THERAPEUTIC ADVANCES in
Drug Safety

Original Research

Physiologically based pharmacokinetic modeling of candesartan to predict the exposure in hepatic and renal impairment and elderly populations

Ther Adv Drug Saf

2023, Vol. 14: 1–14

DOI: 10.1177/20420986231220222

Lingfeng Guo, Xinyu Zhu, Lei Zhang and Yichao Xu

Abstract

Background: Candesartan cilexetil is a widely used angiotensin II receptor blocker with minimal adverse effects and high tolerability for the treatment of hypertension. Candesartan is administered orally as the prodrug candesartan cilexetil, which is wholly and swiftly converted to the active metabolite candesartan by carboxylesterase during absorption in the intestinal tract. In populations with renal or hepatic impairment, candesartan's pharmacokinetic (PK) behavior may be altered, necessitating dosage adjustments.

Objectives: This study was conducted to examine how the physiologically based PK (PBPK) model characterizes the PKs of candesartan in adult and geriatric populations and to predict the PKs of candesartan in elderly populations with renal and hepatic impairment.

Design: After developing PBPK models using the reported physicochemical properties of candesartan and clinical data, these models were validated using data from clinical investigations involving various dose ranges.

Methods: Comparing predicted and observed blood concentration data and PK parameters was used to assess the fit performance of the models.

Results: Doses should be reduced to approximately 94% of Chinese healthy adults for the Chinese healthy elderly population; approximately 92%, 68%, and 64% of that of the Chinese healthy adult dose in elderly populations with mild, moderate, and severe renal impairment, respectively; and approximately 72%, 71%, and 52% of that of the Chinese healthy adult dose in elderly populations with Child–Pugh-A, Child–Pugh-B, and Child–Pugh-C hepatic impairment, respectively.

Conclusion: The results suggest that the PBPK model of candesartan can be utilized to optimize dosage regimens for special populations.

Plain language summary

Develop a physiologically based pharmacokinetic model of candesartan to predict the exposure in Chinese elderly populations

Background: Candesartan cilexetil is a widely used angiotensin II receptor blocker with minimal adverse effects and high tolerability for the treatment of hypertension. Candesartan cilexetil is wholly and swiftly converted to the active metabolite candesartan by carboxylesterase during absorption in the intestinal tract. Candesartan's pharmacokinetic behavior may be altered in patients with renal or hepatic impairment.

Correspondence to:
Yichao Xu
Center of Clinical Pharmacology, The Second Affiliated Hospital of Zhejiang University, School of Medicine, 88 Jiefang Road, Hangzhou, Zhejiang 310009, China
xuyichao0732@zju.edu.cn

Lingfeng Guo
Xinyu Zhu
The First Affiliated Hospital of Zhejiang University Shengzhou Branch, School of Medicine, Shengzhou, Zhejiang, China

Lei Zhang
Department of Pharmacy, The Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, Zhejiang, China

Methods: We developed PBPK models using the reported physicochemical properties of candesartan and clinical data. We validated the PBPK models.
Results: We found that the elderly population needs dosage adjustments.

1. Doses should be reduced to approximately 94% of Chinese healthy adults for the Chinese healthy elderly population
2. Doses should be reduced to approximately 92%, 68%, and 64% of that of the Chinese healthy adult dose in elderly populations with mild, moderate, and severe renal impairment
3. Doses should be reduced to approximately 72%, 71%, and 52% of that of the Chinese healthy adult dose in elderly populations with Child Pugh-A, Child Pugh-B, and Child Pugh-C hepatic impairment.

Conclusion: The PBPK model of candesartan can be utilized to optimize dosage regimens for special populations.

Keywords: candesartan, elderly population, hepatic impairment, physiologically based pharmacokinetics, renal impairment

Received: 23 August 2023; revised manuscript accepted: 27 November 2023.

Introduction

Hypertension is one of the most significant cardiovascular disease risk factors. Antihypertensive medications are required to manage hypertension to reduce blood pressure (BP) to target levels. According to their action mechanisms, antihypertensive medications are divided into five classes: beta-blockers, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.[1,2] Candesartan is administered orally as the prodrug candesartan cilexetil, rapidly and wholly hydrolyzed by carboxylesterase during its absorption in the intestinal tract to the active metabolite candesartan.[3,4] Candesartan has minimal adverse effects and excellent tolerability. It can be used alone or with other antihypertensive medications. It is appropriate for all stages of hypertension, particularly in patients who cannot tolerate angiotensin-converting enzyme inhibitors, and has become one of the most preferred antihypertensive medications.[5,6] The estimated bioavailability for candesartan is 15%. Because this metabolite is firmly bound to plasma proteins, its distribution volume (0.13 L/kg) is relatively low.[7] Candesartan is only partially inactivated by hepatic metabolism (CYP2C9) and is predominantly eliminated unchanged through the urinary and biliary systems. Several clinical pharmacokinetic (PK) studies imply that dose modification may be necessary for specific situations, such as renal/hepatic impairment and elderly populations.[8]

Elderly populations are prone to high BP in general.[9,10] Due to aging and complex underlying diseases treated by multi-drug therapy, the pathophysiological mechanisms and PKs of elderly populations are complex, and they face a substantially increased risk of high BP.[3,11] The balance between the achievement of goal BP and the reduced risk of side effects has become a key concern for clinicians.[12–14] Few randomized controlled studies have evaluated geriatric high BP patients of varying ages, disease stages, and degrees of susceptibility, particularly in the Chinese elderly population. It is essential to reduce the safety risk and maximize the efficacy-to-safety ratio of candesartan in geriatric patients. To maintain the same level of efficacy and safety in elderly adults as in non-elderly adults, it is necessary to forecast the PK profile in virtual Chinese elderly populations.

