Simultaneously Predicting the Pharmacokinetics of CES1-Metabolized Drugs and Their Metabolites Using Physiologically Based Pharmacokinetic Model in Cirrhosis Subjects

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Article

Simultaneously Predicting the Pharmacokinetics of CES1-Metabolized Drugs and Their Metabolites Using Physiologically Based Pharmacokinetic Model in Cirrhosis Subjects

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Abstract: Hepatic carboxylesterase 1(CES1) metabolizes many prodrugs into active ingredients or direct-acting drugs into inactive metabolites. We aim to develop a semi-physiologically based pharmacokinetic model(Semi-PBPK model) to simultaneously predict pharmacokinetics of CES1 substrates and their active metabolites in liver cirrhosis(LC) patients. Six prodrugs(enalapril, benazepril, cilazapril, temocapril, perindopril and oseltamivir) and three direct-acting drugs (flumazenil, pethidine and remimazolam) were selected. The parameters including organ blood flows, plasma binding protein concentrations, functional liver volume, hepatic enzymatic activity, glomerular filtration rate(GFR) and gastrointestinal transit rate were introduced into the simulation. Pharmacokinetic profiles of these drugs and their active metabolites were simulated in 100 virtual subjects. The developed semi-PBPK model, following validation in healthy subjects, was extrapolated to LC patients. Most of the observations are within the 5% and 95% quantile of simulations from 100 virtual patients. The estimated AUC and C_{max} are within 0.5-2-fold of observation. The sensitivity analysis showed that the decreased plasma exposure of active metabolite due to the decreased CES1 was partly attenuated by the decreased GFR. Conclusion: The developed PBPK model has successfully predicted pharmacokinetics of CES1 substrates and their metabolites in healthy subjects and LC patients, which assists in tailoring dosages of CES1 substrates in LC patients.

Keywords: carboxylesterase 1; liver cirrhosis; physiologically based pharmacokinetic model; prodrugs; pharmacokinetics

1. Introduction

Liver cirrhosis (LC) is widely prevalent worldwide and results from different causes, such as obesity, non-alcoholic fatty liver disease, high alcohol consumption, hepatitis B or C infection, autoimmune diseases, cholestatic diseases, and iron or copper overload[1,2]. The Child-Pugh score is often used to classify liver cirrhosis into Child-Pugh A(CP-A), Child-Pugh B(CP-B) and Child-Pugh C(CP-C) according to the severity of LC[3,4]. In addition to impairment of hepatic functions, LC also leads to remarkable alterations in a series of other physiological parameters such as functional liver volume, hepatic artery blood flow, portal venous blood flow, glomerular filtration rate (GFR), α-acid glycoprotein, albumin content, drug-metabolizing enzymes and transporters. The alterations may directly affect the pharmacokinetics of drugs[5]. For example, Duthaler et al investigated effects of LC on pharmacokinetics of CYP450 cocktail probes caffeine(CYP1A2), efavirenz(CYP2B6), flurbiprofen(CYP2C9), omeprazole(CYP2C19), metoprolol(CYP2D6) and midazolam(CYP3A). They found that liver cirrhosis increased plasma exposure of tested probes, the extent of which is dependent on the type of probes and LC severity. The calculated ratio of AUC in patients to that in control subjects (AUCR)values of caffeine, efavirenz, flurbiprofen, omeprazole, metoprolol and midazolam in CP-C patients were 6.2, 0.8, 1.4, 10.5, 4.5 and 6.3, respectively. The calculated AUCR values of omeprazole in CP-A, CP-B and CP-C patients were separately 4.8, 6.5 and 10.5. The AUCR

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values of probes in LC patients were in line with those in the contents of hepatic CYP450s[6]. LC also affects renal excretion and intestinal absorption of drugs. Furosemide is mainly eliminated via kidney. It was reported[7] that clearance(CL) of furosemide was significantly decreased from 154 mL/min in control subjects to 91 mL/min in CP-B or CP-C patients, which mainly results from decreases in renal clearance(CL_K). These results indicate that adjustment of drug dosage for LC patients is required according to the LC severity. Thus, regulatory agencies have recommended pharmacokinetic studies of drugs in LC patients[8]. However, pharmacokinetic study in LC patients is usually costly and time-consuming. More importantly, it is difficult to recruit into patients, especially patients with CP-C. Physiologically based pharmacokinetic (PBPK) modeling is considered an ideal technique for predicting pharmacokinetics of drugs in patients with altered physiology. The alterations in physiological parameters, expressions of hepatic drug-metabolizing enzymes and transporters under various degree severity of LC have been demonstrated. The possibilities for predicting pharmacokinetics of drugs in LC patients using the PBPK model have been demonstrated[9].

Carboxylesterase1 (CES1) is one of the most abundant drug-metabolizing enzymes in human livers, comprising approximately 1% of the entire liver proteome. CES1 is responsible for 80%-95% of total hydrolytic activity in the liver, which mediates the metabolism of a wide range of drugs, pesticides, environmental pollutants, and endogenous compounds[10]. CES1-mediated metabolism leads to the biotransformation of a pharmacologically active drug into its inactive metabolite, as exemplified by methylphenidate hydrolysis. CES1 also mediates the activation of some prodrugs. The typical examples are some angiotensin-converting enzyme inhibitors (such as enalapril, cilazapril and temocapril) and neuraminidase inhibitors(oseltamivir). CES1 also hydrolyzes cholesteryl ester in lipid metabolism in human macrophages and hepatocytes, inferring that CES1 is a potential drug target for the treatment of metabolic diseases, such as diabetes and atherosclerosis[10–13]. LC has been demonstrated to significantly downregulate expressions of hepatic CES1 protein[9] and alter plasma exposure of its substrate drugs such as enalapril and oseltamivir[14,15]. Moreover, metabolites of most CES1 substrates (such as enalapril and oseltamivir) are mainly eliminated via renal excretion. LC also injures renal functions, leading to decreases in renal clearance of the metabolites, indicating that alterations in plasma exposure of metabolites by LC are attributed to integrated effects of the decreases in hepatic CES1 activity and renal clearance.

The study aimed to develop a semi-PBPK model incorporating alterations in hepatic CES1 activity, liver/renal functions, gastrointestinal transit rate and relevant organ blood to simultaneously predict pharmacokinetics of nine CES1 drugs(enalapril, benazepril, cilazapril, perindopril, temocapril, oseltamivir, flumazenil, pethidine and remimazolam) and their metabolites in LC patients. The predicted results were compared with clinical studies in patients with different statuses of LC. The results will assist in tailoring dosages of CES1 substrates in LC patients.

2. Materials and Methods

2.1. General Workflow

The workflow for developing a PBPK model (Figure 1) for LC patients. Initially, a PBPK model was developed for a virtual healthy subject population validated using clinical pharmacokinetic studies in healthy subjects. Then, the developed PBPK model was translated to LC patients by replacing the values of system-specific model parameters. Finally, pharmacokinetic predictions were conducted in 100 virtual patient populations (CL_{int}, $CL_{int,K}$, $f_{u,b}$, V_{system}, P_{eff}, k_a, $K_{L:P}$, $K_{G:P}$ and $K_{K:P}$ vary from 80%-120% of the parameter values) and compared with clinic pharmacokinetic data from the literature.

