text{Predicted} - \text{Observed})^2}{N}} \tag{4}$$

Results

A total 54 of clinical data were collected. Clinical trial data of various doses, administration period, and age of subjects were included. Most of the clinical studies recruited healthy subjects, but several clinical studies targeted patients with osteoarthritis or rheumatoid arthritis. Data of two pharmacogenomic studies (Perini et al. 2005; Perini and Suarez-Kurtz 2006) were used for development of PBPK model.

The summary of input parameters for the PBPK model is presented in Table 2. The fraction unbound (f_u) value was adjusted to be 0.01% lower value than the minimum value of Blocka et al. (1988) to capture the plasma-concentration time profiles more accurately. Simulation for the individual PBPK model after the administration of 20 mg single oral dose properly captured not only the plasma concentration–time profiles but also the metabolized and excreted

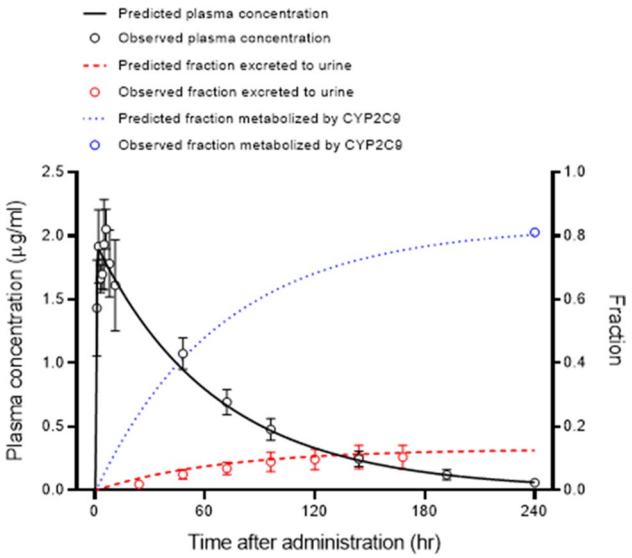


Fig. 1 Predicted and observed plasma concentration–time profiles of piroxicam after a single oral dose of piroxicam 20 mg. Solid, dashed, and dotted lines indicate predicted plasma concentration, fraction excreted to urine, and fraction metabolized by CYP2C9, respectively. The open circles and error bars indicated observed mean and standard deviation (or standard error), respectively. Observed plasma concentration and fraction excreted to urine data were obtained from Perini et al. (2005) and Ishizaki et al. (1979), respectively. Fraction metabolized by CYP2C9 data was estimated based on Perini and Suarez-Kurtz (2006)

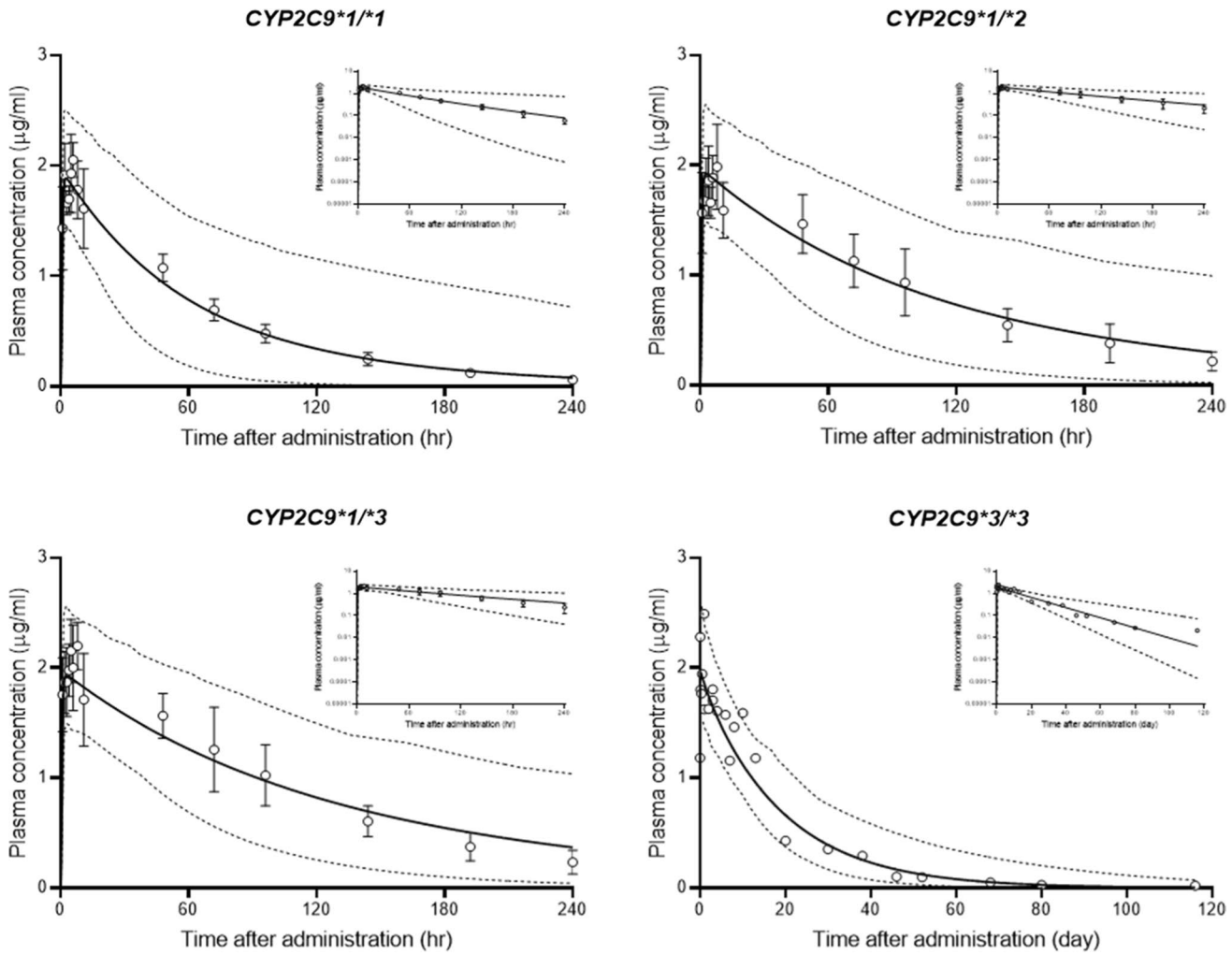


Fig. 2 Predicted and observed plasma concentration–time profiles of piroxicam after a single oral dose of piroxicam 20 mg in different *CYP2C9* genotypes. Solid and dashed lines indicate geometric mean and 5th to 95th percentiles, respectively. Open circles and error bars indicate observed mean and standard deviation (or standard error), respectively. Observed plasma concentration data except *CYP2C9*3/*3* genotype was obtained from Perini et al. (2005) and *CYP2C9*3/*3* genotype was obtained from Perini and Suarez-Kurtz (2006). Plasma concentration–time profiles are expressed using linear and semi-logarithmic plots

fractions (Fig. 1). The estimated volume of distribution (V_d) was 0.15 L/kg which is almost consistent with the previously reported value (0.14 L/kg) (Pfizer 2016).

Predicted plasma concentration–time profiles in different *CYP2C9* genotypes 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 1.83-, 2.07-, and 6.43-fold higher than *CYP2C9*1/*1* genotype, respectively, and significant differences for predicted C_{max} in different *CYP2C9* genotypes were not identified (1.89–1.96 μg/mL) (Table 3) (Fig. 3). In addition, PBPK model overall accurately described and predicted the plasma concentration–time profiles in pediatric, adult, and geriatric populations who received a single or multiple-dose regimens (Fig. 4). All fold error values for AUC, C_{max}, and $t_{1/2}$ were included in the acceptance criterion with the ranges of 0.57–1.59, 0.63–1.39, and 0.65–1.51, respectively (Table 3).

Sensitivity analysis shown in Fig. 3 presented that dose had an equal impact on AUC_{inf} and C_{max} (1.00). Lipophilicity which had the highest impact in C_{max} (− 1.82) was identified as having a relatively low impact in AUC_{inf} (0.03). The parameters related to the enzymatic pathway of CYP2C9, including k_{cat}, K_m, reference concentration, and ontogeny factor, had an impact on the AUC_{inf} and C_{max} with higher influences for AUC_{inf} than C_{max}. Several organ volumes were identified as sensitive physiological characteristics.