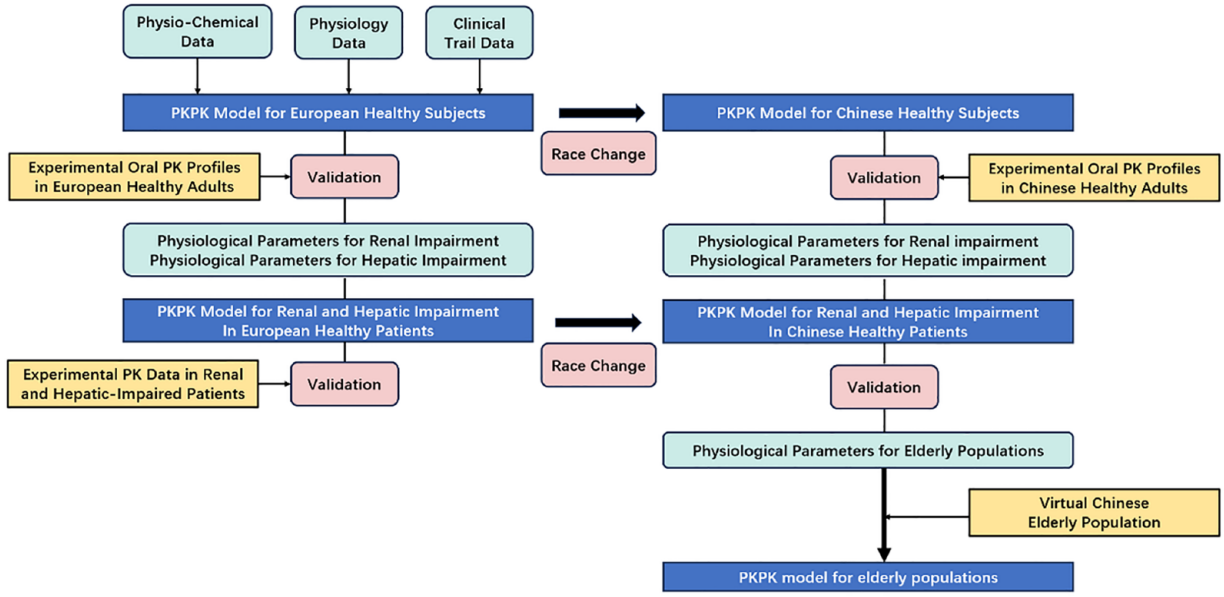

Figure 1. Generic workflow for model development.

A physiologically based PK (PBPK) model considers the physiological and biochemical properties of organisms and the physicochemical, anatomical, and thermodynamic properties of a drug.[15–17] This model simulates drug distribution, transportation, and metabolism in various body regions by treating human tissues and organs as independent compartments linked by blood circulation. To predict the PK and efficacy of drugs in humans, the PBPK model combines the physical and chemical properties of drugs, the parameters of the human physiological system, and the mechanical PK data.[18–21] As such, it can be used to process medical dynamics data based on the material balance principle.[22] Moreover, PBPK is commonly used to characterize PK changes in the body under various complex clinical conditions and, according to previous studies, is an effective method to study the distribution and metabolism of drugs in the human body.[23] In this study, a PBPK model was developed and validated for extrapolation to the healthy elderly Chinese population and the elderly Chinese population with hepatic and renal impairment to serve as a guide for devising individualized medication regimens for these populations.

Methods

Modeling platform and data collection

The whole-body PBPK (WB-PBPK) models of candesartan in European and Chinese healthy adults, the healthy elderly population, and the healthy elderly population with hepatic and renal impairment were developed using the PK-Sim® software (Open Systems Pharmacology Suite, version 11.1). The WebPlotDigitizer® (Ankit Rohatgi, version 4.2) software was used to derive the PK data points from the PK study reported in the literature. PK parameters were computed utilizing noncompartmental model analysis with Phoenix WinNonlin® software (version 8.3.5.340; Pharsight, Mountain View, CA, USA). The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[24]

Generic workflow for model development

Figure 1 depicts the generic workflow for scaling drug PK from healthy subjects to patients with hepatic and renal impairment and from European adults to Chinese adults and elderly populations using the PBPK model.

Adult PBPK model development

This study utilized a combined 'bottom-up' and 'middle-out' strategy to facilitate model development. Candesartan's absorption, distribution, metabolism, and excretion mechanism were determined by accumulating data on its physicochemical properties, conducting *in vitro* experiments, and extending the experiments to humans

with *ex vivo* correlated factors and scalars.[25] The final model was developed using the 18 compartments, each of which could be further divided into sub-compartments built into the PK-Sim software.[26] The input compound parameters of candesartan and candesartan cilexetil, including physicochemical properties, specific intestinal permeability, enzymatic kinetic, and glomerular filtration fraction (f_{GFR}) parameters, were obtained from DrugBank, the guidelines of the US Food and Drug Administration or the European Medicines Agency, and the literature.[27–31]

Using Monte Carlo simulations, system-specific parameters obtained from the PK-Sim built-in database (i.e. physiological and anatomical parameters of the virtual population) were fixed to suit 4 mg oral tablet clinical data in European healthy subjects. The model was validated using clinical data from other concentrations and healthy Chinese subjects. Table 1 summarizes the physicochemical, biopharmaceutical, and PK parameters of candesartan.

PBPK modeling in healthy subjects. Based on the average value obtained from the software, a European virtual adult was created to represent the mean adult of the created population. Based on mean population values, the age, weight, height, and body mass index (BMI) of the individual were 27.00 years, 77.00 kg, 174.20 cm, and 25.37 kg/m^2, respectively. At the same time, a virtual population of 100 individuals (50% female subjects) aged 20–40 years with a BMI of 18–24 kg/m^2 was constructed using the 'population' module of the software to characterize the PK behavior of candesartan in the European healthy population.

The virtual populations were created based on the dosing regimen, and the population prediction means and 5th–95th concentration range were obtained. The average folded error was used to compare predicted and measured concentrations of the maximum concentration (C_{max}) and area under the curve of zero to infinity ($AUC_{0-\infty}$) which were used to evaluate the model fit.[32] Then, an Asian virtual healthy subject individual and population were created and validated in the same way.

Scaling to the European patients with renal impairment. The 'Chronic Kidney Disease' module built into PK-Sim was used to display changes in European patients with renal impairment, including GFR, kidney volume, kidney blood flow, plasma protein binding, hematocrit, gastric emptying time, and small intestinal transit time.[33] Renal clearance in European patients with renal impairment was predicted based on the f_{GFR} and creatinine clearance rate (CL_{cr}). The model was validated based on the real-world PK study reported by Buter *et al.*[34] using the formula

$$f_{GFR} = \frac{CL_R}{f_u \times GFR} \quad (1)$$

$$CL_{R,i} = CL_{R,j} \times \frac{CL_{cr,i}}{CL_{cr,j}} \quad (2)$$

where CL_R represents the value of observed renal clearance, f_u represents the value of fraction unbound, and GFR represents the value of glomerular filtration rate.

