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RESEARCH ARTICLE

Physiologically based pharmacokinetic modeling of candesartan related to *CYP2C9* genetic polymorphism in adult and pediatric patients

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Abstract Candesartan cilexetil is an angiotensin II receptor blocker and it is widely used to treat hypertension and heart failure. This drug is a prodrug that rapidly converts to candesartan after oral administration. Candesartan is metabolized by cytochrome P450 2C9 (CYP2C9) enzyme or uridine diphosphate glucurinosyltransferase 1A3, or excreted in an unchanged form through urine, biliary tract and feces. We investigated the effect of genetic polymorphism of CYP2C9 enzyme on drug pharmacokinetics using physiologically based pharmacokinetic (PBPK) modeling. In addition, by introducing the age and ethnicity into the model, we developed a model that can propose an appropriate dosage regimen taking into account the individual characteristics of each patient. To evaluate the suitability of the model, the results of a clinical trial on twenty-two healthy Korean subjects and their *CYP2C9* genetic polymorphism data was applied. In this study, PK-Sim® was used to develop the PBPK model of candesartan.

Keywords PBPK · CYP2C9 · Genotype · Candesartan · Polymorphism

Introduction

Frequently, a drug administered to a patient through proper diagnosis and prescription does not provide the desired therapeutic effects (Noetzli and Eap 2013). In addition, serious adverse drug reactions may occur in patients who normally use the drug as prescribed. These adverse reactions can significantly influence the quality of life of the patient and, in severe cases, may impose risk to the patient's life. In order to solve these problems, precision medicine, which treats patients considering the individual patient characteristics that may influence the drug effects, such as individual demographic data, enzyme genotype and life style, may be a solution (Jameson and Longo 2015; König et al. 2017). Right dose, one of the most important factors in precision medicine, considers the individual characteristics of these patients and maintains the plasma concentration of the drug properly within the therapeutic window, providing the most appropriate treatment effect to the patient and minimizing the risk of adverse reactions (Lesko and Schmidt 2012). Physiologically based pharmacokinetic (PBPK) modeling a method of predicting drug concentration in plasma or organs by applying individual physiological characteristics, drug characteristics, and biological responses to drugs. Individual differences such as gender, age, weight, genotype, disease severity, co-administered drugs, lifestyle and environmental factors that mainly affect drug responses can be introduced into the modeling (Chetty et al. 2014). In addition, dose regimens such as dose changes, routes of administration, and intervals of administration can be introduced into the

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modeling. Thus, the individual pharmacotherapy can be introduced by using PBPK modeling.

Candesartan cilexetil is an angiotensin II receptor blocker and it is widely used to treat hypertension and heart failure (AstraZeneca 2005). It is a prodrug that is completely converted to the active metabolite candesartan by the carboxylesterase 2 (CES2) enzyme (Laizure et al. 2013; Nishimuta et al. 2014) in the intestinal wall during absorption. Candesartan is highly selective of AT_1 subtype of angiotensin II receptor (Gleiter and Mörike 2002), it undergoes hepatic metabolism through the cytochrome P450 2C9 (CYP2C9) enzyme or is excreted in an unchanged form though urine, biliary tract and feces (Gleiter and Mörike 2002; Zhou et al. 2009). Also, it undergoes glucuronidation through uridine diphosphate glucurinosyltransferase 1A3 (Zhou et al. 2009).

CYP2C9 enzyme is mainly expressed in the liver. It accounts for 15–20% of the total cytochrome P 450 enzymes (Shimada et al, 1994; Mizutani, 2003). About 16% of all drugs currently are metabolized by the CYP2C9 enzyme, such as antidiabetic agents (glipizide, glimepiride and tolbutamide), antihypertensive agents (losartan and candesartan) and some non-steroidal anti-inflammatory drugs (NASIDs). It also metabolizes warfarin and phenytoin, which have a narrow therapeutic index (Kumar et al. 2008). To date, 71 CYP2C9 allele have been confirmed (https://www.pharmvar.org/gene/CYP2C9). In Caucasians, *CYP2C9*2* allele (rs1799853) has been identified with a frequency of 8–19.1% and *CYP2C9*3* allele (rs1057910) has been identified with a frequency of 3.3–16.2% (García-Martín et al. 2006). However, in Asians, the *CYP2C9*2* allele has rarely been identified (0–0.1%), but the *CYP2C9*3* allele has been identified at a frequency of 0.07–6.0% (Bae et al. 2005, 2011; Nakai et al. 2005; García-Martín et al. 2006). In addition, *CYP2C9*13* (rs72558187) has been identified at a very low rate with a frequency of only 0.2–1% in Asians (Bae et al. 2011). Since the pharmacokinetic changes by genetic polymorphism of the CYP2C9 enzyme have been reported in various drugs (Lee et al. 2015; Kim et al. 2017; Byeon et al. 2018), it may be necessary to take into account the pharmacokinetic changes of candesartan metabolized by the CYP2C9 enzyme.