Among the collected articles, except for the two papers used for model establishment, all other papers did not include pharmacogenomic data, so model validation for each genotype using PK data not used for model establishment could not be performed. Therefore, model validation was

Table 3 Results for the development and validation of the piroxicam PBPK model

References	AUC (μg*hr/mL)			C_{max} (μg/mL)			$t_{1/2}$ (hr)		
	Obs	Pred	Fold error[#]	Obs	Pred	Fold error[#]	Obs	Pred	Fold error[#]
Development									
Perini et al. (2005)	154	135.1	0.88	2.5	1.89	0.76	48	60.5	1.26
Perini et al. (2005)	256	246.8	0.96	2.2	1.92	0.87	70.9	96.1	1.36
Perini et al. (2005)	259	279.8	1.08	2.4	1.93	0.80	80	107.2	1.34
Perini and Suarez-Kurtz (2006)	817	868.1	1.06	2.5	1.96	0.78	420	315.6	0.75
Validation – Adult populations									
Al-Shakargi (2012)	91.0[$]	93.6	1.03	2.66	2.00	0.75	44.9	52.5	1.17
Benveniste et al. (1990)	140.7	119.6	0.85	2.13	2.02	0.95	50.3	47.9	0.95
Boudinot and Ibrahim (1988)	144.0	130.7	0.91	2.57	1.98	0.77	77.1	63.4	0.82
Calvo et al. (2016)	78.7	119.6	1.52	2.28	1.96	0.86	50.7	41.7	0.82
Campbell et al. (1985)	N/A[a]	139.6	N/A	2.31	2.12	0.92	57.1	52.1	0.91
Dixon et al. (1984)	110.4	127.5	1.15	1.68	1.98	1.18	46.7	44.7	0.96
Dixon et al. (1990)	133.4	126.7	0.95	2.1	1.97	0.94	53.6	56.7	1.06
Ferry et al. (1990)	138.9	133.7	0.96	1.60	2.22	1.39	53.1	48.0	0.90
Guentert et al. (1988)	75.8	120.9	1.59	2.0	1.91	0.96	46.8	54.4	1.16
Hasan et al. (1997)	124.0	143.2	1.15	2.1	2.25	1.09	45.0	42.7	0.95
Helmy and El-Bedaiwy (2014)	135.8	162.2	1.19	2.3	2.31	1.00	40.5	53.5	1.32
Hobbs and Twomey (1979)	273.9	228.3	0.83	4.3	3.48	0.81	56.8	45.3	0.80
Ishizaki et al. (1979)	214.8	211.9	0.99	4.43	3.39	0.77	36.5	48.0	1.32
Ishizaki et al. (1979)	388.4	424.4	1.09	7.23	6.78	0.94	38.5	48.0	1.25
Ishizaki et al. (1979)	189.9	193.3	1.02	2.98	3.36	1.13	32.9	43.9	1.33
Ishizaki et al. (1979)	312.8	386.9	1.24	6.39	6.71	1.05	32.9	43.9	1.33
Jeon et al. (1998)	57.3[$]	43.9	0.77	3.5	2.28	0.65	28.9	35.2	1.22
Macek and Vácha (1987)	128.2	152.6	1.19	2.19	2.11	0.96	39.5	49.0	1.24
Palma-Aguirre et al. (2010)	169.8	132.0	0.78	2.63	2.09	0.79	49.4	49.4	1.00
Piscitelli et al. (1998)	181.5	131.5	0.72	2.0	1.91	0.96	76.4	51.5	0.67
Rahman et al. (2004)	206.5	126.6	0.61	2.9	2.14	0.74	59.0	49.9	0.85
Rasetti-Escargueil and Grangé (2005)	135.0	113.9	0.84	1.90	1.92	1.01	53.1	51.3	0.97
Richardson et al. (1985)	147.1	133.8	0.91	2.36	2.19	0.93	44.9	54.0	1.20
Richardson et al. (1985)	130.0	132.4	1.02	1.74	1.92	1.10	51.9	57.6	1.11
Riedel and Laufen (1983)	151.2	114.4	0.76	2.05	2.04	1.00	33.9	39.5	1.16
Rudy et al. (1994)	151.2	128.6	0.85	1.9	2.07	1.09	66.7	43.9	0.66
Said and Foda (1989)	64.5	45.5	0.71	3.34	2.40	0.72	37.4	33.0	0.88
Shahbaz et al. (2018)	104.1	158.3	1.52	1.97	2.35	1.20	54.8	47.0	0.86
Song et al. (2009)	123.1	141.2	1.15	2.20	2.20	1.00	48.6	50.5	1.04
Wanwimolruk et al. (1991)	290.0	166.1	0.57	3.8	2.97	0.78	57.3	45.3	0.79
Blocka et al. (1988)	N/A[a]	147.7	N/A	N/A[a]	7.19	N/A	53	46.1	0.87
Darragh et al. (1985)	196	191.3	0.98	9.6	9.22	0.96	55.2	46.9	0.85
Richardson et al. (1987)	165.0	150.7	0.91	7.93	7.40	0.93	54.9	59.9	1.09
Rogers et al. (1981)	119.3	122.1	1.02	7.49	6.95	0.93	52.9	44.4	0.84
Rudy et al. (1994)	188.9	158.8	0.84	9.3	7.84	0.84	50.9	51.7	1.01
Tilstone et al. (1981)	178.9	133.9	0.75	7.81	6.79	0.87	46.2	36.4	0.79
Tilstone et al. (1981)	173.7	144.4	0.83	7.82	7.15	0.91	46.2	39.0	0.84
Validation – Pediatric populations									
Dix et al. (2004)	25.9[$]	21.5	0.83	3.06	2.44	0.80	N/A[b]	37.7	N/A
Dix et al. (2004)	56.8[$]	53.6	0.94	7.52	6.11	0.81	N/A[b]	37.9	N/A
Mäkelä et al. (1991)	121.2	178.4	1.47	6.5	8.95	1.38	32.6	49.2	1.51

Table 3 (continued)

References	AUC (μg*hr/mL)			C_{max} (μg/mL)			$t_{1/2}$ (hr)		
	Obs	Pred	Fold error[#]	Obs	Pred	Fold error[#]	Obs	Pred	Fold error[#]
Validation – Geriatric populations									
Caldwell (1994)	126	143.4	1.14	2.8	1.91	0.68	78	50.6	0.65
Campbell et al. (1985)	N/A[a]	151.3	N/A	2.29	2.19	0.96	57.8	52.5	0.91
Richardson et al. (1985)	240.6	159.4	0.66	3.05	2.34	0.77	61.7	55.9	0.91
Richardson et al. (1985)	149.3	157.3	1.05	2.00	1.92	0.96	54.2	62.9	1.16
Rudy et al. (1994)	150.4	155.0	1.03	1.7	1.81	1.06	70.6	59.1	0.84
Caldwell (1994)	263	177.6	0.68	13.6	8.52	0.63	80	64.1	0.80
Darragh et al. (1985)	179	207.4	1.16	8.8	9.80	1.11	51.6	53.7	1.04
Darragh et al. (1985)	153	220.0	1.44	7.8	10.36	1.33	45.4	55.2	1.21
Ferry et al. (1990)	119.1	164.1	1.38	6.38	8.03	1.26	52.3	54.5	1.04
Rudy et al. (1994)	182.2	181.8	1.00	8.4	8.56	1.02	57	63.2	1.11

AUC are reported as AUC_{inf} or $AUC_{0\text{-}t,\ ss}$ in single or multiple dose administration, respectively

[#]Fold error indicates predicted value divided by observed value (Pred/Obs)

[$]Albeit single dose administration, AUC are reported as $AUC_{0\text{-}t}$

[a]$t_{1/2}$ could not be estimated by non-compartmental analysis

[b]Plasma concentration–time profiles not available in the publication

$AUC_{0\text{-}t}$ area under the plasma concentration–time curve from 0 to time *t*, AUC_{inf} area under the plasma concentration–time curve from 0 to infinity, $AUC_{0\text{-}t,\ ss}$ area under the plasma concentration–time curve over the dosing interval at steady state, C_{max} maximum plasma concentration, $t_{1/2}$ half-life, *Obs* observed value, *Pred* predicted value, *N/A* not available

performed using PK data without pharmacogenomic information. The goodness-of-fit plot for a total 674 of predicted versus observed plasma concentration data is illustrated in Fig. 5. The range of fold error values for plasma concentrations was 0.11–3.13. 93.9% of fold error values were within the two-fold range. AFE, AAFE, and RMSE were 0.93, 1.27, and 0.72, respectively.