Scaling to the European patients with hepatic impairment. Child–Pugh classification is the most widely used method to categorize the hepatic function in populations with hepatic impairment. Scoring is based on clinical features and laboratory-based parameters, and patients are classified into Child–Pugh-A (CP-A), Child–Pugh-B (CP-B), and Child–Pugh-C (CP-C) groups based on the extent of hepatic impairment.[35] Parameter information is shown in Table 2.[36] The model was validated based on the real-world PK study reported by Liu *et al.*[37]

Chinese elderly population PBPK model development

The scaling of elderly Chinese populations was performed in two steps. In the first step, PK-Sim was used to automatically scale the parameter changes of anatomic, anthropometric, and physiological in the Chinese elderly population based on the final PBPK model of Chinese healthy subjects, keeping drug-specific parameters constant. In the second step, the exposure of candesartan was separately simulated within the subpopulations of the elderly with hepatic and renal impairment based on the prevalence of hepatic and renal dysfunction in this population.

Model predictability and dose optimization

The prediction accuracy was evaluated graphically by comparing the *in vivo* observed concentration–time profiles to the simulated profiles.

Table 1. Summary of input compound parameters of candesartan and candesartan cilexetil in the PBPK model.

Parameter	Candesartan	Source	Candesartan cilexetil	Source
Physiochemical properties				
log P	3.44	DrugBank	7.32	DrugBank
f_u (plasma, albumin)	1	DrugBank	1	DrugBank
MW (g/mol)	440.45	PubChem	610.67	PubChem
pKa (acid)	3.44	DrugBank	4.23	DrugBank
pKa (base)	1.50	DrugBank	1.45	DrugBank
Solubility	0.00745	ALOGPS	0.00204	ALOGPS
Absorption				
Specific intestinal permeability (cm/min)	5.75E−05	Thelen *et al.*[28]	6.12E−04	Thelen *et al.*[28]
Distribution				
Specific organ permeability (cm/min)	0.01	Rodgers *et al.*[29]	0.07	Rodgers *et al.*[29]
Metabolism and elimination				
Renal clearance (mL/min/kg)	0.19	Jung *et al.*[31]		
Biliary clearance (mL/min/kg)	0.127	Gleiter and Mörike[30]		
CYP2C9 (liver)				
V_{max}	2.49 nmol/min/pmol rec CYP	Jung *et al.*[31]		
K_m	224.3 µM	Jung *et al.*[31]		
CES2 (liver)			5.4 mL/min/mg mic. protein	Nishimuta *et al.*[27]

CES2: Carboxylesterases 2; f_u, fraction unbound; log P, lipophilicity; MW, molecular weight; PBPK, physiologically based pharmacokinetic; pKa, acid dissociation constant.

Non-compartmental analysis was utilized to derive predicted PK parameters (AUC and C_{max}) from simulated plasma concentration–time profiles. WinNonlin calculated the AUC values using the linear trapezoidal rule and extrapolation to infinity. The C_{max} values were derived directly from the concentration–time profiles of plasma. Based on simulated exposures (AUC and C_{max}) in healthy Chinese subjects, dosing regimens for candesartan in diverse Chinese populations were evaluated. Specifically, the AUC calculation values for each individual were simulated by creating and grouping various categories of special virtual Chinese populations and selecting the optimal clinical dose for normalization. The AUC differences between each group and the group of healthy Chinese subjects were compared, and the data were annotated. Based on the dose-normalization results for healthy Chinese subjects and special Chinese populations, the doses were increased or decreased to obtain exposure levels comparable to those of healthy Chinese subjects. Dose selection recommendations were made for each subtype of the Chinese population.

Table 2. Changes in PBPK parameters that are altered in hepatic impaired individuals *versus* healthy individuals.

Parameter	Healthy	CP-A	CP-B	CP-C
Blood flow rate (L/min)				
Hepatic	0.44	0.45	0.79	0.15
Renal	1.35	0.94	0.69	0.51
Other organs (fractions of healthy)	1	1.75	2.25	2.75
Liver volume (L)	2.44	1.32	1.05	0.53
CYP2C9 (pmol/mg)	73.0	50.4	38.0	24.1
Glomerular filtration rate (mL/min)	120	83.7	69.9	66.5
Hematocrit	0.47	0.39	0.37	0.35
Ontogeny factor (albumin)	1	0.81	0.68	0.5
Ontogeny factor (α1-acid glycoprotein)	1	0.6	0.56	0.3

CP-A, Child–Pugh-A; CP-B, Child–Pugh-B; CP-C, Child-Pugh-C; PBPK, physiologically based pharmacokinetic.

Result

PK profiles in healthy subjects

The PBPK model was first applied to simulate the concentration–time profiles in healthy European subjects after single doses of candesartan at different dose levels. For single-dose simulation, European healthy subjects in each dose group were given candesartan at 4, 8, and 16 mg. Then, the PBPK model was applied to simulate the concentration–time profiles in healthy Chinese subjects after single doses of candesartan at 16 mg. As shown in Figure 2, the model accurately described the observed PK profile across the regimens investigated. These results indicated a reasonable assumption of candesartan's absorption and elimination mechanism.

PK profiles in European elderly patients with renal impairment

Based on the data from the PK study of candesartan in European elderly patients with varying degrees of renal impairment, the PK characteristics of candesartan in the renal-impairment population were explored. As shown in Figure 3, the extrapolation model results showed that the predicted and observed values of plasma drug concentration–time profiles in the normal European adults, and European elderly patients with moderate, and severe renal-impairment populations fit well, with most observations falling within the 5th–95th range. The effect of renal impairment on fold changes of C_{max} and $AUC_{0-\infty}$ of candesartan was predicted and found to be comparable with the observed values in the corresponding group of patients with renal impairment (Table 3). As for the European patients with renal impairment, we simulated the exposure after oral administration of 8 mg candesartan. The results showed that the doses of European elderly patients with moderate and severe renal impairment need to be reduced to about 47% and 49% of the doses of the European healthy adult population to achieve the same therapeutic effect.