In this study, we developed the PBPK modeling of candesartan for prediction of the pharmacokinetic differences of candesartan due to the genetic polymorphism of the CYP2C9 enzyme. In addition, parameters of age groups and ethnic groups were introduced in this modeling. The accuracy of the PBPK model and predicted pharmacokinetic data was evaluated using actually conducted pharmacokinetic data from various ethnic groups with appropriate equations. After evaluating the fit of the model, the model has been applied to pediatric patient groups of various ethnicity and genotypes. As a result, this PBPK model is expected to propose an appropriate drug regimen based on individual patient characteristics.

Methods

In vivo clinical study of candesartan

Subjects

In the pharmacokinetic study of candesartan cilexetil, 22 healthy Korean male subjects with *CYP2C9*1/*1* (n = 12, mean age 25.1 ± 1.3 years, weight 70.0 ± 5.0 kg, height 177.5 ± 4.3 cm and body max index (BMI) 22.2 ± 1.2 kg/m^2), *CYP2C9*1/*3* (n = 8, mean age 25.2 ± 1.3 years, weight 70.1 ± 5.2 kg, height 175.1 ± 3.6 cm and BMI 22.9 ± 2.0 kg/m^2) and *CYP2C9*1/*13* (n = 2, mean age 25.0 ± 1.4 years, weight 68.5 ± 7.8 kg, height 174.5 ± 0.7 cm and BMI 22.5 ± 2.7 kg/m^2) genotypes were selected. Peripheral blood leukocytes were used to isolate genomic DNA using the Genomic DNA Kit (Wizard®, Promega, Madison, WI, USA). After isolation of genomic DNA, we used the polymerase chain reaction restriction fragment length polymorphisms method for *CYP2C9*2*, **3* and **13* allele analysis as described previously (Bae et al. 2005). All subjects were between 24 and 29 years old, and BMI were between 20 and 26 kg/m^2. All subjects had no health problem, including the vital signs (such as body temperature, blood pressure, and pulse), physical examination, and medical history. For the study, all subjects were strictly forbidden to take any drugs, alcohol, or caffeine containing beverages for 10 days before and during the study.

Study protocol

This pharmacogenomic study was conducted according to the Helsinki Declaration on Biomedical Research and the protocol was approved by the Institutional Review Board of Metro Hospital (Anyang, Republic of Korea). Written informed consent was obtained from each participant prior to enrillment. Single oral dose of candesartan cilexetil (Atacand, AstraZeneca Korea, 8 mg, two tablets) with 240 mL of water was provided to all subjects. We collected blood samples before the drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 36 h after the administration of candesartan cilexetil. All blood samples were centrifuged at 3000 rpm for 10 min. After centrifuge, the plasma samples were collected and stored at −70°C until analysis.

Detection of candesartan concentration in human plasma

High performance liquid chromatography-fluorescence detector was used to detect candesartan concentration in

human plasma. Briefly, 0.5 mL of plasma was spiked with 10 µL of an internal standard (valsartan, 20 µg/mL) into a glass tube, and the mixture was acidified with 100 µL of 1 M HCl. After vortex mixing with 6 mL of diethyl ether, the organic phase was moved into a clean glass tube and evaporated at 40°C under a constant flow of nitrogen gas. The residue was reconstituted with 500 µL of the mobile phase. Separation of candesartan and internal standard was performed using Luna C18 CN column (4.6 × 250 mm, 5 µm, Phenomenex, Inc., Torrance, CA, USA). The mobile phase consisted of a mixture of 20 mM phosphate buffer-acetonitrile (65:35, V/V, pH adjusted to 3.5). The flow rate was 1.0 mL/min, and the column oven temperature was 30°C. The effluents were detected with fluorescence detection at excitation and emission wavelengths of 250 nm and 375 nm, respectively. The lower limit of quantification for candesartan was 1 ng/mL. The linear range of the standard curves for candesartan was from 1 to 300 ng/mL in plasma ($r^2 = 0.9998$), in which the mean accuracy of candesartan was 89.38–106.43%. The coefficients of variation (within-day and between-day precision) of candesartan in plasma were 0.73–13.57%.

Enzyme kinetic assay

To measure the drug metabolism of candesartan by CYP2C9, an enzyme kinetics analysis using a recombinant enzyme was performed. Stock solutions of candesartan were prepared at a concentration of 20 mM using dimethyl sulfoxide. 170 µL of 100 mM potassium phosphate buffer (pH 7.4), 10 µL of the prepared candesartan (20–10,000 µM), and 10 µL of CYP2C9 recombinant protein (stored at a concentration of 100 pmol) were transferred into a 1.5 mL glass tube. After pre-incubation (37°C for 10 min), 10 µL of NADPH generation system (6.6 mM glucose-6-phosphate, 0.8 U/mL glucose-6-phosphate dehydrogenase, 2.6 mM $NADP^+$, and 6.6 mM $MgCl_2$) was added to initiate the reaction (final volume: 200 µL). The incubation proceeded for 30 min, and 200 µL of chilled acetonitrile containing an internal standard was added to terminate the reaction. The mixture was centrifuged for 10 min at 4°C at 13,000 rpm, and then the supernatant was collected and injected to LC–MS/MS to analyze for the formation of *O*-desethyl candesartan. The *O*-desethyl candesartan was measured using the method of Hanatani et al. (2001), and calculation of enzyme activity was performed using the Michaelis–Menten equation from GraphPad Prism 6 (San Diego, CA, USA).