Discussion

Genetic polymorphisms of drug metabolizing enzymes and transporters cause the inter-individual variations in drug response to varying degrees (Byeon et al. 2019; Bae et al. 2020; Jung et al. 2020a; Shin et al. 2020; Kim et al. 2022). Also, drug interactions significantly influence the pharmacokinetics of clinically used drugs (Byeon et al. 2018; Lee et al. 2019; Jung et al. 2020b). According to the advance in computational technology, a personalized dose administration strategy considering physiological characteristics of individuals or populations, genetic polymorphisms of drug metabolizing enzymes or transporters, and drug interactions has been proposed via the PBPK modeling approach (Li et al. 2020; Rüdesheim et al. 2020; Cho et al. 2021a, 2021b; Jung et al. 2021; Wojtyniak et al. 2021; Xu et al. 2021).

CYP2C9 is primarily responsible for the metabolism of a number of NSAIDs including ibuprofen, lornoxicam, meloxicam, flurbiprofen, and celecoxib and significant effects of *CYP2C9* genetic polymorphism on the pharmacokinetics or pharmacodynamics of these drugs have been reported (Bae et al. 2011a; Choi et al. 2011; Lee et al. 2014, 2015; Ochoa et al. 2015; Kim et al. 2017). Like these NSAIDs, piroxicam is mainly metabolized by CYP2C9 and the influences of *CYP2C9* genetic polymorphism on the piroxicam actions are known (Perini et al. 2005; Perini and Suarez-Kurtz 2006; Calvo et al. 2017). *CYP2C9* genotype is potentially involved in the adverse events given the relationship between exposure and toxicity of the NSAIDs (Smith et al. 2022). Piroxicam has a longer $t_{1/2}$ than other NSAIDs metabolized by CYP2C9 such as celecoxib, flurbiprofen, and meloxicam (Theken et al. 2020). This amplifies the potential risks in the patients with reduced CYP2C9 metabolism and hampers dose titration due to lack of data (Theken et al. 2020). Drug label and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for piroxicam recommend the consideration of dose reduction or the alteration to other NSAIDs which are not metabolized by CYP2C9 or metabolized by CYP2C9 with short half-life in CYP2C9PM group, respectively (Pfizer 2016; Theken et al. 2020).

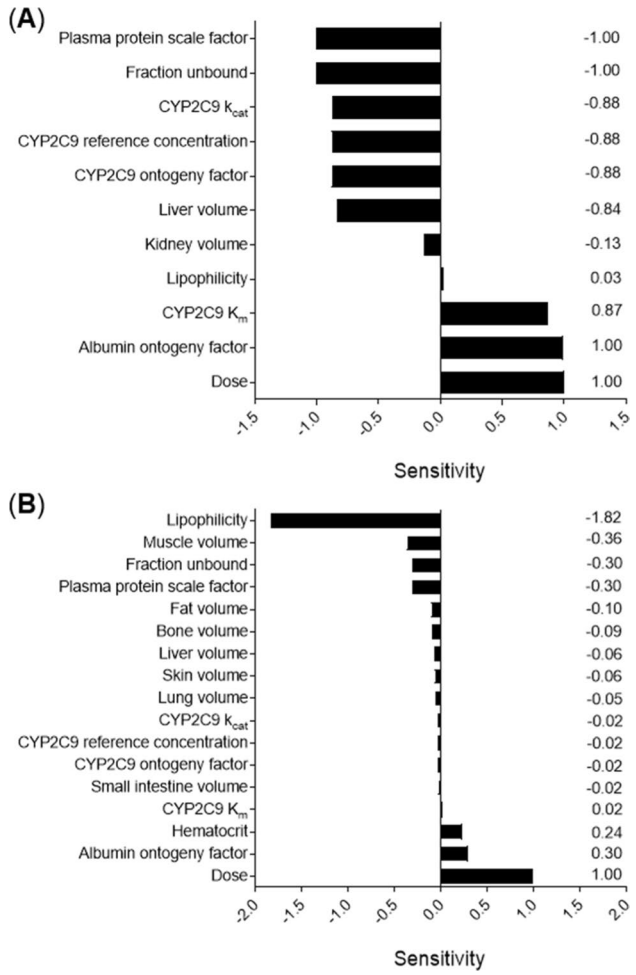


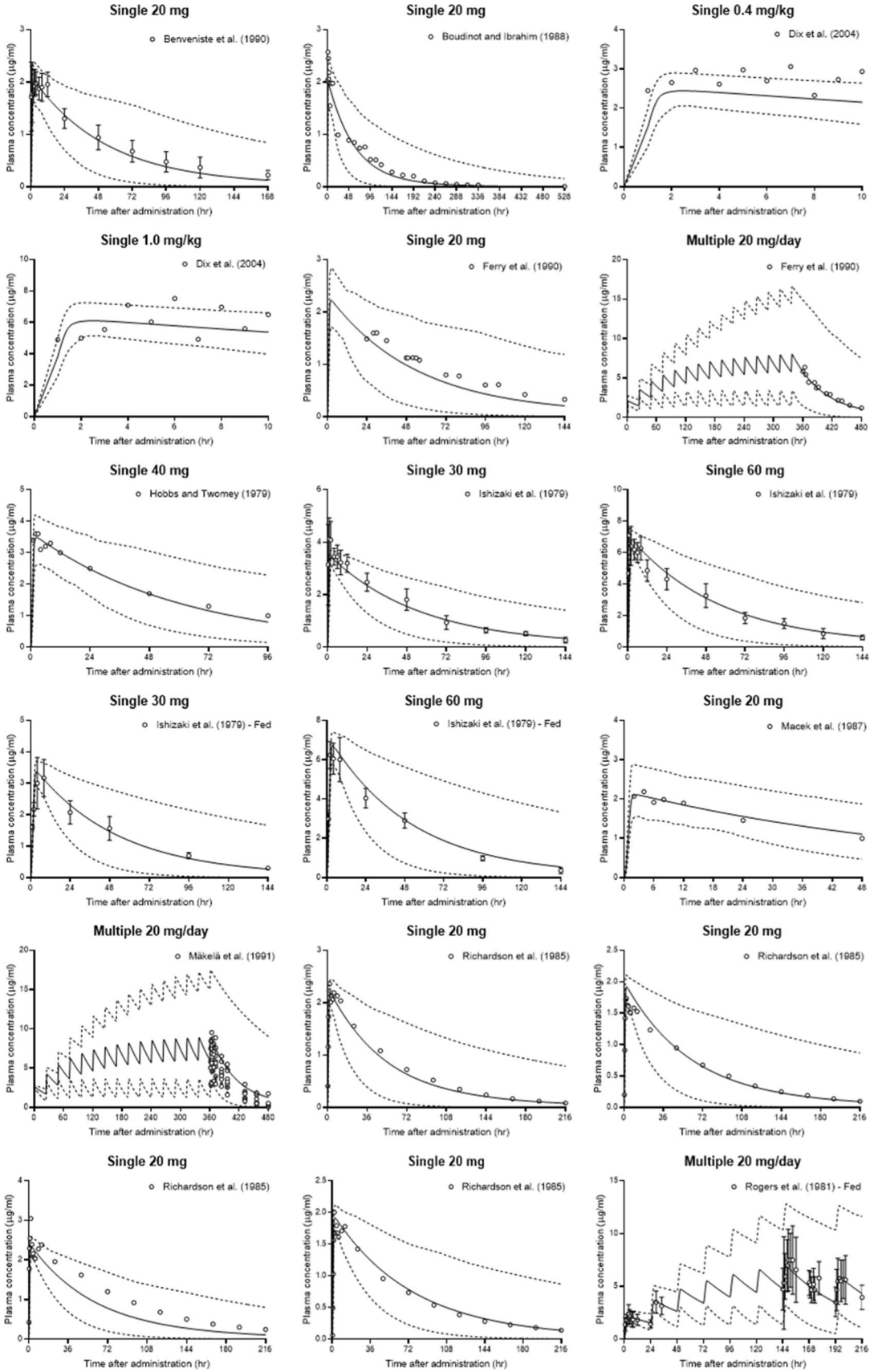
Fig. 3 Results of sensitivity analysis toward AUC_{inf} **A** and C_{max} **B**. *x-axis* and *y-axis* indicate sensitivity and lists of sensitive parameters, respectively