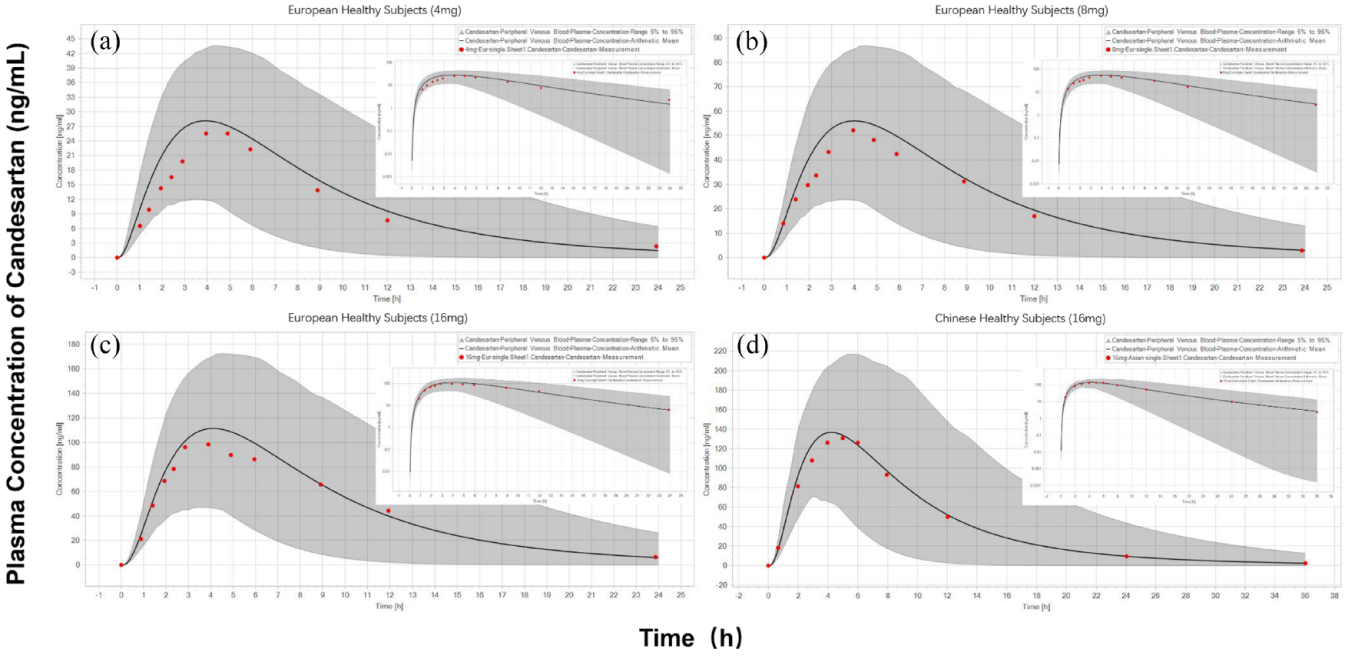

Figure 2. Prediction of the PK profiles for candesartan at a series of doses using the PBPK model. Simulation (mean predictions in black lines and 5th–95th percentiles of predictions in gray shade) of PK profiles for a single oral dose of 4, 8, and 16 mg of candesartan (log scale was on the right top in each dose panel) in European healthy subjects (a–c) and Chinese healthy subjects (d).
PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic.

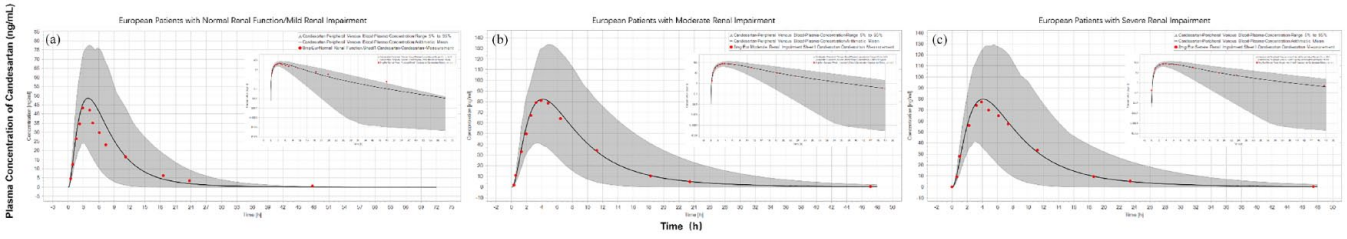

Figure 3. Prediction of the pharmacokinetic profiles for candesartan in European patients with normal/mild (a), moderate (b), and severe (c) renal impairments using the PBPK model. Simulations were compared with the corresponding observed clinical data (red dot).
PBPK, physiologically based pharmacokinetic.

Table 3. Fold changes of candesartan exposure in patients with renal impairment compared with normal function.

Renal impairment	Observed C_{max} ratio	Observed AUC ratio	Predicted C_{max} ratio/AFE* (%)	Predicted AUC ratio/AFE* (%)
Normal/mild (CLCR > 60 mL/min)	1.00	1.00	0.87/–13.0	0.93/–7.0
Moderate (CLCR = 30–60 mL/min)	1.75	2.10	1.49/–14.8	2.13/1.5
Severe (CLCR = 15–30 mL/min)	1.44	2.01	1.44/0.0	2.05/2.0

*AFE, the median simulation as compared to observed data points.
AFE, average fold error; AUC, area under the curve; CLCR:Creatinine Clearance.