Development of candesartan PBPK modeling

PBPK modeling of candesartan was developed using PK-Sim® 7.4 (Bayer AG, Wuppertal, Germany). Quantitative mechanistic framework on human, system-specific properties and drug properties were used to develop PBPK modeling of candesartan. For demographic data used for PBPK modeling, the data from subjects of each clinical studies, were used. Physicochemical and pharmacokinetic (absorption, distribution, metabolism and excretion) data of candesartan cilexetil and candesartan used to develop PBPK modeling are represented in Tables 1 and 2. The time for dissolution of 80% of candesartan cilexetil was measured through the peddle method and applied to modeling. Data on molecular weight, unbound fraction, solubility, pKa, and lipophilicity in plasma were obtained from the DrugBank database (https://go.

Table 1 Candesartan cilexetil input data for development of candesartan PBPK modeling

Parameters	Value	References
Physical-chemistry		
M.W (g/mol)	610.67	PubChem
Fraction, unbound (%)	< 1	DrugBank
Solubility (mg/mL)	0.00204	ALOGPS
Lipophilicity (logP)	5.12	FDA
pKa (acid, base)	4.23, 1.45	DrugBank
Absorption		
Specific intestinal permeability	6.12E−4 cm/min	Thelen et al. 2011
Distribution		
Specific organ permeability	0.07 cm/min	Rodgers et al. 2005
Metabolism		
CES2 (liver)	5.4 mL/min/mg mic. protein	Nishimuta et al. 2014
CES2 (kidney)	0.61 mL/min/mg mic. protein	Nishimuta et al. 2014
CES2 (intestine)	2.9 mL/min/mg mic. protein	Nishimuta et al. 2014
Formulation		
Dissolution time	120 min	Kim et al. 2012

CES2 carboxyesterase 2

Table 2 Candesartan input data for development of candesartan physiologically based pharmacokinetic (PBPK) modeling

Parameters	Value	References
Physical-chemistry		
M.W (g/mol)	440.45	PubChem
Fraction, unbound (%)	> 1	DrugBank
Solubility (mg/mL)	0.00745	ALOGPS
Lipophilicity (logP)	3.44	FDA
pKa (acid, base)	3.44, 1.5	DrugBank
Absorption		
Specific intestinal permeability	5.57E−5 cm/min	Thelen et al. 2011
Distribution		
Specific organ permeability	0.01 cm/min	Rodgers et al. 2005
Metabolism		
Renal clearance	0.19 mL/min/kg	Astrazeneca 2005
Biliary clearance	0.127 mL/min/kg	Gleiter and Mörike 2002
*CYP2C9 *1* (V_{max}, K_m)	2.49 nmol/min/pmol. rec CYP 224.3 μM	Present study
*CYP2C9 *3* (V_{max}, K_m)	1.888 nmol/min/pmol. rec CYP 287.3 μM	Present study
*CYP2C9 *13* (V_{max}, K_m)	1.534 nmol/min/pmol. rec CYP 235.7 μM	Present study

drugbank.com/drugs/DB13919). The specific intestinal permeability was calculated using literature information (Thelen et al. 2011), and partition coefficients for candesartan cilexetil and candesartan were calculated using Rogers and Rowland method (Rodgers and Rowland 2006) for candesartan cilexetil and candesartan.

PBPK model validation

For evaluation of the candesartan PBPK model, acceptance criteria based on the observed human pharmacokinetic data were calculated using the appropriate equation (Eqs. 1–3) (Abduljalil et al. 2014).

$$\sigma = \sqrt{\ln\left[\left(\frac{\mathrm{CV\%}}{100}\right)^2 + 1\right]} \tag{1}$$

$$A\bar{x} = \exp\left[\ln(\bar{x}) - 4.26\frac{\sigma}{\sqrt{N}}\right] \tag{2}$$

$$B\bar{x} = \exp\left[\ln(\bar{x}) + 4.26\frac{\sigma}{\sqrt{N}}\right] \tag{3}$$

CV%, the coefficient of variation, represents the observed mean of the area under curve (AUC), C_{max}, and T_{max} value from identified clinical trials data; σ is the variability of PK parameter that is calculated using PK in the population; $\bar{x}$ is the average of the observed PK data; and N is the average number of subjects participating in the PK study. Each A and B are maximum and minimum boundaries for acceptable fold error, respectively.

Population simulation in diverse ethnic groups were performed to evaluate the candesartan PBPK model. These simulations were based on previously published human clinical PK reports. Demographic data (such as age, height, weight, BMI, and portion of female) and ethnic groups were also based on published clinical PK reports (Table 3) (Hoogkamer et al. 1998; Malerczyk et al. 1998; Buter et al. 1999; Cabaleiro et al. 2013; Jeon et al. 2013; Tjandrawinata et al. 2013; Patel et al. 2017). Demographic data from the population group used for population simulation was randomly formed within the specified demographic data, resulting in different results when modeling. Therefore, to reduce this error, more than 100 repeated experiments on average were performed. The fit of the population model was assessed using a two-fold error method, comparing the results of clinical trials with those derived from the simulation model. When the PK data (such as AUC, C_{max}, T_{max}, and $T_{1/2}$) obtained through simulation divided by the actual PK data, the model was judged to be suitable if the value was within the two-fold error boundary (Eq. 4).