2.2. Model Development

A semi-PBPK model was developed to simultaneously predict pharmacokinetics of CES1 substrate drugs and their metabolites in LC patients. The semi-PBPK model consists of stomach, intestinal wall, intestinal lumen, portal vein, liver, kidney and systemic compartment.

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It was assumed that no absorption and metabolism of drugs occurs in stomach. The amount(A_0) in stomach is controlled by the constant of gastric emptying rate ($K_{t,0}$), i,e

$$\frac{dA_0}{dt} = -K_{t0} \times A_0 \quad (1)$$

Small intestine is divided into duodenum, jejunum and ileum, which is further divided into the gut lumen and the gut wall. Drug amount (A_i) in the i^{th} gut lumen is illustrated by

$$\frac{dA_i}{dt} = K_{t,i-1} \times A_{i-1} - K_{ti} \times A_i - k_{a,i} \times A_i \quad (2)$$

Where $K_{t,i}$ represents the constant of intestinal transit rate. $k_{a,i}$ represents the absorption rate constant from the gut lumen to the gut wall, which may be calculated using equation,

$$k_{ai} = \frac{2 \times P_{eff,A-B}}{r_i} \quad (3)$$

Where r_i is the intestinal radius. $P_{eff\ A\text{-}B}$ is effective permeability coefficient (P_{eff}) from gut lumen to gut wall. The P_{eff} ($\times 10^{-4}$) values were estimated using the in vitro apparent permeability coefficient of drugs ($P_{app} \times 10^{-6}$) in Caco-2 cells based the equation[16]:

$$LogP_{eff} = 0.4926 \times LogP_{app,Caco-2} - 0.1454 \quad (4)$$

The drug concentration in the i^{th} gut wall (C_{GWi}) is expressed as follows:

$$\frac{V_{GWi} \times dC_{GWi}}{dt} = k_{a,i} \times A_i + Q_{GWi} \times C_{sys} - Q_{GWi} \times C_{GWi} \times R_b / K_{G:P} \quad (5)$$

Where Q_{GWi} and $K_{G:P}$ represent the blood flow rate in i^{th} gut wall and ratio of drug concentration in intestinal wall to plasma, respectively. C_{GWi} and V_{GWi} represent separately drug concentration in the i^{th} intestinal and wall volume of the i^{th} gut wall. C_{sys} represent drug concentrations in the systemic compartment. R_b is the ratio of drug concentrations in blood to plasma.

The drug enters the liver through the portal vein and the concentration in the portal vein (C_{PV}) is:

$$\frac{V_{PV} \times dC_{PV}}{dt} = \sum Q_{GWi} \times C_{GWi} \times R_b / K_{G:P} - Q_{PV} \times C_{PV} \quad (6)$$

Q_{PV} and C_{PV} represent portal vein blood flow rate and volume of portal vein, respectively.

It was assumed that metabolism of CES1-mediated drugs mainly occurs in liver. Drug concentration (C_L) in liver is illustrated by

$$\frac{V_L \times dC_L}{dt} = Q_{PV} \times C_{PV} + Q_{LA} \times C_{sys} - Q_L \times C_L \times R_b / K_{L:P} - CL_{int} \times f_{u,b} \times C_L \times R_b / K_{L:P} \quad (7)$$

Where Q_{LA} and Q_L represent the hepatic artery blood flow rate to the liver and hepatic blood flow to the systemic compartment, respectively. V_L and $K_{L:P}$ represent the volume of liver and ratio of drug concentration in liver to plasma, respectively. CL_{int} and $f_{u,b}$ represent intrinsic clearance in the liver and free fraction of drug in blood, respectively. $f_{u,b}$ is generated from the fraction unbound in plasma ($f_{u,p}$), i.e

$$f_{u,b} = \frac{f_{u,p}}{R_b} \quad (8)$$

CL_{int} can be estimated using in vitro enzyme kinetics from human hepatic microsomes.

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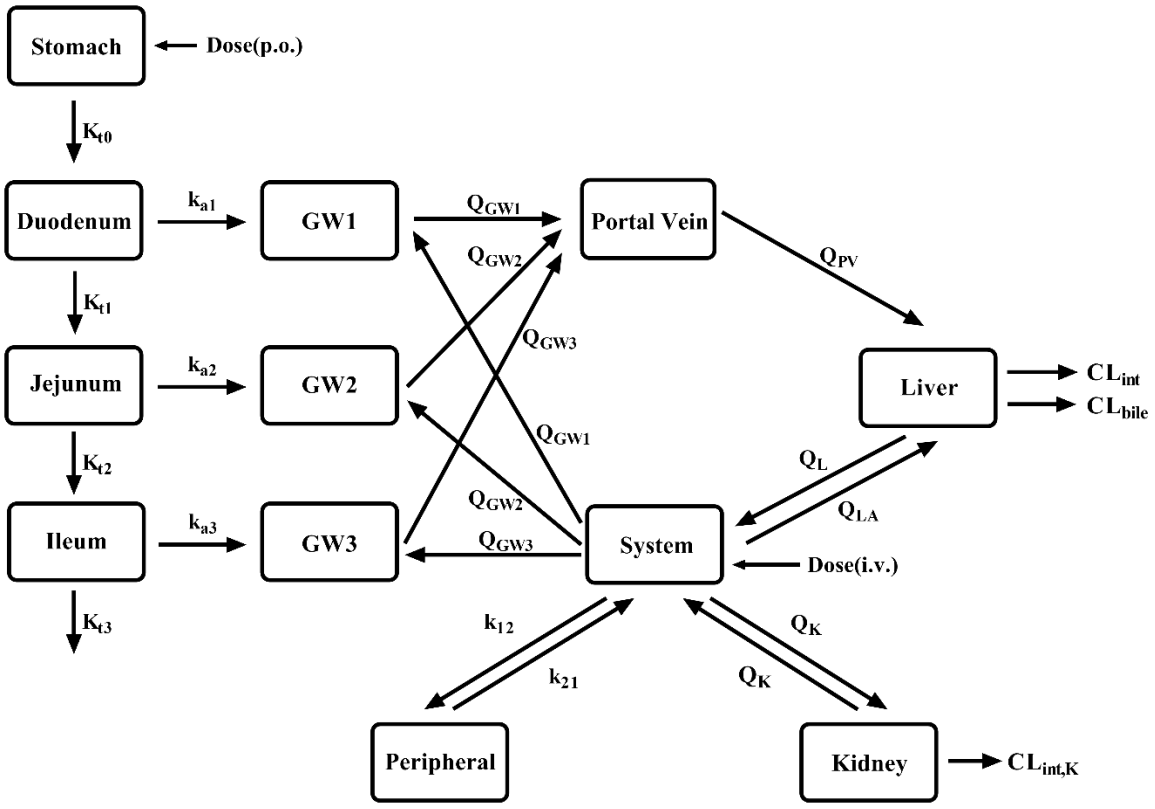