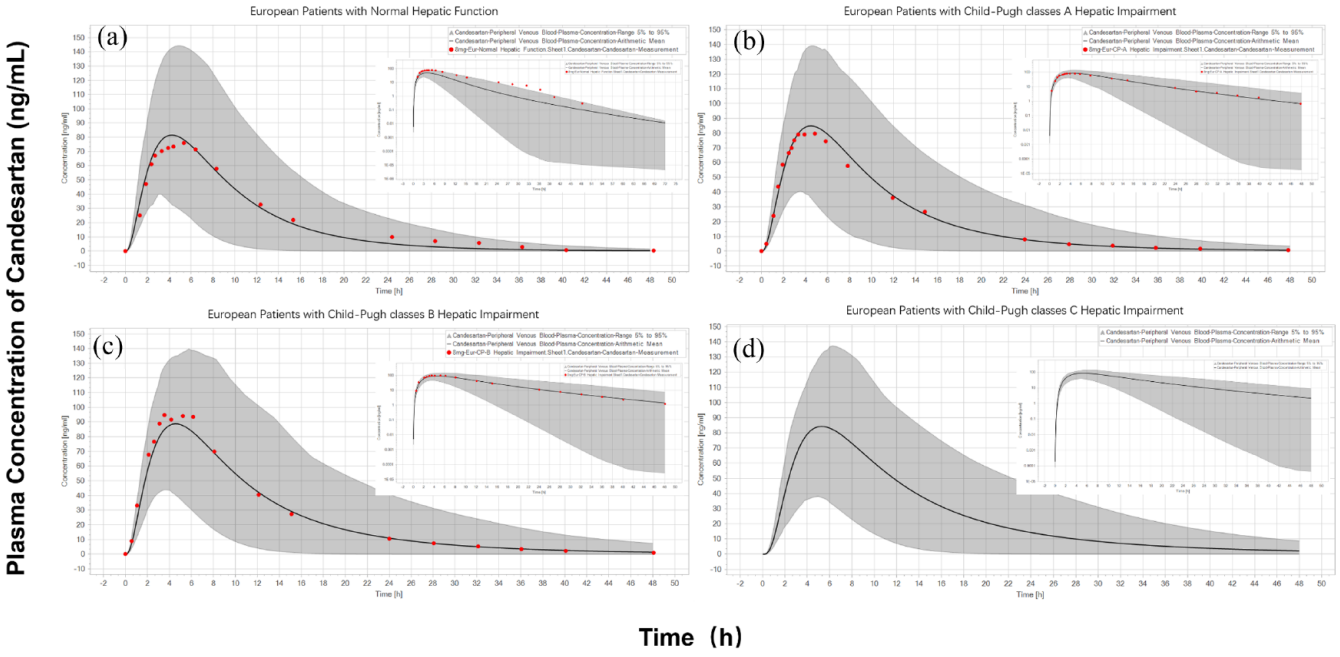

Figure 4. Prediction of the pharmacokinetic profiles for candesartan in European patients with normal (a), CP-A (b), CP-B (c), and CP-C (d) hepatic impairments using the PBPK model. Simulations were compared with the corresponding observed clinical data (red dot).
CP-A, Child–Pugh-A; CP-B, Child–Pugh-B; CP-C, Child-Pugh-C; PBPK, physiologically based pharmacokinetic.

Table 4. Fold changes of candesartan exposure in patients with hepatic impairment compared with normal function.

Hepatic impairment	Observed C_{max} ratio	Observed AUC ratio	Predicted C_{max} ratio/AFE* (%)	Predicted AUC ratio/AFE* (%)
Normal	1.00	1.00	0.98/–2.0	0.93/–7.0
Mild (CP-A)	1.03	1.20	1.01/–1.9	1.14/–5.0
Moderate (CP-B)	1.31	1.92	1.19/–9.2	1.83/–4.7
Severe (CP-C)	NA	NA	1.02/NA	1.39/NA

*AFE, the median simulation as compared to observed data points.
AFE, average fold error, AUC, area under the curve; CP-A, Child–Pugh-A; CP-B, Child–Pugh-B; CP-C, Child-Pugh-C.

PK profiles in European elderly patients with hepatic impairment

Based on data from a PK study of candesartan in European elderly patients with varying degrees of hepatic impairment, the PK characteristics of candesartan in the hepatic impairment population were further explored. As shown in Figure 4, the extrapolation model results showed that the predicted and observed values of plasma drug concentration–time profiles in European adults, and European elderly patients with CP-A and CP-B hepatic impairment populations fitted well, with most observations falling within the 5th–95th range. On this basis, we predicted the plasma drug concentration–time curve profiles in CP-C of hepatic impairment populations. The effect of hepatic impairment on fold changes of C_{max} and $AUC_{0-\infty}$ of candesartan was predicted and was comparable with the observed values in corresponding group patients with hepatic impairment (Table 4). As for the European patients with hepatic impairment, we simulated the exposure after oral administration of 8 mg candesartan. The results showed that the doses of European

elderly patients with CP-A, CP-B, and CP-C hepatic impairment need to be reduced to about 88%, 55%, and 72% of the doses of the European healthy adult population to achieve the same therapeutic effect.

PK profiles in Chinese elderly patients

Scaling the age-dependent parameters according to the software's built-in algorithm, a cohort of Chinese elderly population (50% women) aged 40–80 years. Exposure to 8 mg candesartan administered orally *in vivo* was predicted in the healthy elderly Chinese population and compared to the healthy Chinese subjects. As shown in Figure 5, the results showed that the $AUC_{0-\infty}$ of 8 mg of candesartan administered orally was 724.6 and 771.4 ng h/mL and that the C_{max} was 68.69 and 81.51 ng/mL for the healthy Chinese subjects and elderly population, respectively. These findings suggested that the *in vivo* dosage of orally administered candesartan in the healthy elderly population should be reduced to approximately 94% of that of the healthy population. The reaction of exposure to 8 mg of candesartan administered orally was also predicted in the elderly populations with hepatic and renal impairment. The results showed that the $AUC_{0-\infty}$ of the elderly population with mild, moderate, and severe renal impairment was 787.5, 1073, and 1137 ng h/mL, respectively, and that the dosage for these populations should be reduced to approximately 92%, 68%, and 64%, respectively, of the dosage of the healthy adult subjects to achieve the same therapeutic effect. Similarly, the results showed that the $AUC_{0-\infty}$ of elderly with CP-A, CP-B, and CP-C hepatic impairment was 1005, 1022, and 1385 ng h/mL, respectively, and that the dosage for these populations should be reduced to approximately 72%, 71%, and 52%, respectively, of the dosage of the healthy adult subjects. The predicted fold changes of C_{max} and $AUC_{0-\infty}$ of candesartan in Chinese elderly patients with renal/hepatic impairment are shown in Table 5.

Discussion

In recent years, there has been an increase in the clinical demand for antihypertensive medications among special patients. An angiotensin II receptor blocker, candesartan cilexetil, is extensively used to treat hypertension and has shown promise in exceptional circumstances such as renal/hepatic impairment and elderly patients. Candesartan has the prospective advantages of being easy to administer, requiring less frequent drug monitoring, and having fewer drug–drug interactions. Due to a lack of clinical data in this patient population, however, off-label candesartan use in these patients must be extrapolated from the dosage regimen in healthy adults.

Traditional compartmental modeling approaches have limited predictive ability because they do not account for all of the physiological, anatomical, and biochemical changes associated with drug exposure, nor all the changes associated with drug absorption, distribution, metabolism, and excretion. By contrast, PBPK modeling utilizes existing drug disposition and physiology knowledge and enables extrapolation across various life stages. In this study, PBPK-based scaling from healthy populations to populations with renal impairment or hepatic impairment and from adults to elderly patients was used to predict the PK profiles of candesartan in populations with renal impairment or hepatic impairment and in elderly populations with or without renal or hepatic impairment. Utilizing age-specific physiology parameters, such as organ volume, blood flow, and hepatic and renal function, the model was then scaled to geriatric populations using adult-specific data.