To overcome the potential risk in patients carrying *CYP2C9* allele variants and fulfill the lack of data related to piroxicam and *CYP2C9* genotype to some extent, we developed and validated the first PBPK model for piroxicam according to *CYP2C9* genetic polymorphism. In the model development, physicochemical and ADME properties for piroxicam were incorporated. In vitro enzyme kinetic data (Tracy et al. 2002) significantly under-estimated in vivo clearance of piroxicam in *CYP2C9*1/*1* genotype. Hence, we estimated the fraction metabolized by CYP2C9 based on the previously reported pharmacogenetic study (Perini and Suarez-Kurtz 2006). CPIC assigned *CYP2C9*1/*1* genotype as CYP2C9EM phenotype and *CYP2C9*3/*3* genotype as CYP2C9PM phenotype, respectively (Theken et al. 2020). Accordingly, the fraction was calculated based on the ratio of AUC_{inf} in *CYP2C9*1/*1* and *CYP2C9*3/*3* genotypes (Ito et al. 2005; Perini and Suarez-Kurtz 2006; Huang et al. 2017). Minor enzymatic pathways such as dealkylation and glucuronidation of piroxicam were identified, but it is not well reported and no candidate genes have been published (Brogden et al. 1981; Milligan et al. 1993). Thus, only the 5'-hydroxylation of piroxicam, the principal metabolic pathway mediated by CYP2C9, was applied in our model.

Our model successfully captured the pharmacokinetic alterations according to *CYP2C9* genetic polymorphism. Especially, the pharmacokinetics of piroxicam in the *CYP2C9*3/*3* genotype which had been traced for an extremely long period (120 days), were properly captured in this model. Furthermore, the range of fold error values for the pharmacokinetic parameters (AUC 0.57–1.59, C_{max} 0.63–1.39, and $t_{1/2}$ 0.65–1.51) was within the acceptance criterion (Table 3) and the goodness-of-fit plot showed that the predicted data were overall in agreement with the observed data (AFE 0.93, AAFE 1.27, and RMSE 0.72). It suggests the present model was properly established for single and multiple doses of 0.4 or 1.0 mg/kg in children and 20–60 mg in adults, including the elderly, in both fasting and eating conditions. Although the sample size used for the modeling of the *CYP2C9*3/*3* genotype was very small (n = 1), the present model could provide an insight for grasping the pharmacokinetics of piroxicam, simultaneous considering genetic and non-genetic factors.

Several modeling studies for the pharmacokinetics of piroxicam in humans have been reported (Wang et al. 2000; Tvrdonova et al. 2009; Li et al. 2019). Wang et al. (2000) reported population pharmacokinetic and pharmacodynamic model for piroxicam and piroxicam-β-cyclodextrin to investigate the pharmacokinetic-pharmacodynamic relationship of piroxicam. In their model, the physiological and anatomical characteristics of human were not incorporated because it was conducted as a "top-down" approach based on clinical data. Tvrdonova et al. (2009) showed a physiologically motivated time-delay model. This study accurately captured the multiple peak phenomenon of piroxicam, but in vitro data of piroxicam was not considered. Li et al. (2019) developed the PBPK model to predict the pharmacokinetics of piroxicam in beagle dogs and performed interspecies extrapolation to humans. Albeit a successful model, the application of the PBPK model to pediatric or geriatric populations could not be certain since it was only verified with clinical data on an adult population. In the present study, we developed the PBPK model for piroxicam by incorporating in vitro and in vivo data, robustly validated using a number of clinical studies, and demonstrated the applicability of the PBPK model for almost the entire age populations.

In this study, the PBPK model for only the two most common *CYP2C9* allele variants (**2* and **3*) was developed because of the lack of available pharmacogenetic studies. Two pharmacogenetic studies used for the PBPK


Single 20 mg
Benveniste et al. (1990)
Single 20 mg
Boudinot and Ibrahim (1988)
Single 0.4 mg/kg
Dix et al. (2004)
Single 1.0 mg/kg
Dix et al. (2004)
Single 20 mg
Ferry et al. (1990)
Multiple 20 mg/day
Ferry et al. (1990)
Single 40 mg
Hobbs and Twomey (1979)
Single 30 mg
Ishizaki et al. (1979)
Single 60 mg
Ishizaki et al. (1979)
Single 30 mg
Ishizaki et al. (1979) - Fed
Single 60 mg
Ishizaki et al. (1979) - Fed
Single 20 mg
Macek et al. (1987)
Multiple 20 mg/day
Mäkelä et al. (1991)
Single 20 mg
Richardson et al. (1985)
Single 20 mg
Richardson et al. (1985)
Single 20 mg
Richardson et al. (1985)
Single 20 mg
Richardson et al. (1985)
Multiple 20 mg/day
Rogers et al. (1981) - Fed
Plasma concentration (µg/ml)
Time after administration (hr)

◂**Fig. 4** Representative predicted and observed plasma concentration–time profiles of piroxicam for different populations and dose regimens. Solid and dashed lines indicate geometric mean and 5th to 95th percentiles, respectively. Open circles and error bars indicate observed mean and standard deviation (or standard error), respectively. Observed data in Mäkelä et al. (1991) are depicted as individual values

modeling were performed in the Brazilian population (Perini et al. 2005; Perini and Suarez-Kurtz 2006). *CYP2C9*13* (rs72558187, c.269 T > C, p.Leu90Pro) allele variant, found only in East Asians with a frequency of 0.5% (Bae et al. 2011b), significantly influences the plasma exposures for various CYP2C9 substrates (Bae et al. 2011a, 2012; Choi et al. 2011, 2012). Previous studies reported the PBPK models related to *CYP2C9*13* allele variants for celecoxib (Kim et al. 2021), meloxicam (Cho et al. 2021b), and candesartan (Jung et al. 2021) based on the clinical trials performed in the healthy Korean population. Further pharmacogenetic and modeling studies would be needed for the proper prescription of piroxicam in the East Asian population carrying the *CYP2C9*13* allele.

There were several limitations in the present study. First, physiological differences between healthy volunteers and subjects with arthritis were not considered. Several studies were performed on the subjects with osteoarthritis or rheumatoid arthritis (Darragh et al. 1985; Blocka et al. 1988; Mäkelä et al. 1991; Caldwell 1994), but we developed and validated the PBPK model based on the parameters used in healthy volunteers without any modifications for these diseases. Second, in most clinical studies, all subjects were assumed to be carrying homozygous *CYP2C9*1* allele due to the low frequencies of *CYP2C9*2* or **3* allele variants (Daly et al. 2017). Nevertheless, a few of the subjects in the clinical data could be carrying allele variants and it could be one of the causes for the discrepancies between the predicted and observed data. Third, digitized plasma concentration–time profiles could be discrepant with the raw data. Wojtyniak et al. (2020) reported the greatest pitfall for the data digitizing comes from the pre-existing errors and they recommended making published data available as raw values. However, raw data for the pharmacokinetics of piroxicam were not available and the resolution of the piroxicam profiles was relatively low since the most of clinical studies used in this study were reported a long time ago. It would be better to interpret the results of the modeling under the consideration of these potential limitations.

In conclusion, the PBPK model for piroxicam related to *CYP2C9* genetic polymorphism was properly established and described the pharmacokinetics of piroxicam in different *CYP2C9* genotypes. It could be used as a cornerstone to predict the pharmacokinetics of piroxicam in a number of clinical scenarios. We expect the present model could contribute to personalized pharmacotherapy for patients treated with piroxicam.