Figure 1. Schematic structure of the semi-PBPK model. K_{ti} represents the gastric emptying rate and intestinal transit rate, respectively. k_{ai} represents the rate of drug absorption into the gut wall. Q_{GWi} represents the blood flow rate in gut wall. Q_{LA}, Q_L and Q_{PV} represent the hepatic artery blood flow rate, hepatic blood flow rate and portal vein blood flow rate, respectively. CL_{int}, CL_{bile} and $CL_{int,K}$ represent the intrinsic hepatic clearance, biliary intrinsic clearance and renal intrinsic clearance, respectively.

$$CL_{int} = \Sigma \frac{V_{max,i}}{K_{m,i} + f_{u,b} \times \frac{A_L \times R_b}{V_L \times K_{L:P}}} \approx \Sigma \frac{V_{max,i}}{K_{m,i}} \quad (9)$$

Where $V_{max,i}$ and $K_{m,i}$ represent the maximum velocity and Michaelis-Menten constant in vitro enzyme kinetic experiments, respectively.

Hepatic clearance (CL_L) of a drug may be deprived from total CL(CL_T) and renal CL(CL_K), i.e

$$CL_L = CL_T - CL_K \quad (10)$$

Thus, The CL_{int} is also recalculated by hepatic blood clearance ($CL_{L,b}$) using equation

$$CL_{L,b} = \frac{Q_L \times f_{u,b} \times CL_{int}}{Q_L + f_{u,b} \times CL_{int}} \quad (11)$$

The CL values by clinic are often plasma clearance of drug (CL_p), which may be transferred to blood clearance (CL_b) using equation 12.

$$CL_b = \frac{CL_p}{1 - Hct + R_b \times Hct} \quad (12)$$

Where Hct is hematocrit, 0.43 in healthy subjects[17].

Some metabolites of some drugs are also eliminated via bile. Amount of metabolites ($A_{L,m}$) in liver is illustrated by equation 13.

$$\begin{aligned} \frac{V_L \times dC_{L,m}}{dt} = {} & Q_{PV} \times C_{PV,m} + Q_{LA} \times C_{sys,m} + CL_{int,CSE1} \times f_{u,b} \times C_L \times R_b / K_{L:p} \\ & - Q_L \times C_{L,m} \times R_{b,m} / K_{L:P,m} \\ & - (CL_{int,m} + CL_{int,b,m}) \times f_{u,b,m} \times C_{L,m} \times R_{b,m} / K_{L:P,m} \end{aligned} \quad (13)$$

Where $CL_{int,b,m}$ and $CL_{int,\ m}$ are intrinsic bile clearance and intrinsic metabolic clearance, respectively. If metabolism of the metabolite did not occur in the body, the $CL_{int,b,m}$ may be recalculated from CL_K using equations 10 and 11.

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Kidney is involved in elimination of drugs, especially their metabolites. Amount of drugs in kidney is illustrated by equation

$$\frac{V_K \times dC_K}{dt} = Q_K \times C_{sys} - (Q_K + f_{u,b} \times CL_{int,K}) \times C_K \times R_b / K_{K,P} \quad (14)$$

Where Q_K and V_K represent kidney blood flow and volume of the kidney, respectively. $CL_{int,K}$ and $K_{K,P}$ represent intrinsic clearance in kidney and tissue-to-plasma concentration ratio in the kidney, respectively. $CL_{int,K}$ was also estimated from CL_K using equation 11.

Disposition of drugs in the systemic compartment is illustrated using one-compartment, two-compartment model or three-compartment model.

For one-compartment model

Drug concentration (C_{sys}) in systemic compartment

$$\frac{V_{sys} \times dC_{sys}}{dt} = Q_L \times C_L \times R_b / K_{L:p} + Q_K \times C_K \times R_b / K_{K:p} - (Q_{LA} + Q_K) \times C_{sys} - \sum Q_{GWi} \times C_{sys} \quad (15)$$

For two-compartment model

Drug concentration (C_{sys}) in systemic compartment.

$$\frac{V_{sys} \times dC_{sys}}{dt} = Q_L \times C_L \times R_b / K_{L:P} + Q_K \times C_K \times R_b / K_{K:P} + k_{21} \times A_p - k_{12} \times V_{sys} \times C_{sys} - (Q_K + Q_{LA}) \times C_{sys} - \sum Q_{GWi} \times C_{sys} \quad (16)$$

$$\frac{dA_P}{dt} = k_{12} \times V_{sys} \times C_{sys} - k_{21} \times A_P \quad (17)$$

For three-compartment model

Drug concentration (C_{sys}) in systemic compartment.

$$\frac{V_{sys} \times dC_{sys}}{dt} = Q_L \times C_L \times R_b / K_{L:P} + Q_K \times C_K \times R_b / K_{K:P} + k_{21} \times A_{p1} - k_{12} \times V_{sys} \times C_{sys} + k_{31} \times A_{p2} - k_{13} \times V_{sys} \times C_{sys} - (Q_K + Q_{LA}) \times C_{sys} - \sum Q_{GWi} \times C_{sys} \quad (18)$$

$$\frac{dA_{P1}}{dt} = k_{12} \times V_{sys} \times C_{sys} - k_{21} \times A_{P1} \quad (19)$$

$$\frac{dA_{P2}}{dt} = k_{13} \times V_{sys} \times C_{sys} - k_{31} \times A_{P2} \quad (20)$$

Where V_{sys} represents the apparent distribution volume in systemic compartment. A_P and A_{P1} are the amount of drug in two peripheral compartments. k_{12}, k_{21}, k_{13} and k_{31} represent the transfer rates between the systemic compartment and peripheral compartment, respectively.

All available information on anatomical physiological and ADME parameters of the tested drugs was collected for the initial model construction (Table 1 and Table 2). Coding and solving of the PBPK model were conducted on WinNonlin 8.1 (Pharsight, St. Louis, MO, USA). After the initial model was developed, part of plasma concentrations-curves of drugs from healthy subjects were used to estimate and optimize some parameters. Then, the developed PBPK model was validated using plasma concentration-time curves from the rest of clinical studies.

2.3. PBPK model development in LC patients

The anatomical and physiological parameters in healthy subjects were replaced with those (Table 1) in LC patients. The LC-induced alterations in parameters related to ADME were estimated according to their values in healthy(HT) subjects and the altered physiological parameters.

For CES1-mediated hepatic metabolism

$$CL_{int,CI,CES1} = CL_{int,HT,CES1} \times f_{CES1} \times f_{liver} \quad (21)$$

Where $CL_{int,CI,CES1}$ and $CL_{int,HT,CES1}$ represent the values of CES1-mediated intrinsic clearance in liver of patients and healthy subjects, respectively. f_{CES1} and f_{liver} represent the ratio of CES1 content in patients to healthy subjects and liver volume in patients to healthy subjects, respectively.