In comparison to traditional PK methods, PBPK models have a significant impact on the formulation of clinical medication regimens for special populations, primarily by predicting plasma concentrations of drugs and providing an accurate method for assessing efficacy and risk.[38,39] PBPK models have been used to predict exposure profiles in special populations *in vivo* due to their adaptability in data integration and excellent predictive power.[40] We have experience with PBPK modeling and have developed accurate PBPK models for a variety of innovative and generic medications.[41,42] Based on the study reported by Jung *et al.*,[31] we developed PBPK models for candesartan in healthy European and Asian subjects in this investigation. Then, the PBPK model specific for candesartan in the population with hepatic and renal impairment was developed and validated by relevant clinical investigations, taking into account the physiological differences between disease stages and healthy populations. In the meantime, we characterized the exposure behavior of candesartan in the elderly Chinese population based on age-scaling-related parameters and

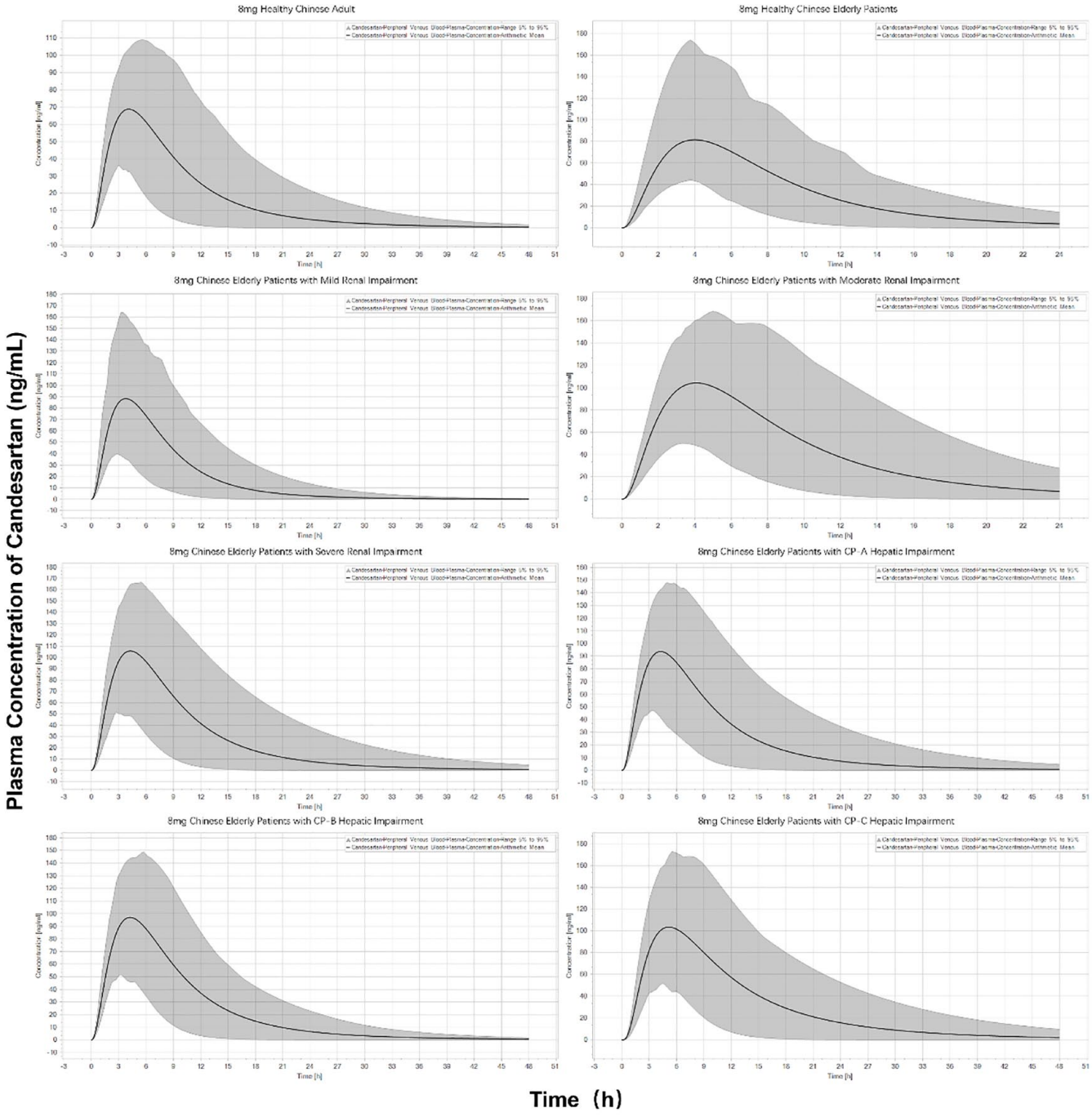

Figure 5. Comparison of oral 8 mg candesartan plasma drug concentration–time profiles in Chinese healthy subjects and elderly patients at different renal/hepatic disease stages.

extended it to the standard elderly population with hepatic and renal impairment. It provides the opportunity to use the PBPK model to guide the clinical development of reasonable dosing regimens for candesartan in special Chinese populations.

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 CES2 enzyme in the intestinal wall during absorption. During the

Table 5. Fold changes of predicted candesartan exposure in Chinese elderly patients with renal or hepatic impairment compared with healthy subjects.

Pharmacokinetic parameters	Healthy subjects	Healthy elderly patients	Elderly patients with renal impairment			Elderly patients with hepatic impairment		
			Mild	Moderate	Severe	CP-A	CP-B	CP-C
C_{max} ratio	1.00	1.19	1.29	1.52	1.54	1.36	1.41	1.51
AUC ratio	1.00	1.06	1.09	1.48	1.57	1.39	1.41	1.91

AUC, area under the curve; CP-A, Child–Pugh-A; CP-B, Child–Pugh-B; CP-C, Child-Pugh-C.

PBPK modeling, we found that the lipophilicity of candesartan provided by the DrugBank did not truly describe the absorption process of candesartan in the body. Therefore, we optimized the parameters affecting the absorption process of candesartan through published PK literature[43–46] and evaluated the accuracy of the PBPK model by comparing the Bias% between the predicted and the measured values of key PK parameters (such as C_{max}, $AUC_{0-\infty}$, etc.). Finally, the optimized lipophilicity was used in the PBPK models.

In terms of substance PKs, both the liver and kidneys play a crucial role. The bioavailability of a drug is significantly influenced by the quantity of drug absorbed and the liver's first-pass metabolism. As a prodrug, candesartan cilexetil is rapidly and completely converted to candesartan by the CES2 enzyme in the intestinal wall during absorption. For candesartan, it undergoes hepatic metabolism through the CYP2C9 enzyme. Plasma protein binding in humans is >99%. By contrast, the GFR is primarily responsible for the elimination of the drug. Determining drug dosages for populations with hepatic and renal insufficiency has been a significant clinical challenge.[47] Because candesartan is partially excreted through the kidneys, patients with renal impairment may lead to decreases in CYP2C9 activities, which, in turn, affect the metabolism of candesartan.[48,49] Candesartan is metabolized by CYP2C9 liver enzymes in the hepatically impaired population, necessitating dose modification. In the current study, all changes *in vivo* parameters associated with renal and hepatic impairment were taken into account so that PBPK models for the renal- and hepatic-impaired populations could be extrapolated and the dosage for these populations could be adjusted, with the adjustments being supplemented by normalization of the *in vivo* exposure in adults.