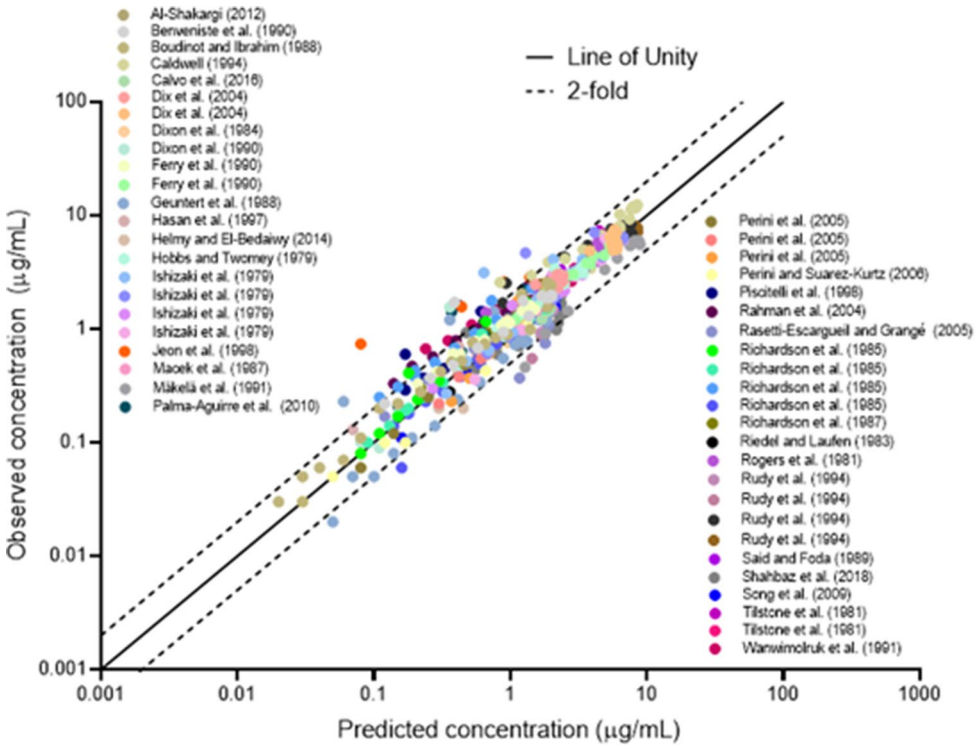


Fig. 5 Goodness-of-fit plot of predicted versus observed plasma concentrations. Solid and dashed lines indicate line of unity and two-fold range, respectively

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Declarations

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

References

Abduljalil K, Badhan RKS (2020) Drug dosing during pregnancy-opportunities for physiologically based pharmacokinetic models. J Pharmacokinet Pharmacodyn 47(4):319–340. https://doi.org/10.1007/s10928-020-09698-w

Al-Shakargi SDMS (2012) Bioequivalency of two piroxicam products in plasma by high performance liquid chromatography. Tikret Journal of Pharmceutical Sciences 8(2):242–247

Bae JW, Choi CI, Jang CG, Lee SY (2011a) Effects of *CYP2C9*1/*13* on the pharmacokinetics and pharmacodynamics of meloxicam. Br J Clin Pharmacol 71(4):550–555. https://doi.org/10.1111/j.1365-2125.2010.03853.x

Bae JW, Choi CI, Kim MJ, Oh DH, Keum SK, Park JI, Kim BH, Bang HK, Oh SG, Kang BS, Park HJ, Kim HD, Ha JH, Shin HJ, Kim YH, Na HS, Chung MW, Jang CG, Lee SY (2011b) Frequency of *CYP2C9* alleles in Koreans and their effects on losartan pharmacokinetics. Acta Pharmacol Sin 32(10):1303–1308. https://doi.org/10.1038/aps.2011.100

Bae JW, Choi CI, Lee HI, Lee YJ, Jang CG, Lee SY (2012) Effects of *CYP2C9*1/*3* and **1/*13* on the pharmacokinetics of losartan and its active metabolite E-3174. Int J Clin Pharmacol Ther 50(9):683–689. https://doi.org/10.5414/cp201467

Bae JW, Oh KY, Yoon SJ, Shin HB, Jung EH, Cho CK, Lim CW, Kang P, Choi CI, Jang CG, Lee SY, Lee YJ (2020) Effects of *CYP2D6* genetic polymorphism on the pharmacokinetics of metoclopramide. Arch Pharm Res 43(11):1207–1213. https://doi.org/10.1007/s12272-020-01293-4

Benveniste C, Striberni R, Dayer P (1990) Indirect assessment of the enterohepatic recirculation of piroxicam and tenoxicam. Eur J Clin Pharmacol 38(6):547–549. https://doi.org/10.1007/BF00278579

Berg J, Fellier H, Christoph T, Grarup J, Stimmeder D (1999) The analgesic NSAID lornoxicam inhibits cyclooxygenase (COX)-1/-2, inducible nitric oxide synthase (iNOS), and the formation of interleukin (IL)-6 in vitro. Inflamm Res 48(7):369–379. https://doi.org/10.1007/s000110050474

Blanco FJ, Guitian R, Moreno J, de Toro FJ, Galdo F (1999) Effect of anti-inflammatory drugs on COX-1 and COX−2 activity in human articular chondrocytes. J Rheumatol 26(6):1366–1373

Blocka KL, Richardson CJ, Wallace SM, Ross SG, Verbeeck RK (1988) The effect of age on piroxicam disposition in rheumatoid arthritis. J Rheumatol 15(5):757–763

Boudinot FD, Ibrahim SS (1988) High-performance liquid chromatographic assay for piroxicam in human plasma. J Chromatogr 430(2):424–428. https://doi.org/10.1016/s0378-4347(00)83181-3

Brogden RN, Heel RC, Speight TM, Avery GS (1981) Piroxicam: a review of its pharmacological properties and therapeutic efficacy. Drugs 22(3):165–187. https://doi.org/10.2165/00003495-198122030-00001

Byeon JY, Lee YJ, Kim YH, Kim SH, Lee CM, Bae JW, Jang CG, Lee SY, Choi CI (2018) Effects of diltiazem, a moderate inhibitor of CYP3A4, on the pharmacokinetics of tamsulosin in different *CYP2D6* genotypes. Arch Pharm Res 41(5):564–570. https://doi.org/10.1007/s12272-018-1030-6

Byeon JY, Lee CM, Lee YJ, Kim YH, Kim SH, Jung EH, Chae WK, Lee YJ, Jang CG, Lee SY (2019) Influence of *CYP2D6* genetic polymorphism on pharmacokinetics of active moiety of tolterodine. Arch Pharm Res 42(2):182–190. https://doi.org/10.1007/s12272-018-1099-y

Caldwell JR (1994) Comparison of the efficacy, safety, and pharmacokinetic profiles of extended-release ketoprofen and piroxicam in patients with rheumatoid arthritis. Clin Ther 16(2):222–235

Calvo AM, Santos GM, Dionísio TJ, Marques MP, Brozoski DT, Lanchote VL, Fernandes MHR, Faria FAC, Santos CF (2016) Quantification of piroxicam and 5′-hydroxypiroxicam in human plasma and saliva using liquid chromatography–tandem mass spectrometry following oral administration. J Pharm Biomed Anal 120:212–220. https://doi.org/10.1016/j.jpba.2015.12.042

Calvo AM, Zupelari-Gonçalves P, Dionísio TJ, Brozoski DT, Faria FA, Santos CF (2017) Efficacy of piroxicam for postoperative pain after lower third molar surgery associated with CYP2C8*3 and CYP2C9. J Pain Res 10:1581–1589. https://doi.org/10.2147/jpr.S138147

Campbell AJ, Ferry DG, Edwards IR (1985) Pharmacokinetic projections for isoxicam and piroxicam in old and young subjects. Br J Rheumatol 24(2):176–178. https://doi.org/10.1093/rheumatology/24.2.176

Cho CK, Kang P, Park HJ, Lee YJ, Bae JW, Jang CG, Lee SY (2021a) Physiologically based pharmacokinetic (PBPK) modelling of tamsulosin related to *CYP2D6*10* allele. Arch Pharm Res 44(11):1037–1049. https://doi.org/10.1007/s12272-021-01357-z