Table 1. Physiological parameters used in the physiologically based pharmacokinetic model in normal adults[18,19] and cirrhosis.

	Normal	Child-Pugh class			Units
		A	B	C	

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Blood flow rates					
Liver	1450	1436.5	1176.9	1656.3	mL/min
Hepatic arterial	300	390[17]	486.9[9]	1020[17]	mL/min
Portal vein	1150	1046.5[9]	690[20]	636.3[9]	mL/min
Kidney	1240	1091.2[17]	806[17]	595.2[17]	mL/min
Duodenum	45	45	45	45	mL/min
Jejunum	173	173	173	173	mL/min
Ileum	102	102	102	102	mL/min
Volume					
Liver	1690	1368.9[21]	1098.5[21]	895.7[21]	mL
Portal vein	70	70	70	70	mL
Kidney	280	280	280	280	mL
Duodenum	21	21	21	21	mL
Jejunum	63	63	63	63	mL
Ileum	42	42	42	42	mL
Transit rates					
Stomach	0.04	0.0504[22]	0.0504[22]	0.0504[22]	min^{-1}
Duodenum	0.07	0.0889[22]	0.0889[22]	0.0889[22]	min^{-1}
Jejunum	0.03	0.0381[22]	0.0381[22]	0.0381[22]	min^{-1}
Ileum	0.04	0.0508[22]	0.0508[22]	0.0508[22]	min^{-1}
Gut radius					
r1	2	2	2	2	cm
r2	1.63	1.63	1.63	1.63	cm
r3	1.45	1.45	1.45	1.45	cm
Glomerular filtration rate	105	82[23]	82[23]	82[23]	mL/min
Albumin	44.7	36.2[17]	30.4[17]	26.3[9]	g/L
α1-acid glycoprotein	0.8	0.57[21]	0.52[21]	0.46[21]	g/L
CES1	2.45	2.45[9]	1.715[9]	0.735[9]	mg/g Liver
CYP2B6	17	17[21]	15.3[21]	13.6[21]	pmol/mg
Lactulose/Rhamnose ratio	0.037	0.046[24]	0.052[24]	0.057[24]	/
MRP2 ratio	1	0.54[20]	0.54[20]	0.54[20]	/

Table 2. Simultaneously predicting the pharmacokinetics of CES1-metabolized drugs and their metabolites using the physiologically based pharmacokinetic model.

Drug	logP	pka	CL_{int}	V_{max}	K_m	$K_{L:P^d}$	$K_{G:P^d}$	$K_{K:P^d}$	CL_b
			mL/min	nmoL/min/mg protein	μmol/L				mL/min
Enalapril	0.59[25]	5.20[25]	784[26]	/	/	1.66	2.29	1.79	/
Enalaprilat	-0.74[27]	2.03[27]	/	/	/	1.12	1.04	1.25	/
Oseltamivir	0.36[28]	7.7[28]	20255.4[28]	/	/	1.19	1.12	1.29	/
OC	-1.3[a]	4.19[a]	/	/	/	1.71	1.89	1.91	/

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Benazepril	1.11[29]	4.74[29]	6696[30]	/	/	0.087	0.122	0.088	385.8[31] [g]
Benazepril at	0.56[29]	1.97[29]	/	/	/	0.093	0.088	0.101	/
Cilazapril	0.55[32]	3.3[33]	199.7 [c]	/	/	1.32	1.31	1.43	205[a]
Cilazaprilat	-0.48[a]	3.17 [a]	/	/	/	1.28	1.22	1.42	/
Temocapril	2.102[34]	2.8[35]	5359.7[36]	/	/	2.82	3.17	2.47	/
Temocapril at	2.215[37]	2.09[38]	/	/	/	0.289	0.322	0.251	/
Perindopril	-1.31[39]	3.2[40]	1011.15[41] 156.47[42] [c, j]	/	/	0.665	0.633	0.742	/
Perindopril at	-0.08[a]	3.08[a]	/	/	/	1.45	1.38	1.61	/
Remimazolam	3.68[a]	5.99[a]	79212.96[c]	/	/	36.34	63.19	31.2	1180[43]
Flumazenil	1.64[44]	0.86[45]	8169.9[c]	/	/	2.57	2.71	2.41	1120[46]
Pethidine	2.35[47]	8.7[47]	/	1.56[48] [h] 5.382[49] [i]	261[48] [h] 356[49] [i]	14.82	4.18	12.02	/

Drug	V_{sys}	K_{12}	K_{21}	$P_{eff,A-B}$	$CL_{int,K}$	R_b	$f_{u,b}$	F	k_a
	L	min^{-1}	min^{-1}	10^{-4}cm/s	mL/min				1/min
Enalapril	40[50]	/	/	1.60[51]	624.6[52]	0.74[53]	0.74[27]	/	
Enalaprilat	46.1[54]	0.001[54]	0.0009[54]	/	186.4[55]	0.73[53]	0.68[27]	/	
Oseltamivir	61.289[56] [f]	/	/	/	1357.95[57]	1[e]	0.58[28]	/	0.061[58] [g]
OC	160.729[59] [f]	/	/	/	438.5[60]	1[e]	0.97[28]	/	
Benazepril	4.8[61] [g]	0.0215[61] [g]	0.0238[61] [g]	1.21[62]	8391.6[c]	1[e]	0.03[63]	0.35[50]	
Benazepril at	1.204[64] [f]	0.0438[64] [f]	0.00837[64] [f]	/	447.9[63]	1[e]	0.05[63]	/	
Cilazapril	18.23[65] [f]	0.00325[65] [f]	0.00155[65] [f]	/	118.095[66]	1[e]	0.7[32]	/	0.099[67] [g]
Cilazaprilat	10.3517[65] [f]	0.00084[65] [f]	0.008[65] [f]	/	75.48[66]	1[e]	0.76[68]	/	/
Temocapril	15.398[69] [g]	/	/	/	110.2[70]	1[e]	0.3[38]	0.65[71]	0.065[69] [g]
Temocapril at	58.535[72] [f]	0.00184[72] [f]	0.000078[72] [f]	/	949.84[73] 1899.68[74] [b]	1[e]	0.025[38]	/	/
Perindopril	13.119[75] [g]	0.0028[75] [g]	0.0024[75] [g]	1.34[30]	130.2[76]	1[e]	0.4[77]	0.66[73]	/

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Perindopril at	53.44[78] f	0.271[78] f	0.0996[78] f	/	231.78[79]	1 e	0.85[77]	/	/
Remimazolam	15.0768[80]	0.01638[80] 0.3117[80](K13)	0.000476[80] 0.5057[80](K31)	/	/	1 e	0.08[81]	/	
Flumazenil	24.054[82] g	0.0376[82] g	0.0427[82] g	3.78[83]	1.67[84]	1[85]	0.6[86]	/	
Pethidine	328.676[87] f	0.002224[87] f	0.0003697[87] f	/	58.78[88]	0.87[89]	0.48[49]	/	0.117[90] g

a: Data from www.drugbank.com; b: bile intrinsic clearance of temocaprilat; c: recalculated from $CL_{L,b}$; d: Calculations using Rodgers-Rowland method; e: Assumed values; f: Simulation by WinNonlin, cilazapril and cilazaprilat using 0.5 mg dose pharmacokinetic, remimazolam using 0.025mg/kg dose pharmacokinetic and flumazenil using T.F. pharmacokinetic to simulation; g: Calculated by WinNonlin; h: CES1-mediated CL_{int}; i: CYP2B6-mediated CL_{int}; j: UGT intrinsic clearance of perindopril.