$$0.5 < \mathit{Simulation\ data}/\mathit{Observed\ data} < 2 \tag{4}$$

Pediatric model development

For PBPK modeling of candesartan in pediatric groups, PK-Sim® random population generation was used within the defined demographic data. Two pediatric groups were used for modeling. The first Caucasian pediatric group consisted of a population of 1000 with a male to female ratio of 50:50, age of 0.1–12 years, and weight of 3–50 kg (Sy et al. 2014). The second Asian pediatric group was divided

Table 3 Demographic and ethnicity data of clinical PK reports used for population simulation of candesartan

Ethnicity	BMI (kg/m^2)	Height (cm)	Weight (kg)	Age (years)	References
Argentina	22.3 ± 1.7	162.9 ± 4.7	59.2 ± 5.7	29.4 ± 6.5	Patel et al. 2017
Germany	–	–	66–93	23–34	Malerczyk et al. 1998
Indonesia	18.8–24.7	–	–	18–55	Tjandrawinata et al. 2013
Korea	–	176.2 ± 5.3	69.7 ± 7.5	22.9 ± 2.5	Jeon et al. 2013
Spain (male)	–	–	73.9 ± 9.7	25.3 ± 4.3	Cabaleiro et al. 2013
Spain (female)	–	–	60.3 ± 8.3	25.8 ± 5.2	Cabaleiro et al. 2013
USA	–	165–180	59–85	32–71	Hoogkamer et al. 1998
Netherland	–	–	–	26–49	Buter et al. 1999

Mean ± SD

into two groups of all males and all females. The Asian male pediatric group consisted of a population of 1000, age of 0.1–12 years, weight of 3.41–40.3 kg, and height of 50.12–146.71 cm and the Asian female pediatric group consisted of a population of 1000, age of 0.1–12 years, weight of 3.29–39.24 kg, and height of 49.35–146.71 cm (Kim et al. 2018). In the modeling, a single oral dose of candesartan 12 mg or 16 mg, and *CYP2C9*1*, *CYP2C9*3* and *CYP2C9*13* genetic polymorphisms were applied.

Results

In this study, PBPK modeling of candesartan was developed in three phases. First, after developing the model, the generated model evaluated the fit of the model using appropriate equations and clinical data with a 99.998% confidence interval (Abduljalil et al. 2014). Second, after modeling the fitness for the diverse population, the model was evaluated by comparing the literature with PK data in the literature using the two-fold error equation. Finally, we derived the results by application to a model that assessed fitness to pediatric models of various ethnicities and genotypes.

The PBPK modeling of candesartan was developed based on a single oral dose of 16 mg of candesartan cilexetil. Candesartan cilexetil is rapidly and completely metabolized to the potent metabolite candesartan by CES2 enzyme (Laizure et al. 2013; Nishimuta et al. 2014) in the intestinal wall during absorption. In humans, two carboxylesterases, CES1 and CES2, are expressed in the liver, but only high levels of CES2 are expressed in the intestine (Laizure et al. 2013). CES2 is mainly present in the liver, kidney, and intestine, and the metabolic rate of candesartan cilexetil to each organ was used for modeling. Among candesartan metabolism, biliary clearance and renal clearance were applied with reference to the published literature (Gleiter and Mörike 2002). Also, metabolism of candesartan using a recombinant enzyme measured for PBPK modeling of the genetic polymorphism of the CYP2C9 enzyme was calculated through the Michaelis–Menten equation (Table 2). The results of the PBPK modeling of 16 mg single oral dose of candesartan in relation to the *CYP2C9* genetic polymorphism are presented in Table 4. In addition, the time-concentration profile of each *CYP2C9* genetic polymorphic group is shown in Fig. 1A. As a result, pharmacokinetic parameters such as AUC_{0-36}, AUC_{inf}, C_{max} and T_{max} were within the acceptance criteria based on clinically observed human PK data in vivo. In these modeling, the AUC_{0-36} of candesartan in *CYP2C9*1/*3* and *CYP2C9*1/*13* groups were 1.4-fold and 1.58-fold higher than *CYP2C9*1/*1* group, respectively. The AUC_{inf} of candesartan in *CYP2C*1/*3* and *CYP2C9*1/*13* groups were 1.43-fold and 1.63-fold higher than *CYP2C9*1/*1* group, respectively. The C_{max} of candesartan in *CYP2C*1/*3* and *CYP2C9*1/*13* groups were 1.21-fold and 1.33-fold higher than *CYP2C9*1/*1* group, respectively. However, there was no significant difference in the T_{max} of candesartan in each group. To evaluate the suitability of the developed candesartan PBPK model, pharmacokinetic parameters were observed by applying the model to various population groups. Modeling was conducted considering the demographic data, ethnic group and dose. The suitability of the model was evaluated through a two-fold ratio. As a result of modeling, the results of PK data such as AUC, C_{max}, T_{max} and $T_{1/2}$ were within the acceptance criteria, and it was confirmed that this model is suitable for application in various conditions (Table 4).