Cho CK, Park HJ, Kang P, Moon S, Lee YJ, Bae JW, Jang CG, Lee SY (2021b) Physiologically based pharmacokinetic (PBPK) modeling of meloxicam in different *CYP2C9* genotypes. Arch Pharm Res 44(12):1076–1090. https://doi.org/10.1007/s12272-021-01361-3

Choi CI, Kim MJ, Jang CG, Park YS, Bae JW, Lee SY (2011) Effects of the *CYP2C9*1/*13* genotype on the pharmacokinetics of lornoxicam. Basic Clin Pharmacol Toxicol 109(6):476–480. https://doi.org/10.1111/j.1742-7843.2011.00751.x

Choi CI, Kim MJ, Chung EK, Lee HI, Jang CG, Bae JW, Lee SY (2012) *CYP2C9*3* and **13* alleles significantly affect the pharmacokinetics of irbesartan in healthy Korean subjects. Eur J Clin Pharmacol 68(2):149–154. https://doi.org/10.1007/s00228-011-1098-0

Coppola P, Kerwash E, Cole S (2021) Physiologically based pharmacokinetics model in pregnancy: a regulatory perspective on model evaluation. Front Pediatr 9:687978. https://doi.org/10.3389/fped.2021.687978

Daly AK, Rettie AE, Fowler DM, Miners JO (2017) Pharmacogenomics of CYP2C9: functional and clinical considerations. J Pers Med 8(1):1. https://doi.org/10.3390/jpm8010001

Darragh A, Gordon AJ, O'Byrne H, Hobbs D, Casey E (1985) Single-dose and steady-state pharmacokinetics of piroxicam in elderly vs young adults. Eur J Clin Pharmacol 28(3):305–309. https://doi.org/10.1007/BF00543328

Dean L (2019) Piroxicam Therapy and CYP2C9 Genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kane MS, Kattman BL, Malheiro AJ (ed) Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US) [Online] Available from https://www.ncbi.nlm.nih.gov/books/NBK537367/ Accessed 18 April 2022

Dessain P, Estabrooks TF, Gordon AJ (1979) Piroxicam in the treatment of osteoarthrosis: A multicentre study in general practice involving 1218 patients. J Int Med Res 7(5):335–343. https://doi.org/10.1177/030006057900700501

Dix P, Prosser DP, Streete P (2004) A pharmacokinetic study of piroxicam in children. Anaesthesia 59(10):984–987. https://doi.org/10.1111/j.1365-2044.2004.03806.x

Dixon JS, Lowe JR, Galloway DB (1984) Rapid method for the determination of either piroxicam or tenoxicam in plasma using high-performance liquid chromatography. J Chromatogr 310(2):455–459. https://doi.org/10.1016/0378-4347(84)80116-4

Dixon JS, Lacey LF, Pickup ME, Langley SJ, Page MC (1990) A lack of pharmacokinetic interaction between ranitidine and piroxicam. Eur J Clin Pharmacol 39(6):583–586. https://doi.org/10.1007/BF00316100

Ferry DG, Gazeley LR, Busby WJ, Beasley DM, Edwards IR, Campbell AJ (1990) Enhanced elimination of piroxicam by administration of activated charcoal or cholestyramine. Eur J Clin Pharmacol 39(6):599–601. https://doi.org/10.1007/BF00316105

Guentert TW, Defoin R, Mosberg H (1988) The influence of cholestyramine on the elimination of tenoxicam and piroxicam. Eur J Clin Pharmacol 34(3):283–289. https://doi.org/10.1007/bf00540957

Hasan MM, Jilani JA, Salem MS, Najib NM, Pillai GK, Ganem E (1997) Bioequivalence of two capsule formulations of piroxicam. Acta Pharm Sci 39(3):93–97

Heimbach T, Chen Y, Chen J, Dixit V, Parrott N, Peters SA, Poggesi I, Sharma P, Snoeys J, Shebley M, Tai G, Tse S, Upreti VV, Wang YH, Tsai A, Xia B, Zheng M, Zhu AZX, Hall S (2021) Physiologically-based pharmacokinetic modeling in renal and hepatic impairment populations: a pharmaceutical industry perspective. Clin Pharmacol Ther 110(2):297–310. https://doi.org/10.1002/cpt.2125

Helmy SA, El-Bedaiwy HM (2014) Piroxicam immediate release formulations: A fasting randomized open-label crossover bioequivalence study in healthy volunteers. Clin Pharmacol Drug Dev 3(6):466–471. https://doi.org/10.1002/cpdd.106

Hindmarsh AC, Reynolds DR, Serban R, Woodward CS, Gardner, DJ, Cohen SD, Taylor A, Peles S, Banks L, Shumaker D (2021) Open Systems Pharmacology Suite Manual version 10. [Online] Available from https://docs.open-systems-pharmacology.org/. Accessed 18 April 2022

Hobbs DC, Twomey TM (1979) Piroxicam pharmacokinetics in man: aspirin and antacid interaction studies. J Clin Pharmacol 19(5–6):270–281. https://doi.org/10.1002/j.1552-4604.1979.tb02480.x

Huang W, Nakano M, Sager J, Ragueneau-Majlessi I, Isoherranen N (2017) Physiologically based pharmacokinetic model of the CYP2D6 probe atomoxetine: extrapolation to special populations and drug-drug interactions. Drug Metab Dispos 45(11):1156–1165. https://doi.org/10.1124/dmd.117.076455

Ishizaki T, Nomura T, Abe T (1979) Pharmacokinetics of piroxicam, a new nonsteroidal anti-inflammatory agent, under fasting and postprandial states in man. J Pharmacokinet Biopharm 7(4):369–381. https://doi.org/10.1007/BF01062535

Ito K, Hallifax D, Obach RS, Houston JB (2005) Impact of parallel pathways of drug elimination and multiple cytochrome P450 involvement on drug-drug interactions: CYP2D6 paradigm. Drug Metab Dispos 33(6):837–844. https://doi.org/10.1124/dmd.104.003715

Jeon SS, Cha HR, Park YJ, Lee BC, Kim ND (1998) Comparison of absorption rate between piroxicam-β-cyclodextrin and piroxicam in Korean healthy subjects after a single dose administration. Korean J Clin Pharm 8(2):95–100

Jung EH, Lee CM, Byeon JY, Shin HB, Oh KY, Cho CK, Lim CW, Jang CG, Lee SY (2020) Lee YJ (2020a) Relationship between plasma exposure of zolpidem and *CYP2D6* genotype in healthy Korean subjects. Arch Pharm Res 43(9):976–981. https://doi.org/10.1007/s12272-020-01250-1

Jung EH, Lee YJ, Kim DH, Kang P, Lim CW, Cho CK, Jang CG, Lee SY, Bae JW (2020) Effects of paroxetine on the pharmacokinetics of atomoxetine and its metabolites in different *CYP2D6* genotypes. Arch Pharm Res 43(12):1356–1363. https://doi.org/10.1007/s12272-020-01300-8

Jung EH, Cho CK, Kang P, Park HJ, Lee YJ, Bae JW, Choi CI, Jang CG, Lee SY (2021) Physiologically based pharmacokinetic modeling of candesartan related to *CYP2C9* genetic polymorphism in adult and pediatric patients. Arch Pharm Res 44(12):1109–1119. https://doi.org/10.1007/s12272-021-01363-1

Kim SH, Kim DH, Byeon JY, Kim YH, Kim DH, Lim HJ, Lee CM, Whang SS, Choi CI, Bae JW, Lee YJ, Jang CG, Lee SY (2017) Effects of *CYP2C9* genetic polymorphisms on the pharmacokinetics of celecoxib and its carboxylic acid metabolite. Arch Pharm Res 40(3):382–390. https://doi.org/10.1007/s12272-016-0861-2

Kim SH, Byeon JY, Kim YH, Lee CM, Lee YJ, Jang CG, Lee SY (2018) Physiologically based pharmacokinetic modelling of atomoxetine with regard to *CYP2D6* genotypes. Sci Rep 8(1):12405. https://doi.org/10.1038/s41598-018-30841-8