For hepatic elimination of drug mediated by other routes

$$CL_{int,CI,other} = CL_{int,HT} \times f_{other} \times f_{liver} \quad (22)$$

Where $CL_{int,cirr,other}$ and $CL_{int,heal,other}$ represent the values of intrinsic clearance by other routes in liver of patients and healthy subjects, respectively. f_{other} is ratio of other target content in patients to healthy subjects.

Among the tested drugs, pethidine binds mainly to α1-acid glycoprotein and the rest bind mainly to albumin[49,91–97] (no data on binding protein for temocapril, so binding to albumin was assumed based on pka < 7.4, acidic). Free fraction of drug in patient plasma was estimated using equation 23[21]:

$$f_{u,p,CI} = \frac{1}{1 + \frac{(1 - f_{u,p,HT}) \times P_{prot,CI}}{P_{prot,HT} \times f_{u,p,HT}}} \quad (23)$$

Where $f_{u,p,CI}$, $f_{u,p,HT}$, $P_{prot,CI}$ and $P_{prot,HT}$ represent unbound fraction of the drug in plasma of patients and healthy subjects, concentration of drug-bound proteins in plasma of patient and healthy subjects, respectively.

It was assumed that the free apparent volume of distribution of the drug is unaltered, the apparent volume of distribution in cirrhosis patients ($V_{sys,CI}$) was derived from the apparent volume of distribution in healthy subjects, i,e.

$$V_{sys,CI} = \frac{f_{u,p,CI}}{f_{u,p,HT}} \times V_{sys,HT} \quad (24)$$

Liver cirrhosis also impairs renal function and is characterized by decreases in glomerular filtration rate(GFR). The renal intrinsic clearance($CL_{int,\ K,CI}$) in patients may be estimated using equation[17]:

$$CL_{int,K,CI} = CL_{int,K,HT} \times GFR_{CI}/GFR_{HT} \quad (25)$$

Where $CL_{int,k,HT}$, GFR_{HT} and GFR_{CI} represent renal intrinsic clearance in healthy subjects, GFR in healthy subjects and patients, respectively.

Lactulose/Rhamnose ratio is used to assess intestinal permeability[24]. The ratio of cirrhosis patients to healthy subjects was used to correct the absorption rate constant in LC patients.

One hundred virtual populations in healthy subjects, CP-A, CP-B and CP-C patients based on parameters (such as $f_{u,b}$, $CL_{int,K}$, $CL_{int,\ L}$ and $k_{a,i}$) related to ADME process of drugs were randomly generated for population simulation. Effects of cirrhosis on plasma exposure of the tested drugs were indexed as AUCR or C_{max}R

$$AUCR = \frac{AUC_{CI}}{AUC_{HT}} \quad (26)$$

Or

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$$AUCR = \frac{CL_{HT}}{CL_{CI}} \quad (27)$$

$$C_{max}R = \frac{C_{max,CI}}{C_{max,HT}} \quad (28)$$

Where AUC_{CI}, AUC_{HT}, CL_{CI}, CL_{HT}, $C_{max,CI}$ and $C_{max,HT}$ are respectively AUC, CL and C_{max} of the tested drugs in cirrhosis patients and healthy subjects.

2.4. Criterion of the developed PBPK model.

The PBPK model was considered to be successful if the simulated AUC or C_{max} fell within 0.5- to 2-fold of the observed data or the observed data were within the 5th and 95th percentiles of the simulation derived from 100 virtual subjects.

3. Results

3.1. Collection of data and selection of the tested drugs

Liver cirrhosis obviously alters CES1 enzyme content. The CES1 contents in CP-B patients and CP-C patients were respectively reported to decrease to 70% and 30% of healthy subjects, the CES1 enzyme content in CP-A patients was comparable to that of healthy subjects[9]. LC also leads to alterations in other physiological parameters such as liver volume, hepatic blood flow, renal blood flow, GFR and intestinal transit, which are listed in Table 1.

Clinical pharmacokinetic studies of the CES1 drugs were collected from data published on PubMed based on the following criteria. (1) the tested drug must be metabolized primarily by CES1. (2) pharmacokinetic parameters (such as AUC or plasma drug concentrations) following intravenous (i.v.) and/or oral (p.o.) administration to liver cirrhosis populations must be available. (3) the clinical pharmacokinetic data might come from different reports. Based on these criteria, nine CES1 substrates were included in the simulations. The nine drugs are primarily metabolized by CES1, which included six prodrugs (enalapril, benazepril, cilazapril, perindopril, temocapril and oseltamivir) and three direct-acting drugs (flumazenil, pethidine and remimazolam). Flumazenil and remimazolam are mainly administered by intravenous injection. Pethidine is administrated via intravenous or oral routes. The remaining drugs are administered as oral immediate-release formulations. The parameters related to drugs in the PBPK simulation are listed in Table 2. The detailed information on clinic reports of the tested drugs is illustrated in Table 3.

Enalapril and enalaprilat

Enalapril, an angiotensin-converting enzyme inhibitor (ACEI), is the prodrug, which is mainly metabolized to active product enalaprilat via hepatic CES1[12,98]. Enalaprilat is eliminated primarily through the kidneys[99]. In plasma, enalapril and enalaprilat are mainly bound to albumin, whose free factions in plasma are 0.55 and 0.5[27]. Five clinic reports including two reports involving liver cirrhosis were selected in the simulations.

Benazepril and benazeprilat

Benazepril, a prodrug, is metabolized by hepatic CES1 to the active product benazeprilat[12,98], showing inhibition of angiotensin-converting enzyme. Benazeprilat is eliminated via renal excretion. Benazepril and benazeprilat are mainly bound to albumin, belonging to drugs with high plasma binding, whose free factions in plasma are 0.03 and 0.05[63], respectively. Six clinic reports including one report involving liver cirrhosis were selected in the simulations.

Cilazapril and cilazaprilat

Cilazapril is also metabolized by hepatic CES1 into cilazaprilat[12,98]. Cilazaprilat is mainly eliminated via kidney[66]. Cilazapril and cilazaprilat are mainly bound to albumin, belonging to medium plasma binding, whose free factions in plasma are 0.70 and 0.76[33], respectively. Six clinic reports including one report involving liver cirrhosis were selected in the simulations.