Modeling in pediatric group

In the Caucasian pediatric model, oral administration of 12 mg candesartan showed that AUC_{inf} and C_{max} increased rapidly compared to the adult group. Applying the *CYP2C9* genotype, the pharmacokinetic differences between the adult and pediatric groups were more pronounced. In the *CYP2C9*1/*1* pediatric group, AUC_{inf} increased by 4.20-fold and C_{max} increased by 3.71-fold compared to the Caucasian *CYP2C9*1/*1* adult group. In

Table 4 Results of the physiologically-based pharmacokinetic modeling of candesartan in relation to the *CYP2C9* genetic polymorphism and various populations

Genotype or ethnicity (reference)	Dose	Model validation	$AUC_{0\text{-}36}$ (ng h/mL)	AUC_{inf} (ng h/mL)	C_{max} (ng/mL)	T_{max} (h)
*CYP2C9*1/*1* (present study)	16 mg	Observation	1607.4	1667.2	164.2	3.7
		Simulation	1454.9	1573.1	152.5	3.3
		Acceptance criteria (min–max)	1233.8–2093.9	1291.6–2151.9	120.5–223.6	2.7–4.9
*CYP2C9*1/*3* (present study)	16 mg	Observation	2106.1	2192.1	191.0	5.0
		Simulation	2042.2	2255.1	185.0	3.5
		Acceptance criteria (min–max)	1801.3–2462.4	1866.6–2574.3	160.9–226.5	3.22–7.74
*CYP2C9*1/*13* (present study)	16 mg	Observation	2198.3	2334.9	213.8	4.0
		Simulation	2308.7	2579.3	204.0	3.5
		Acceptance criteria (min–max)	1972.2–2450.1	2107.5–2586.6	161.4–283.0	4
Argentina (Patel et al. 2017)	16 mg	Observation	1593 ± 449	1622 ± 456	163 ± 42	3.5
		Simulation	1150.4	1195.8	129.6	3.3
		Two-fold error ratio (0.5–2.0)	0.72	0.73	0.79	
Germany (Malerczyk et al. 1998)	8 mg	Observation	–	541.9 ± 242.6	52.8 ± 17.9	4.3 ± 1.1
		Simulation	691.1	740.5	67.4	3.4
		Two-fold error ratio (0.5–2.0)		1.25	1.19	0.79
Germany (Malerczyk et al.1998)	4 mg	Observation		264.3 ± 85.6	52.8 ± 17.9	4.3 ± 1.1
		Simulation	359.9	371.6	43.0	3.2
		Two-fold error ratio (0.5–2.0)		1.28	1.11	0.70
Indonesia (Tjandrawinata et al. 2013)	16 mg	Observation	1515.1 ± 392.9	1619.7 ± 425.1	155.4 ± 52.6	4 (2.0–7.0)
		Simulation	1638.5	1728.6	172.8	3.4
		Two-fold error ratio (0.5–2.0)	1.08	1.06	1.11	
Korea (Jeon et al. 2013)	16 mg	Observation	1530.1 ± 434.6	1670 ± 454.5	142.6 ± 41	5 (2.0–8.0)
		Simulation	1836.2	1912.4	187.6	3.4
		Two-fold error ratio (0.5–2.0)	1.2	1.14	1.31	
Spain (male) (Cabaleiro et al. 2013)	32 mg	Observation		3258.9 ± 692	216.3 ± 61.6	5.1 ± 1.3
		Simulation	2955.4	3165.4	288.8	3.5
		Two-fold error ratio (0.5–2.0)		0.97	1.33	0.67
Spain (female) (Cabaleiroet al. 2013)	32 mg	Observation		3814.7 ± 910.6	260.1 ± 63.9	4.9 ± 1.2
		Simulation	3025.9	3282.1	300.5	3.4
		Two-fold error ratio (0.5–2.0)		0.86	1.15	0.69
USA (Hoogkamer et al. 1998)	16 mg	Observation	708 ± 314	909 ± 307	95.2 ± 29.9	3.0 ± 1.4
		Simulation	924.0	972.5	94.6	3.4
		Two-fold error ratio (0.5–2.0)	1.3	1.06	0.99	1.11
Netherland (Buter et al. 1999)	8 mg	Observation	392.0 ± 110	485 ± 142	55 ± 14	3.8 ± 1.8
		Simulation	594.0	618.1	62.2	3.4
		Two-fold error ratio (0.5–2.0)	1.5	1.27	1.13	0.88

addition, in the pediatric group of the *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes, AUC_{inf} increased by 6.08-fold and 6.04-fold, respectively, and C_{max} increased by 4.49-fold and 4.48-fold, respectively, compared to the Caucasian adult group (Fig. 1D). In the Asian pediatric group, modeling was conducted by dividing into male and female groups. The Asian pediatric group with 16 mg single oral dose of candesartan had increased AUC_{inf} and C_{max} compared to adult group, but the increase rate was not as sharp as the Caucasian pediatric group. In the *CYP2C9*1/*1* male pediatric group, AUC_{inf} increased by 2.50-fold and C_{max} increased by 2.61-fold compared to the Asian adult patient group. In addition, in the male pediatric group of the *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes, AUC_{inf} increased by 3.64-fold and 3.61-fold, respectively, and C_{max} increased by 3.19-fold and 3.18-fold, respectively, compared to the Asian adult group (Fig. 1B). In the *CYP2C9*1/*1* female pediatric group, AUC_{inf} increased by 2.55-fold and C_{max} increased by 2.61-fold compared to the Asian adult patient group. In addition, in the female pediatric group of the *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes, AUC_{inf} increased by 3.70-fold and by 3.67-fold,