Due to the fragility and susceptibility of the geriatric, clinical drug development has historically favored younger and middle-aged adults. Although those aged 65 and older receive the majority of drug prescriptions, they continue to be underrepresented in clinical trials.[50] Consequently, there is a lack of knowledge regarding the PK and PD (Pharmacodynamics) responses of the elderly, rendering the safety and efficacy of drugs in this population uncertain.[51] To contribute to its elucidation, this study extrapolated the reaction of healthy adults to candesartan exposure to describe the reaction of healthy elderly individuals and elderly individuals with hepatic or renal impairment. The results indicate that elderly populations with hepatic and renal impairment should have their dosages adjusted on a similar scale to the healthy elderly population.

Although the PBPK model developed in this study has a stable structure and excellent predictive ability, several limitations must be considered when evaluating the results. One limitation is that all the data used were extracted using software from published literature. Even though these data were not obtained directly from the researchers, the PK parameters calculated from these extracted data points were comparable to previously reported PK parameters, for which minor errors were inevitable but within acceptable limits. As only the immediate-release formulation of candesartan was considered during the development of the PBPK model, the model only provides a broad explanation of the PKs of candesartan at various oral dosages. Using the findings of this study, however, the model can be further evaluated and optimized in future studies.

Conclusion

The PBPK model developed in this study contributes to a more accurate description of candesartan's PKs in elderly populations with renal and hepatic impairment. By incorporating changes in pathophysiological factors into the model and accurately extrapolating the model to these populations, this study demonstrated a method for enhancing the predictive capacity of the drug-disease model, thereby making it a valuable resource for future clinical individualized drug administration and evaluation.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (2017) No. 230. Written informed consent was obtained from individual or guardian participants.

Consent for publication

All the authors consent for publication.

Author contributions

Lingfeng Guo: Data curation; Formal analysis; Investigation; Resources; Software; Validation; Writing – original draft.

Xinyu Zhu: Data curation; Resources.

Lei Zhang: Data curation; Investigation.

Yichao Xu: Investigation; Software; Writing – review & editing.

Acknowledgements

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Major Science and Technology Projects of China (No. 2020ZX09201022).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data and materials included in this study are available upon request by contact with the corresponding author.

ORCID iD

Yichao Xu https://orcid.org/0000-0002-0476-9787

Supplemental material

Supplemental material for this article is available online.

References

1. James PA, Oparil S, Carter BL, *et al*. Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311: 507–520.
2. Kim JR, Kim S, Huh W, *et al*. No pharmacokinetic interactions between candesartan and amlodipine following multiple oral administrations in healthy subjects. *Drug Des Devel Ther* 2018; 12: 2475–2483.
3. Kassem I, Sanche S, Li J, *et al*. Population pharmacokinetics of candesartan in patients with chronic heart failure. *Clin Transl Sci* 2021; 14: 194–203.
4. Zhenfeng Z, Huilan S, Junya J, *et al*. A systematic review and meta-analysis of candesartan and losartan in the management of essential hypertension. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 365–374.
5. Rayner BL, Trinder YA, Baines D, *et al*. Effect of losartan versus candesartan on uric acid, renal function, and fibrinogen in patients with hypertension and hyperuricemia associated with diuretics. *Am J Hypertens* 2006; 19: 208–213.
6. Ross A and Papademetriou V. Candesartan cilexetil in cardiovascular disease. *Expert Rev Cardiovasc Ther* 2004; 2: 829–835.
7. Gleiter CH, Jagle C, Gresser U, *et al*. Candesartan. *Cardiovasc Drug Rev* 2004; 22: 263–284.
8. Mizutani T. PM frequencies of major CYPs in Asians and Caucasians. *Drug Metab Rev* 2003; 35: 99–106.
9. McInnes GT, O'Kane KP, Jonker J, *et al*. The efficacy and tolerability of candesartan cilexetil

in an elderly hypertensive population. *J Hum Hypertens* 1997; 11(Suppl. 2): S75–S80.

10. Morgan T and Anderson A. A comparison of candesartan, felodipine, and their combination in the treatment of elderly patients with systolic hypertension. *Am J Hypertens* 2002; 15: 544–549.
11. Hoen L, Pfeffer D, Zapf R, *et al*. Association of drug application and hydration status in elderly patients, *Nutrients* 2021; 13: 1929.
12. Hansson L, Zanchetti A, Carruthers SG, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. HOT Study Group. *Lancet (London, England)* 1998; 351: 1755–1762.
13. Ikeda H, Inoue T, Uemura S, *et al*. Effects of candesartan for middle-aged and elderly women with hypertension and menopausal-like symptoms. *Hypertens Res* 2006; 29: 1007–1012.
14. Choi WJ, Kim GA, Park J, *et al*. Incidence and pattern of aminotransferase elevation during anti-hypertensive therapy with angiotensin-II receptor blockers. *J Korean Med Sci* 2022; 37: e255.
15. Sager JE, Yu J, Ragueneau-Majlessi I, *et al*. Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches: a systematic review of published models, applications, and model verification. *Drug Metab Dispos* 2015; 43: 1823–1837.
16. Tan YM, Chan M, Chukwudebe A, *et al*. PBPK model reporting template for chemical risk assessment applications. *Regul Toxicol Pharmacol* 2020; 115: 104691.
17. Kuepfer L, Niederalt C, Wendl T, *et al*. Applied concepts in PBPK modeling: how to build a PBPK/PD model. *CPT Pharmacometrics Syst Pharmacol* 2016; 5: 516–531.
18. Zhuang X and Lu C. PBPK modeling and simulation in drug research and development. *Acta Pharm Sin B* 2016; 6: 430–440.
19. Kaur N, Narang A and Bansal AK. Use of biorelevant dissolution and PBPK modeling to predict oral drug absorption. *Eur J Pharm Biopharm* 2018; 129: 222–246.
20. Bouzom F, Ball K, Perdaems N, *et al*. Physiologically based pharmacokinetic (PBPK) modelling tools: how to fit with our needs? *Biopharm Drug Dispos* 2012; 33: 55–71.
21. Verscheijden LFM, Koenderink JB, Johnson TN, *et al*. Physiologically-based pharmacokinetic models for children: starting to reach maturation? *Pharmacol Ther* 2020; 211: 107541.
22. Utembe W, Clewell H, Sanabria N, *et al*. Current approaches and techniques in physiologically based pharmacokinetic (PBPK) modelling of nanomaterials. *Nanomaterials (Basel, Switzerland)* 2020; 10(7): 1267.
23. Zhang X, Yang Y, Grimstein M, *et al*. Application of PBPK modeling and simulation for regulatory decision making and its impact on US prescribing information: an update on the 2018–2019 submissions to the US FDA's Office of Clinical Pharmacology. *J Clin Pharmacol* 2020; 60(Suppl. 1): S160–S178.
24. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
25. Saharan VA. *Computer aided pharmaceutics and drug delivery: an application guide for students and researchers of pharmaceutical sciences*. Springer Nature, 2022.
26. Willmann S, Thelen K and Lippert J. Integration of dissolution into physiologically-based pharmacokinetic models III: PK-Sim®. *J Pharm Pharmacol* 2012; 64: 997–1007.
27. Nishimuta H, Houston JB and Galetin A. Hepatic, intestinal, renal, and plasma hydrolysis of prodrugs in human, cynomolgus monkey, dog, and rat: implications for *in vitro–in vivo* extrapolation of clearance of prodrugs. *Drug Metab Dispos* 2014; 42: 1522–1531.
28. Thelen K, Coboeken K, Willmann S, *et al*. Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, Part 1: Oral solutions. *J Pharm Sci* 2011; 100: 5324–5345.
29. Rodgers T, Leahy D and Rowland M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J Pharm Sci* 2005; 94: 1259–1276.
30. Gleiter CH and Mörike KE. Clinical pharmacokinetics of candesartan. *Clin Pharmacokinet* 2002; 41: 7–17.
31. Jung EH, Cho CK, Kang P, *et al*. Physiologically based pharmacokinetic modeling of candesartan related to CYP2C9 genetic polymorphism in adult and pediatric patients. *Arch Pharm Res* 2021; 44: 1109–1119.
32. Shen C, Liang D, Wang X, *et al*. Predictive performance and verification of physiologically