Perindopril and perindoprilat

Prodrug perindopril is mainly metabolized by hepatic CES1 to perindoprilat, showing its inhibition of ACE. The bioavailability of perindopril is 66%[73]. Perindopril is primarily converted to

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perindoprilat in the liver and other major metabolites of perindopril are perindopril glucuronide and perindopril lactam[100]. Since it is not clear which isoenzyme of UGT metabolizes perindopril to perindopril glucuronide, the change rate of $AUC_{0\text{-}inf}$ (0.62) for metoprolol in cirrhosis was used as a variation coefficient of intrinsic clearance for UGT[101]. Perindoprilat is eliminated via renal excretion. Perindopril and perindoprilat are predominantly bound to albumin. Perindopril shows higher plasma binding(percent binding 60%) than that of perindoprilat(mean percent binding 15%)[77]. Four clinic reports including two reports involving liver cirrhosis were selected in the simulations. Cirrhosis in perindopril and perindoprilat have only pharmacokinetic parameters and no specific drug concentration-time profile, so only a comparison of parameters was made.

Table 3. Clinic information about CES1 substrates in the simulations.

No	Authors	Drug	Dose (mg)	*Analytes*	Subjects(n)	Ref
1	Ohnishi A et al. 1989	enalapril maleate	10, p.o	enalapril, enalaprilat	Healthy (7)	[14]
		enalapril maleate	10, p.o	enalapril, enalaprilat	CP-C (7)	
2	Todd PA et al. 1986	enalapril maleate	10, p.o	enalapril, enalaprilat	Healthy(12)	[102]
3	Weisser K et al.1991	enalapril maleate	10, p.o	enalapril, enalaprilat	Healthy (8)	[103]
4	Dickstein K et al. 1987	enalapril maleate	10, p.o	enalapril, enalaprilat	Healthy(10)	[104]
5	Baba T et al. 1990	enalapril maleate	10 , p.o	enalapril, enalaprilat	CP-B (7)	[105]
6	Kaiser G et al. 1989	benazepril.HC1	10, p.o	benazepril, benazeprilat	Healthy(59)	[106]
7	Schweizer C et al. 1993	benazepril.HC1	10,p.o	benazepril, benazeprilat	Healthy(11)	[107]
8	Sioufi A et al.1994	benazepril.HC1	20 , p.o	benazepril, benazeprilat	Healthy(24)	[108]
9	Waldmeier F et al. 1991	benazepril.HC1	20, p.o	benazepril, benazeprilat	Healthy (4)	[109]
10	Kaiser G et al. 1990	benazepril.HC1	20, p.o	benazepril, benazeprilat	CP-B(12)	[110]
11	Macdonald NJ et al.1993	benazepril HCl	10 , p.o	benazeprilat	Healthy(18)	[111]
12	Massarella J et al 1989	cilazapril	1.0,2.5,5, p.o	cilazapril, cilazaprilat	Healthy(24)	[65]
13	Williams PEO et al. 1990	cilazapril	2.5,p.o	cilazapril, cilazaprilat	Healthy(13)	[112]
14	Gross V et al.1993	cilazapril	1,p.o	cilazapril, cilazaprilat	Healthy(10)	[113]
		cilazapril	1,p.o	cilazapril, cilazaprilat	CP-B(9)	
15	Williams PEO et al. 1989	cilazapril	1,p.o	cilazapril, cilazaprilat	Healthy(12)	[114]
16	Massarella JW et al. 1989	cilazapril	5.p.o	cilazapril, cilazaprilat	Healthy(16)	[115]
17	Francis RJ et al. 1987	cilazapril	1.25,2.5,5,10,p.o	cilazaprilat	Healthy(12)	[116]
18	Lecocq B et al. 1990	perindopril[a]	4,p.o	perindopril, perindoprilat	Healthy(12)	[117]
19	Tsai HH et al. 1989	perindopril[a]	8,p.o	perindopril, perindoprilat	CP-A(8)	[118]
20	Thiollet M et al. 1992	perindopril[a]	8,p.o	perindopril, perindoprilat	CP-B(10)	[119]
21	Lees KR et al. 1988	perindopril[a]	8,p.o	perindoprilat	Healthy(8)	[120]
22	Furuta S et al. 1993	temocapril HCL	1.p.o	temocapril, temocaprilat	Healthy(6)	[121]
		temocapril HCL	1,p.o	temocapril, temocaprilat	CP-C(7)	

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No	Authors	Drug	Dose (mg)	*Analytes*	Subjects(n)	Ref
23	Abe M et al. 2006	oseltamivir[b]	75,p.o	oseltamivir,OC	Healthy(7)	[122]
24	Brewster M et al. 2006	oseltamivir[b]	75,p.o	oseltamivir,OC	Healthy(18)	[123]
25	Jittamala P et al. 2014	oseltamivir[b]	75,p.o	oseltamivir,OC	Healthy(12)	[124]
26	Snell P et al. 2005	oseltamivir[b]	150,p.o	oseltamivir,OC	Healthy(12)	[15]
		oseltamivir[b]	75, p.o	oseltamivir,OC	CP-B(11)	
27	Amrei R et al. 1990	flumazenil	10mg,i.v.	flumazenil	Healthy(NA)	[125]
28	Breimer LTM et al. 1991	flumazenil	10/10 min,iv	flumazenil	Healthy(7)	[126]
29	Pomier-Layrargues G et al. 1989	flumazenil	2/5min,iv	flumazenil	CP-B(8)	[127]
		flumazenil	2/5min,iv	flumazenil	CP-C(8)	
30	Klotz U, et al.1984	flumazenil	2.5,i.v	flumazenil	Healthy(6)	[82]
31	Janssen U,et al.1989	flumazenil	30 p.o	flumazenil	Healthy(8)	[128]
		flumazenil	2,i.v; 30 p.o	flumazenil	CP-C(8)	
32	Verbeeck RK et al.1981	pethidine HCL	25,i.v	pethidine	Healthy(6)	[129]
		pethidine HCL	25,p.o	pethidine	Healthy(6)	
33	Mather LE et al. 1975	pethidine HCL	50,i.v	pethidine	Healthy(4)	[130]
34	Kuhnert BR et al. 1980	pethidine HCL	50,i.v	pethidine	Healthy(7)	[131]
35	Guay DR et al. 1984	pethidine HCL	70,i.v	pethidine	Healthy(8)	[132]
36	Guay DR et al. 1985	pethidine HCL	70,i.v	pethidine	Healthy(8)	[133]
37	Pond SM et al. 1981	pethidine HCL	60, iv;112, po	pethidine	CP-A (5)	[134]
38	Pond SM et al. 1980	pethidine HCL	54.4, iv;108.8, po	pethidine	CP-B (4)	[135]
39	Mather LE et al. 1976	pethidine HCL	50, iv;100, po	pethidine	Healthy(4)	[136]
40	Klotz U et al. 1974	pethidine HCL	63.9,i.v	pethidine	Healthy(8)	[137]
		pethidine HCL	53.1,i.v	pethidine	CP-A(10)	
41	Neal EA et al. 1979	pethidine HCL	56, iv; 56, po	pethidine	Healthy(4)	[138]
		pethidine HCL	56, iv; 56, po	pethidine	CP-A(8)	
42	Sheng XY et al. 2020	remimazolam besylate	1.5425,3.315,i.v	remimazolam	Healthy(3)	[80]
		remimazolam besylate	4.8675,6.18,i.v	remimazolam	Healthy(7)	
		remimazolam besylate	13.26,24.6,i.v	remimazolam	Healthy(8)	
		remimazolam besylate	18.3,i.v	remimazolam	Healthy(10)	
43	Stohr T et al. 2021	remimazolam besylate	10.4,i.v	remimazolam	CP-B(8)	[139]
		remimazolam besylate	8.2,i.v	remimazolam	CP-C(3)	

a, perindopril tert-butylamine; b, oseltamivir phosphate.