Kim YH, Kang P, Cho CK, Jung EH, Park HJ, Lee YJ, Bae JW, Jang CG, Lee SY (2021) Physiologically based pharmacokinetic (PBPK) modeling for prediction of celecoxib pharmacokinetics according to *CYP2C9* genetic polymorphism. Arch Pharm Res 44(7):713–724. https://doi.org/10.1007/s12272-021-01346-2

Kim NT, Cho CK, Kang P, Park H-J, Lee YJ, Bae JW, Jang C-G, Lee S-Y (2022) Effects of *CYP2C9*3* and **13* alleles on the pharmacokinetics and pharmacodynamics of glipizide in healthy Korean subjects. Arch Pharm Res 45(2):114–121. https://doi.org/10.1007/s12272-021-01366-y

Kirchheiner J, Tsahuridu M, Jabrane W, Roots I, Brockmöller J (2004) The *CYP2C9* polymorphism: from enzyme kinetics to clinical dose recommendations. Per Med 1(1):63–84. https://doi.org/10.1517/17410541.1.1.63

Lee HI, Bae JW, Choi CI, Lee YJ, Byeon JY, Jang CG, Lee SY (2014) Strongly increased exposure of meloxicam in *CYP2C9*3/*3* individuals. Pharmacogenet Genomics 24(2):113–117. https://doi.org/10.1097/fpc.0000000000000025

Lee YJ, Byeon JY, Kim YH, Kim SH, Choi CI, Bae JW, Sohn UD, Jang CG, Lee J, Lee SY (2015) Effects of *CYP2C9*1/*3* genotype on the pharmacokinetics of flurbiprofen in Korean subjects. Arch Pharm Res 38(6):1232–1237. https://doi.org/10.1007/s12272-015-0580-0

Lee CM, Jung EH, Byeon JY, Kim SH, Jang CG, Lee YJ, Lee SY (2019) Effects of steady-state clarithromycin on the pharmacokinetics of zolpidem in healthy subjects. Arch Pharm Res 42(12):1101–1106. https://doi.org/10.1007/s12272-019-01201-5

Li X, Yang Y, Zhang Y, Wu C, Jiang Q, Wang W, Li H, Li J, Luo C, Wu W, Wang Y, Zhang T (2019) Justification of biowaiver and dissolution rate specifications for piroxicam immediate release products based on physiologically based pharmacokinetic modeling: an in-depth analysis. Mol Pharm 16(9):3780–3790. https://doi.org/10.1021/acs.molpharmaceut.9b00350

Li X, Frechen S, Moj D, Lehr T, Taubert M, Hsin C-h, Mikus G, Neuvonen PJ, Olkkola KT, Saari TI, Fuhr U (2020) A physiologically based pharmacokinetic model of voriconazole integrating time-dependent inhibition of CYP3A4, genetic polymorphisms of CYP2C19 and predictions of drug–drug Interactions. Clin Pharmacokinet 59(6):781–808. https://doi.org/10.1007/s40262-019-00856-z

Loisios-Konstantinidis I, Cristofoletti R, Jamei M, Turner D, Dressman J (2020) Physiologically based pharmacokinetic/pharmacodynamic modeling to predict the impact of CYP2C9 genetic polymorphisms, co-medication and formulation on the pharmacokinetics and pharmacodynamics of flurbiprofen. Pharmaceutics 12(11):1049. https://doi.org/10.3390/pharmaceutics12111049

Macek J, Vácha J (1987) Rapid and sensitive method for determination of piroxicam in human plasma by high-performance liquid

chromatography. J Chromatogr 420(2):445–449. https://doi.org/10.1016/0378-4347(87)80203-7
Mäkelä AL, Olkkola KT, Mattila MJ (1991) Steady state pharmacokinetics of piroxicam in children with heumatic diseases. Eur J Clin Pharmacol 41(1):79–81. https://doi.org/10.1007/BF00280114
Milligan PA, McGill PE, Howden CW, Kelman AW, Whiting B (1993) The consequences of H2 receptor antagonist—piroxicam coadministration in patients with joint disorders. Eur J Clin Pharmacol 45(6):507–512. https://doi.org/10.1007/BF00315306
Nishimura M, Naito S (2005) Tissue-specific mRNA expression profiles of human ATP-binding cassette and solute carrier transporter superfamilies. Drug Metab Pharmacokinet 20(6):452–477. https://doi.org/10.2133/dmpk.20.452
Nishimura M, Naito S (2006) Tissue-specific mRNA expression profiles of human phase I metabolizing enzymes except for cytochrome P450 and phase II metabolizing enzymes. Drug Metab Pharmacokinet 21(5):357–374. https://doi.org/10.2133/dmpk.21.357
Nishimura M, Yaguti H, Yoshitsugu H, Naito S, Satoh T (2003) Tissue Distribution of mRNA expression of human cytochrome p450 isoforms assessedby high-sensitivity real-time reverse transcription PCR. Yakugaku Zasshi 123(5):369–375. https://doi.org/10.1248/yakushi.123.369
Ochoa D, Prieto-Pérez R, Román M, Talegón M, Rivas A, Galicia I, Abad-Santos F, Cabaleiro T (2015) Effect of gender and CYP2C9 and CYP2C8 polymorphisms on the pharmacokinetics of ibuprofen enantiomers. Pharmacogenomics 16(9):939–948. https://doi.org/10.2217/pgs.15.40
Palma-Aguirre JA, Lopez-Gamboa M, Cariño L, Burke-Fraga V, González-de la Parra M (2010) Relative bioavailability of two oral formulations of piroxicam 20 mg: a single-dose, randomized-sequence, open-label, two-period crossover comparison in healthy Mexican adult volunteers. Clin Ther 32(2):357–364. https://doi.org/10.1016/j.clinthera.2010.02.002
Perini JA, Suarez-Kurtz G (2006) Impact of *CYP2C9*3/*3* genotype on the pharmacokinetics and pharmacodynamics of piroxicam. Clin Pharmacol Ther 80(5):549–551. https://doi.org/10.1016/j.clpt.2006.08.003
Perini JA, Vianna-Jorge R, Brogliato AR, Suarez-Kurtz G (2005) Influence of *CYP2C9* genotypes on the pharmacokinetics and pharmacodynamics of piroxicam. Clin Pharmacol Ther 78(4):362–369. https://doi.org/10.1016/j.clpt.2005.06.014
Pfizer (2016) FELDENE® (piroxicam) Prescribing information. [Online] Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018147s044lbl.pdf. Accessed 18 April 2022
Piscitelli DA, Bigora S, Propst C, Goskonda S, Schwartz P, Lesko LJ, Augsburger L, Young D (1998) The impact of formulation and process changes on in vitro dissolution and the bioequivalence of piroxicam capsules. Pharm Dev Technol 3(4):443–452. https://doi.org/10.3109/10837459809028625
Rahman NU, Ahamd M, Akhtar N (2004) Bioequivalence of a generic piroxicam capsule formulation. J Pure Appl Sci 23(2):52–61
Rasetti-Escargueil C, Grangé V (2005) Pharmacokinetic profiles of two tablet formulations of piroxicam. Int J Pharm 295(1–2):129–134. https://doi.org/10.1016/j.ijpharm.2005.02.006
Rettie AE, Korzekwa KR, Kunze KL, Lawrence RF, Eddy AC, Aoyama T, Gelboin HV, Gonzalez FJ, Trager WF (1992) Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-4502C9 in the etiology of (S)-warfarin-drug interactions. Chem Res Toxicol 5(1):54–59. https://doi.org/10.1021/tx00025a009
Richardson CJ, Blocka KL, Ross SG, Verbeeck RK (1985) Effects of age and sex on piroxicam disposition. Clin Pharmacol Ther 37(1):13–18. https://doi.org/10.1038/clpt.1985.4
Richardson C, Blocka K, Ross S, Verbeeck R (1987) Piroxicam and 5'-hydroxypiroxicam kinetics following multiple dose administration of piroxicam. Eur J Clin Pharmacol 32(1):89–91. https://doi.org/10.1007/BF00609964
Riedel KD, Laufen H (1983) High-performance thin-layer chromatographic assay for the routine determination of piroxicam in plasma, urine and tissue. J Chromatogr 276:243–248. https://doi.org/10.1016/s0378-4347(00)85090-2
Rodrigues AD (1999) Integrated cytochrome P450 reaction phenotyping: attempting to bridge the gap between cDNA-expressed cytochromes P450 and native human liver microsomes. Biochem Pharmacol 57(5):465–480. https://doi.org/10.1016/s0006-2952(98)00268-8
Rogers HJ, Spector RG, Morrison PJ, Bradbrook ID (1981) Comparative steady state pharmacokinetic study of piroxicam and flurbiprofen in normal subjects. Eur J Rheumatol Inflamm 4(3):303–308
Rüdesheim S, Wojtyniak JG, Selzer D, Hanke N, Mahfoud F, Schwab M, Lehr T (2020) Physiologically based pharmacokinetic modeling of metoprolol enantiomers and α-Hydroxymetoprolol to Describe CYP2D6 drug-gene interactions. Pharmaceutics 12(12):1200. https://doi.org/10.3390/pharmaceutics12121200
Rudy AC, Figueroa NL, Hall SD, Brater DC (1994) The pharmacokinetics of piroxicam in elderly persons with and without renal impairment. Br J Clin Pharmacol 37(1):1–5. https://doi.org/10.1111/j.1365-2125.1994.tb04230.x
Said SA, Foda AM (1989) Influence of cimetidine on the pharmacokinetics of piroxicam in rat and man. Arzneimittelforschung 39(7):790–792
Schmitt W (2008) General approach for the calculation of tissue to plasma partition coefficients. Toxicol in Vitro 22(2):457–467. https://doi.org/10.1016/j.tiv.2007.09.010
Shahbaz N, Iqbal Z, Nasir F, Khan FU, Hassan AM, Khan SI (2018) Simultaneous determination of piroxicam and 5-hydroxypiroxicam: HPLC/UV method development, validation and application for pharmacokinetic evaluation in Pakistani population. J Chem Soc Pak 40(05):856–865
Shin HB, Jung EH, Kang P, Lim CW, Oh KY, Cho CK, Lee YJ, Choi CI, Jang CG, Lee SY, Bae JW (2020) ABCB1 c.2677G>T/c.3435C>T diplotype increases the early-phase oral absorption of losartan. Arch Pharm Res 43(11):1187–1196. https://doi.org/10.1007/s12272-020-01294-3
Smith DM, Stevenson JM, Ho TT, Formea CM, Gammal RS, Cavallari LH (2022) Pharmacogenetics: A precision medicine approach to combatting the opioid epidemic. J Am Coll Clin Pharm 5(2):239–250. https://doi.org/10.1002/jac5.1582
Song HH, Choi KS, Kim CW, Kwon YE (2009) Pharmacokinetic profiles of two branded formulations of piroxicam 20mg in healthy Korean volunteers by a rapid isocratic HPLC method. J Bioequiv Availab 1(3):74–79
Suri A, Chapel S, Lu C, Venkatakrishnan K (2015) Physiologically based and population PK modeling in optimizing drug development: A predict–learn–confirm analysis. Clin Pharmacol Ther 98(3):336–344. https://doi.org/10.1002/cpt.155
Tang C, Shou M, Rushmore TH, Mei Q, Sandhu P, Woolf EJ, Rose MJ, Gelmann A, Greenberg HE, De Lepeleire I, Van Hecken A, De Schepper PJ, Ebel DL, Schwartz JI, Rodrigues AD (2001) In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in-vivo pharmacokinetics. Pharmacogenet Genomics 11(3):223–235
Theken KN, Lee CR, Gong L, Caudle KE, Formea CM, Gaedigk A, Klein TE, Agúndez JAG, Grosser T (2020) Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2C9