based pharmacokinetic model of propylthiouracil. *Front Pharmacol* 2022; 13: 1013432.

33. Malik PRV, Yeung CHT, Ismaeil S, *et al*. A physiological approach to pharmacokinetics in chronic kidney disease. *J Clin Pharmacol* 2020; 60(Suppl. 1): S52–S62.
34. Buter H, Navis GY, Woittiez AJ, *et al*. Pharmacokinetics and pharmacodynamics of candesartan cilexetil in patients with normal to severely impaired renal function. *Eur J Clin Pharmacol* 1999; 54: 953–958.
35. Kalam MN, Rasool MF, Alqahtani F, *et al*. Development and evaluation of a physiologically based pharmacokinetic drug-disease model of propranolol for suggesting model informed dosing in liver cirrhosis patients. *Drug Des Devel Ther* 2021; 15: 1195–1211.
36. Johnson TN, Boussery K, Rowland-Yeo K, *et al*. A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. *Clin Pharmacokinet* 2010; 49: 189–206.
37. Liu Y, Boettcher MF, Schmidt A, *et al*. Pharmacokinetics and safety of nifedipine GITS/candesartan fixed-dose combination in subjects with hepatic impairment. *Int J Clin Pharmacol Ther* 2017; 55: 246–255.
38. Jin YW and Ma YM. [Progress in methodology of establishing physiologically based pharmacokinetic models]. *Acta Pharm Sin* 2014; 49: 16–22.
39. Stader F, Kinvig H, Penny MA, *et al*. Physiologically based pharmacokinetic modelling to identify pharmacokinetic parameters driving drug exposure changes in the elderly. *Clin Pharmacokinet* 2020; 59: 383–401.
40. Strougo A, Yassen A, Krauwinkel W, *et al*. A semiphysiological population model for prediction of the pharmacokinetics of drugs under liver and renal disease conditions. *Drug Metab Dispos* 2011; 39: 1278–1287.
41. Xu Y, Chen J, Ruan Z, *et al*. Simulation of febuxostat pharmacokinetics in healthy subjects and patients with impaired kidney function using physiologically based pharmacokinetic modeling. *Biopharm Drug Dispos* 2022; 43: 140–151.
42. Chen J, Ruan Z, Lou H, *et al*. First-in-human study to investigate the safety and pharmacokinetics of salvianolic acid A and pharmacokinetic simulation using a physiologically based pharmacokinetic model. *Front Pharmacol* 2022; 13: 907208.
43. Jeon J-Y, Im Y-J, Kim Y, *et al*. Pharmacokinetic properties and bioequivalence of candesartan cilexetil in Korean healthy volunteers. *Drug Dev Ind Pharm* 2012; 39: 1296–1299.
44. Kumari Karra V, Rao Pilli N, Kumar Inamadugu J, *et al*. Simultaneous determination of pioglitazone and candesartan in human plasma by LC-MS/MS and its application to a human pharmacokinetic study. *J Pharm Anal* 2012; 2: 167–173.
45. Malerczyk C, Fuchs B, Belz GG, *et al*. Angiotensin II antagonism and plasma radioreceptor-kinetics of candesartan in man. *Br J Clin Pharmacol* 1998; 45: 567–573.
46. Ogawa R, Stachnik JM and Echizen H. Clinical pharmacokinetics of drugs in patients with heart failure: an update (part 2, drugs administered orally). *Clin Pharmacokinet* 2014; 53: 1083–1114.
47. Hafsa H, Zamir A, Rasool MF, *et al*. Development and evaluation of a physiologically based pharmacokinetic model of labetalol in healthy and diseased populations. *Pharmaceutics* 2022; 14: 2362.
48. Otsuka Y, Choules MP, Bonate PL, *et al*. Physiologically-based pharmacokinetic modeling for the prediction of a drug–drug interaction of combined effects on P-glycoprotein and cytochrome P450 3A. *CPT Pharmacometrics Syst Pharmacol* 2020; 9: 659–669.
49. Rowland Yeo K, Aarabi M, Jamei M, *et al*. Modeling and predicting drug pharmacokinetics in patients with renal impairment. *Expert Rev Clin Pharmacol* 2011; 14: 261–274.
50. Milton JC, Hill-Smith I and Jackson SH. Prescribing for older people. *BMJ* 2008; 336: 606–609.
51. Schlender JF, Meyer M, Thelen K, *et al*. Development of a whole-body physiologically based pharmacokinetic approach to assess the pharmacokinetics of drugs in elderly individuals. *Clin Pharmacokinet* 2016; 55: 1573–1589.