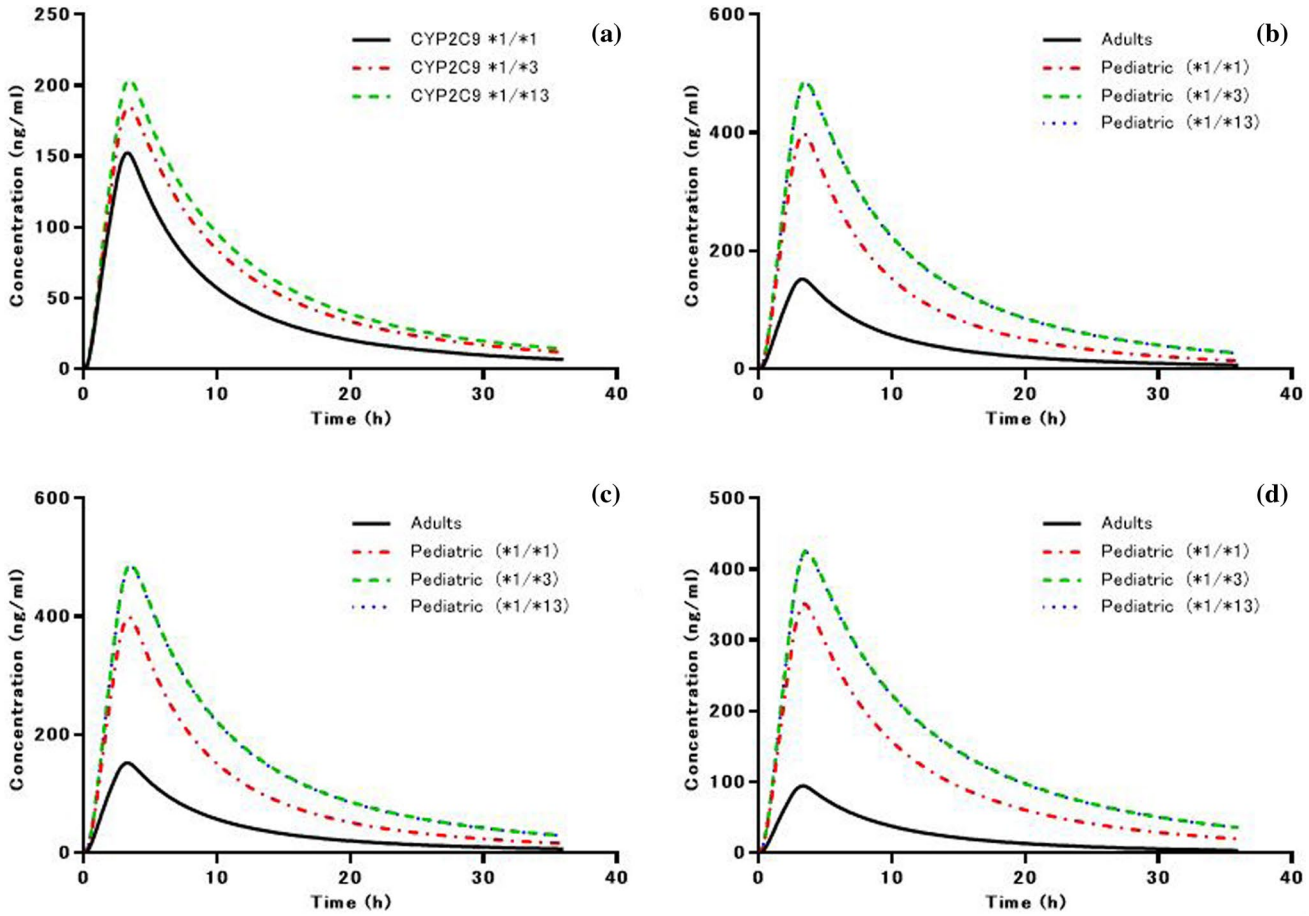

Fig. 1 Simulated candesartan plasma concentration after 16 mg single oral dose of candesartan cilexetil by *CYP2C9* genotypes in the first phase development of candesartan PBPK modeling (**a**). Plasma concentration of candesartan by *CYP2C9* genotype of Asian male pediatrics (**b**). Plasma concentration of candesartan by *CYP2C9* genotype of Asian female pediatrics (**c**). Plasma concentration of candesartan by *CYP2C9* genotype of Caucasian pediatrics (**d**)

respectively, and C_{max} increased by 3.20-fold and by 3.19-fold, respectively, compared to the Asian adult group (Fig. 1C). In Asian pediatric groups, no pharmacokinetic differences due to gender differences were found. Among ethnic groups in the pediatric population, higher pharmacokinetic concentrations (AUC_{inf} and C_{max}) were observed in Caucasians than in Asians when applying the same dose (16 mg). When comparing the same *CYP2C9* genotypes, AUC_{inf} increased by 1.36-fold and C_{max} increased by 1.15-fold (Table 5).