and nonsteroidal anti-inflammatory drugs. Clin Pharmacol Ther 108(2):191–200. https://doi.org/10.1002/cpt.1830

Thelen K, Coboeken K, Willmann S, Burghaus R, Dressman JB, Lippert J (2011) Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part 1: oral solutions. J Pharm Sci 100(12):5324–5345. https://doi.org/10.1002/jps.22726

Thelen K, Coboeken K, Willmann S, Dressman JB, Lippert J (2012) Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part II: extension to describe performance of solid dosage forms. J Pharm Sci 101(3):1267–1280. https://doi.org/10.1002/jps.22825

Tilstone WJ, Lawson DH, Omara F, Cunningham F (1981) The steady-state pharmacokinetics of piroxicam: effect of food and iron. Eur J Rheumatol Inflamm 4(3):309–313

Tracy TS, Hutzler JM, Haining RL, Rettie AE, Hummel MA, Dickmann LJ (2002) Polymorphic variants (CYP2C9*3 and CYP2C9*5) and the F114L active site mutation of CYP2C9: effect on atypical kinetic metabolism profiles. Drug Metab Dispos 30(4):385–390. https://doi.org/10.1124/dmd.30.4.385

Trnavská Z, Trnavský K (1984) Plasma protein binding and interaction studies with piroxicam. Naunyn Schmiedeberg's Arch Pharmacol 327(1):81–85. https://doi.org/10.1007/BF00504996

Tvrdonova M, Dedik L, Mircioiu C, Miklovicova D, Durisova M (2009) Physiologically motivated time-delay model to account for mechanisms underlying enterohepatic circulation of piroxicam in human beings. Basic Clin Pharmacol Toxicol 104(1):35–42. https://doi.org/10.1111/j.1742-7843.2008.00304.x

Verscheijden LFM, Koenderink JB, Johnson TN, de Wildt SN, Russel FGM (2020) Physiologically-based pharmacokinetic models for children: Starting to reach maturation? Pharmacol Ther 211:107541. https://doi.org/10.1016/j.pharmthera.2020.107541

Wang D, Miller R, Zheng J, Hu C (2000) Comparative population pharmacokinetic-pharmacodynamic analysis for piroxicam-beta-cyclodextrin and piroxicam. J Clin Pharmacol 40(11):1257–1266

Wang L, Bao SH, Pan PP, Xia MM, Chen MC, Liang BQ, Dai DP, Cai JP, Hu GX (2015) Effect of CYP2C9 genetic polymorphism on the metabolism of flurbiprofen in vitro. Drug Dev Ind Pharm 41(8):1363–1367. https://doi.org/10.3109/03639045.2014.950274

Wanwimolruk S, Wanwimolruk SZ, Zoest A (1991) A simple and sensitive HPLC assay for piroxicam in plasma and its application to bioavailability study. J Liq Chromatogr 14(12):2373–2381. https://doi.org/10.1080/01483919108049697

Weintraub M, Jacox RF, Angevine CD, Atwater EC (1977) Piroxicam (CP 16171) in rheumatoid arthritis: a controlled clinical trial with novel assessment techniques. J Rheumatol 4(4):393–404

Wojtyniak JG, Britz H, Selzer D, Schwab M, Lehr T (2020) Data digitizing: accurate and precise data extraction for quantitative systems pharmacology and physiologically-based pharmacokinetic modeling. CPT Pharmacometrics Syst Pharmacol 9(6):322–331. https://doi.org/10.1002/psp4.12511

Wojtyniak JG, Selzer D, Schwab M, Lehr T (2021) Physiologically based precision dosing approach for drug-drug-gene interactions: a simvastatin network analysis. Clin Pharmacol Ther 109(1):201–211. https://doi.org/10.1002/cpt.2111

Xu M, Zheng L, Zeng J, Xu W, Jiang X, Wang L (2021) Physiologically based pharmacokinetic modeling of tramadol to inform dose adjustment and drug-drug interactions according to CYP2D6 phenotypes. Pharmacotherapy 41(3):277–290. https://doi.org/10.1002/phar.2494

Yellepeddi V, Rower J, Liu X, Kumar S, Rashid J, Sherwin CMT (2019) State-of-the-art review on physiologically based pharmacokinetic modeling in pediatric drug development. Clin Pharmacokinet 58(1):1–13. https://doi.org/10.1007/s40262-018-0677-y

Zhuang X, Lu C (2016) PBPK modeling and simulation in drug research and development. Acta Pharm Sin B 6(5):430–440. https://doi.org/10.1016/j.apsb.2016.04.004