Temocapril and temocaprilat

Temocapril is also a prodrug and metabolized by hepatic CES1 to temocaprilat. Temocaprilat is eliminated via both bile and kidney. The biliary clearance of temocaprilat was about 2-fold of renal clearance[74]. The $CL_{int,K}$ of temocaprilat was calculated to be 949.84 mL/min[73]. Thus, $CL_{bile,m}$ of temocaprilat was estimated to be 1899.68 mL/min, assuming that the ratio of $CL_{bile,m}$ to $CL_{int,K}$ was 2.0. Biliary excretion of temocaprilat is considered to be mediated by multidrug resistance-associated

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protein2(MRP2)[140]. One clinic report involving both liver cirrhosis patients and healthy subjects was selected in the simulations.

Oseltamivir and oseltamivir carboxylate

Oseltamivir, a prodrug, is metabolized via hepatic CES1[12,98] to its active metabolite oseltamivir carboxylate (OC) which has an antiviral effect. About 80% of an orally administered dose of oseltamivir reaches the systemic circulation as the active metabolite. The absolute bioavailability of the active metabolite from orally administered oseltamivir is 75%[141]. About 60 to 70% of an oral oseltamivir dose appears in urine as the active metabolite, and less than 5% as oseltamivir. Oseltamivir carboxylate is primarily eliminated via renal excretion, accounting for 93% of intravenous dose[57]. $CL_{int,K}$ values of both oseltamivir and oseltamivir carboxylate exceed GFR, indicating that renal elimination occurs via a combination of glomerular filtration and renal tubular secretion. Both oseltamivir and oseltamivir carboxylate are primarily bound to albumin; their bound fractions in plasma were approximately 42% and less than 3%[28]. Four clinic reports including one report involving liver cirrhosis were selected in the simulations.

Flumazenil

Flumazenil, a benzodiazepine receptor antagonist, is usually administered by intravenous injection[84]. Flumazenil was inactivated by hepatic CES1 to flumazenil acid and probably by CYP450 catalyzed N-dealkylation to N-demethylated flumazenil[142]. Flumazenil was predominantly bound to serum albumin, whose plasma protein binding is about 40%[86]. Five clinic reports including two reports involving liver cirrhosis were selected in the simulations.

Pethidine

Pethidine(meperidine) is a synthetic opioid commonly used for analgesia in humans. Pethidine is metabolized in the body by two different pathways[49,98]. The predominant pathway is hepatic CES1 metabolism to pethidinic acid, an inactive metabolite. Another pathway is N-demethylation by CYP2B6 to normeperidine, a nonopioid active metabolite. Oral bioavailability of pethidine varies from 48% -56%[143]. Pethidine was predominantly bound to α1-acid glycoprotein. In the simulation for healthy subjects, free fraction of pethidine in plasma was 0.418[49]. Ten clinic reports including four reports involving liver cirrhosis were selected in the simulations.

Remimazolam

Remimazolam, as an ultrashort-acting sedative agent, is metabolized by hepatic CES1 to inactive carboxy acid metabolite. The plasma protein binding of remimazolam is approximately 92%, predominantly serum albumin[81]. In the clinic, remimazolam is normally administered intravenously. Two clinic reports including one report involving liver cirrhosis were selected in the simulations.

3.2. Development of PBPK model and validation using pharmacokinetic parameters from healthy subjects following i.v. or oral administrations

Plasma concentration-time profiles of the tested CES1 substrates and their active metabolites following i.v. or oral administration to healthy subjects were simulated using the developed PBPK model and compared with clinic observations. The results showed that most of the observed data of the tested agents fell within the 5th and 95th percentiles of the simulated data (Figure 2 and Figure S1). The corresponding pharmacokinetic parameters AUC, CL and C_{max} were estimated using the mean of the simulated profiles derived from 100 virtual individuals and compared with clinic observations (Table S1-S9). Most of the simulated pharmacokinetic parameters (AUC, CL and C_{max}) values for all drugs were also within two-fold of observations (Table S1-S9 and Figure 3). All the results demonstrated that the PBPK model was successfully developed.

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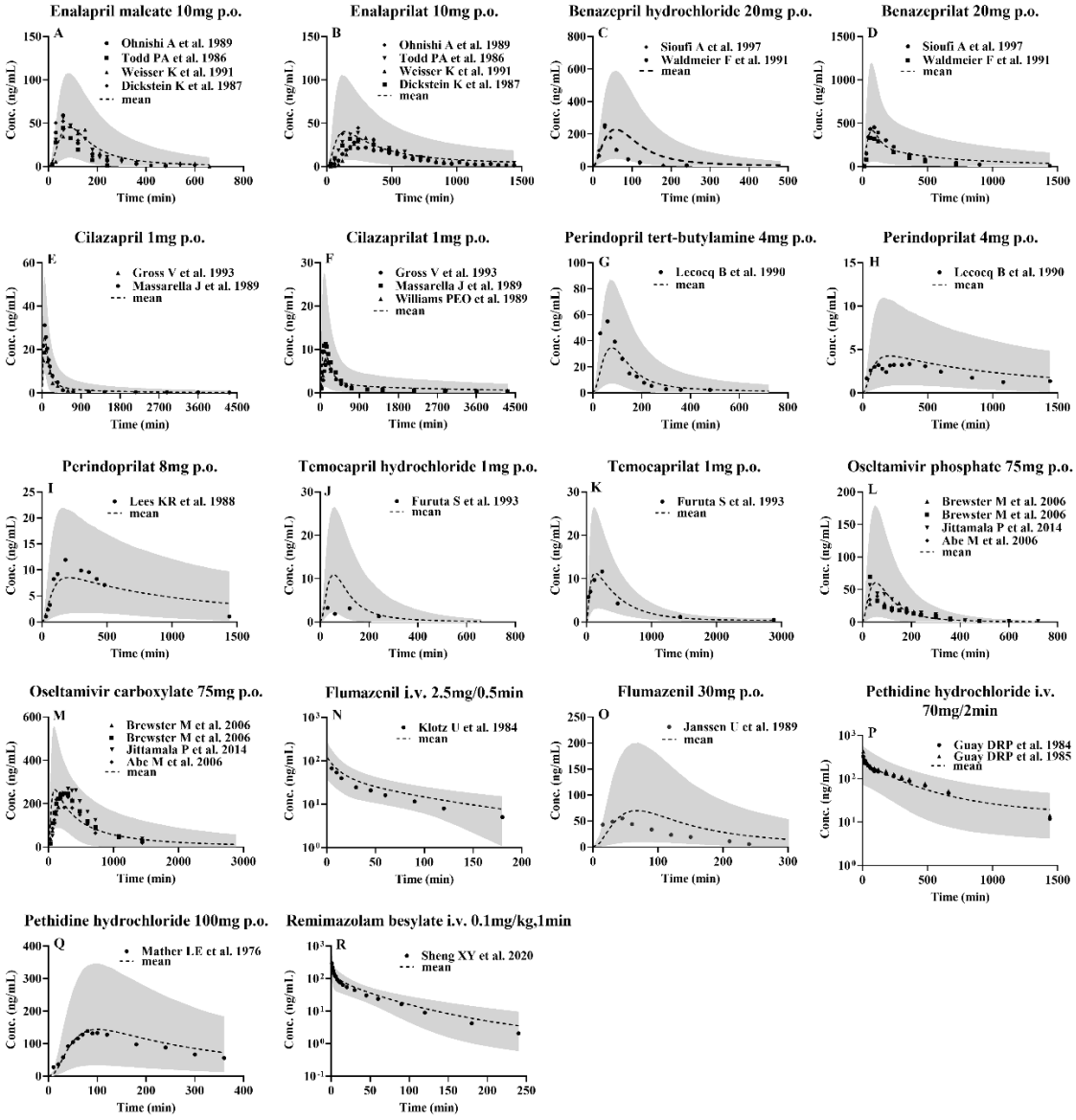