Discussion

Most drug metabolizing enzymes and transporters involved in drug absorption, distribution, metabolism, or excretion are genetically polymorphic, and these genetic polymorphisms affect drug dispositions and drug responses to varying degrees (Bae et al. 2011, 2020; Lee et al. 2015; Kim et al. 2017; Byeon et al. 2018, 2019; Jung et al. 2020a, b; Shin et al. 2020). Drug interactions also have significant effects on drug responses (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, 2021).

To date, there have been many pharmacokinetic studies of candesartan in various populations. However, these studies have not sufficiently considered the genetic polymorphism of the CYP2C9 enzyme. In addition, pharmacokinetic studies of candesartan in pediatric groups have been conducted (Trachtman et al. 2008; Schaefer et al. 2010; Hoy and Keating 2010), but studies on pediatric pharmacokinetics of various ethnic groups taking into account the genetic polymorphism of CYP2C9 enzyme are not sufficient. Even more than the

Table 5 Results of the physiologically-based pharmacokinetic modeling of candesartan in relation to the *CYP2C9* genetic polymorphism and various populations in adults and pediatrics

Ethnicity	Dose	Population	AUC_{0-36} (ng h/mL)	AUC_{inf} (ng h/mL)	C_{max} (ng/mL)	T_{max} (h)
Caucasian	12 mg	Adults	924.02	972.49	94.56	3.35
		Pediatric *CYP2C9*1/*1*	3772.02	4087.78	350.90	3.45
		Pediatric *CYP2C9*1/*3*	5277.34	5918.84	425.41	3.60
		Pediatric *CYP2C9*1/*13*	5244.57	5877.67	423.91	3.60
	16 mg	Pediatric *CYP2C9*1/*1*	4979.66	5414.32	462.10	3.50
		Pediatric *CYP2C9*1/*3*	6961.62	7834.41	559.97	3.60
		Pediatric *CYP2C9*1/*13*	6918.66	7780.21	558.03	3.60
Asian	16 mg	Adults	1454.91	1573.10	152.47	3.30
		Male pediatric *CYP2C9*1/*1*	3746.17	3941.36	398.44	3.40
		Male pediatric *CYP2C9*1/*3*	5311.38	5732.65	487.10	3.50
		Male pediatric *CYP2C9*1/*13*	5276.91	5692.19	485.30	3.50
	16 mg	Female pediatric *CYP2C9*1/*1*	3761.39	4014.39	398.94	3.40
		Female pediatric *CYP2C9 *1/*3*	5323.65	5824.04	488.20	3.55
		Female pediatric *CYP2C9*1/*13*	5289.22	5783.20	486.39	3.55

adult patients, the dose regimen of a medication is crucial for pediatric patients. Because children are not little adults, age-dependent values such as tissue size, tissue composition, plasma-protein concentration and hematocrit that can influence the drug absorption, distribution, metabolism and excretion (ADME) must be considered (Kearns et al. 2003; Lukacova et al. 2016). This model was confirmed to be suitable for Asians, Europeans, White Americans, and Mexican American-whites through population simulation. The results of this study in adult groups showed higher AUC_{inf} and C_{max} in Asians when comparing the pharmacokinetics of Europeans, Caucasians, Mexicans, and American Caucasians. However, in the pediatric group, AUC_{inf} and C_{max} concentrations in Caucasian pediatric group were higher than those in Asian pediatric group (AUC_{inf}: 1.36-fold increased, C_{max}: 1.15-fold increased). To identify the rationale for these differences, we compared the demographic data between the Caucasian and Asian pediatric groups, which is thought to have a large impact on the PK of the drug. As a result of the demographic analysis, the weight and height of Caucasians were higher than that of Asians, which did not provide the explanation for the pharmacokinetic differences, making it difficult attribute the pharmacokinetic difference due to demographic data. Therefore, it is thought that there are other age-ethnic-dependent factors that are yet to be identified.

In this study we developed a PBPK modeling of candesartan in relation to *CYP2C9* genotypes that are frequently confirmed in Caucasian and Asian population with diverse age groups and ethnic groups. As a result of the modeling, AUC and C_{max} were observed to be significantly increased in *CYP2C9*1/*3* and *CYP2C9*1/*13* groups compared to *CYP2C9*1/*1* (wild type) group in adult groups. Through this result, it was confirmed that dose control is necessary in the *CYP2C9*1/*3* and *CYP2C9*1/*13* groups. In the case of *CYP2C9*1/*3* and *CYP2C9*1/*13* groups, it is necessary to reduce the dose to about 25% of the original dose to achieve the PK parameters similar to the wild type (*CYP2C9*1/*1*). When this developed model was applied to the pediatric groups and compared to the adult groups, AUC $_{inf}$ and C_{max} were significantly increased in the Caucasian pediatric groups. Right dose, one of the most important factors in precision medicine, was calculated using the PBPK modeling. In order to obtain pharmacokinetic data similar to that of the adult group administered a 12 mg single oral dose of candesartan cilexetil in the Caucasian pediatric group, the *CYP2C9*1/*1* genotype requires approximately 75% dose reduction and *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes require an approximately 84% dose reduction. In the case of the Asian pediatric group, to obtain pharmacokinetic data similar to that of the adult group administered a 16 mg single oral dose of candesartan cilexetil, the *CYP2C9*1/*1* genotype requires approximately 60% dose reduction and *CYP2C9*1/*3* and *CYP2C9*1/*13* genotypes require an approximately 73% dose reduction. In this study, we developed a PBPK model of candesartan through a three-phase process. In the first phase, a model was developed using the clinical data from healthy Korean male subjects. However, the quantitative mechanism model used to model healthy Korean male subjects is a model that considers Asians in general, and it is difficult to accurately apply it to Koreans particularly. According to the previous studies, liver volume of Koreans was larger than that of other Asians, such as (Japanese and Chinese, and Caucasians (Yu et al. 2004; Johnson et al. 2005; Chan et al. 2006; Yuan et al. 2008; Fu-Gui et al. 2009; Shi et al. 2009; Kim et al. 2019). Also, the mean kidney volume in Koreans is measured to be 205.29 cm^3 which was a little smaller than that used in the model (Shin et al. 2009). Such differences can possibly influence

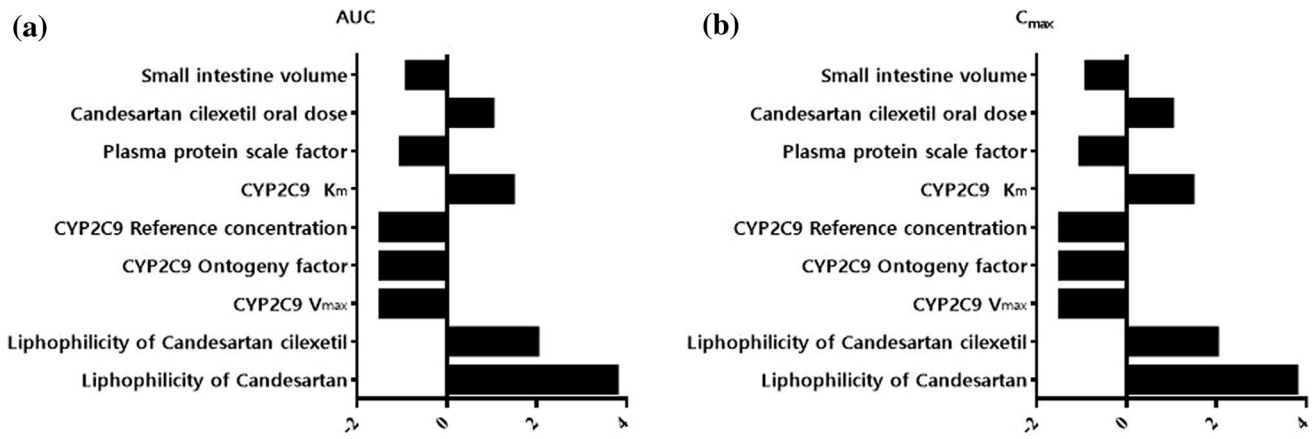

Fig. 2 Sensitivity analysis results of the PBPK modeling of candesartan (**a**) AUC and (**b**) C_{max}

the liver plasma clearance, renal plasma clearance, and biliary plasma clearance. The volumes of these organs are very important factors in determining the blood flow rate and plasma clearance during the modeling process and it is likely to influence pharmacokinetics. Also, the hematocrit of Koreans was 45.5% for men and 42% for women (Kim et al. 2019), which is slightly lower than the 47% hematocrit set in the modeling. Hematocrit has a great effect on the volume of fraction (Vf) of neutral lipids, neutral phospholipids, extracellular water and intracellular water, and may affect liver plasma clearance and kidney plasma clearance in modeling. Changes in the Vf change the composition of the tissue, which affects the distribution coefficient, which significantly affects the passive distribution of the drug. This has a great influence on PK in the drug modeling process. Despite these problems, there is a lack of basic research to implement the quantitative mechanistic framework for Koreans, which limits the research. Sensitivity analysis showed that the lipophilicity (logP) of candesartan and candesartan cilexetil had the greatest influence on the PK parameters (AUC and C_{max}). Subsequently, it was found that the reference concentration, ontogeny factor, K_m and V_{max} of CYP2C9 enzyme greatly influenced the PK parameters (Fig. 2). As a result of the sensitivity analysis, it was confirmed that kidney volume, liver volume, and hematocrit can affect the PK parameters, but the effect was not significant. In addition, as a result of the modeling, the relationship between kidney volume, liver volume, or hematocrit and PK parameters could not be confirmed. Because the individual characteristics of patients are so diverse, it is very difficult to deal with many variables in one study. This study covered genetic polymorphism, ethnicity, and age as factors and applied them into the model. However, in the case of patients receiving candesartan cilexetil, drugs to treat other diseases are frequently administered together, and in serious cases, the composition of organs in the body may be changed by surgery. These factors can also affect PK and may need to be considered when deciding on a dosage regimen. In a further study, we would like to suggest the appropriate dose regimen for these patients through PBPK modeling that considers these factors.

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Declarations

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

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