Figure 2. The observed(points) and predicted(lines) plasma concentrations of the tested CES1 substrates and their active metabolites following intravenous or oral administration to healthy subjects. Enalapril(A) and enalaprilat(B) following oral 10 mg enalapril maleate; benazepril(C) and benazeprilat(D) following oral 20 mg benazepril hydrochloride; cilazapril(E) and cilazaprilat(F) following oral 1 mg cilazapril; perindopril(G) and perindoprilat(H) following oral 4 mg perindopril tert-butylamine; perindoprilat(I) following oral 8 mg perindopril tert-butylamine; temocapril(J) and temocaprilat(K) following 1 mg temocapril hydrochloride; oseltamivir(L) and oseltamivir carboxylate(M) following oral 75 mg oseltamivir phosphate; flumazenil following intravenous 2.5 mg/0.5 min(N) and oral 30 mg(O); pethidine following intravenous 70 mg/2 min pethidine hydrochloride(P) and oral 100 mg pethidine hydrochloride(Q); remimazolam(R) following intravenous 0.1 mg/kg remimazolam besylate. Shaded areas indicate the 5% and 95% quantile of simulations derived from 100 virtual individuals. The dashed lines indicate the mean of the simulated profiles.

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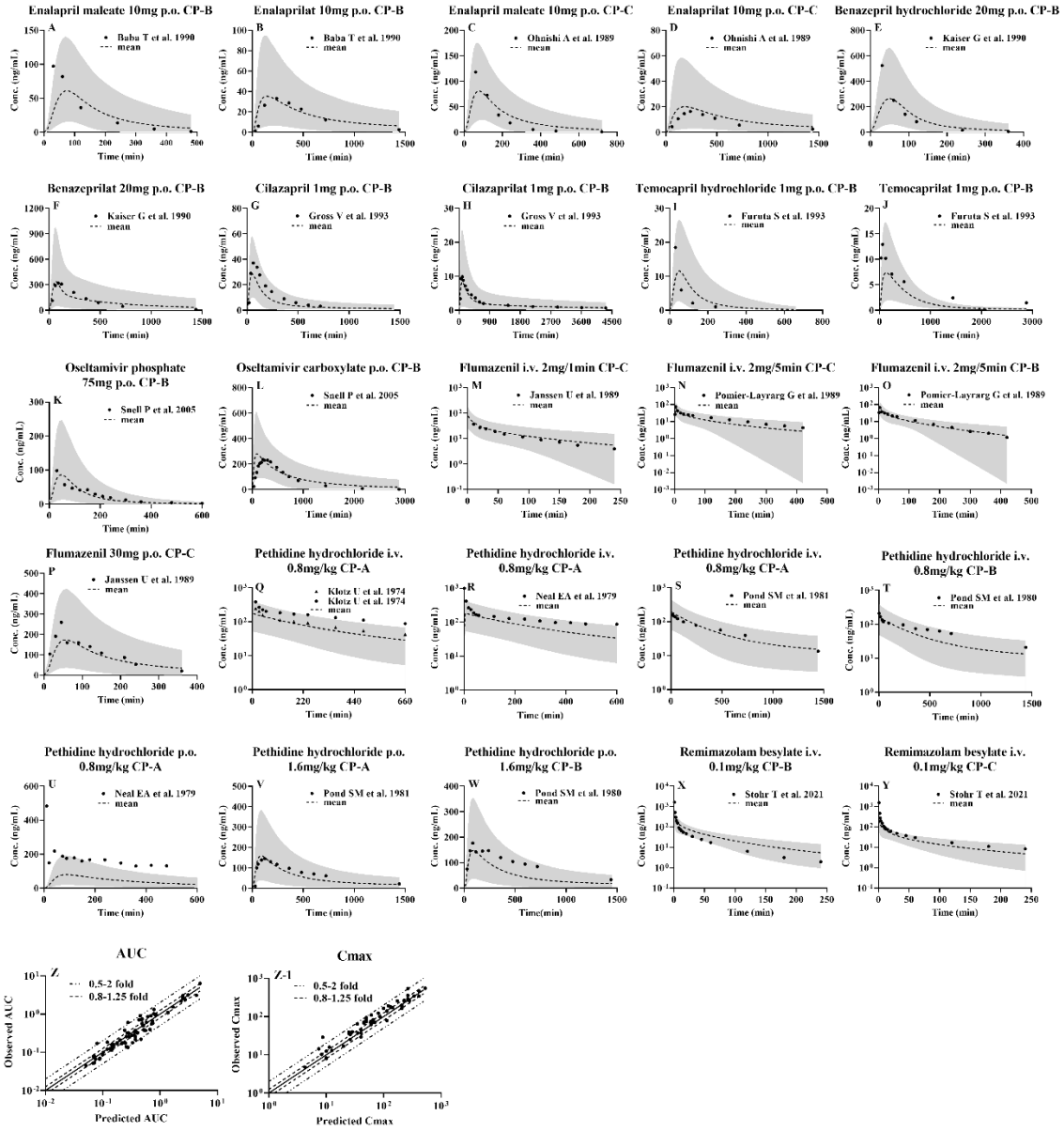

Figure 3. The observed(points) and predicted(lines) plasma concentrations of the tested CES1 substrates and their active metabolites following intravenous or oral administration to LC patients. Enalapril(A,C) and enalaprilat(B,D) following oral 10 mg enalapril maleate to CP-B(A, B) and CP-C(C, D); benazepril(E) and benazeprilat(F) following oral 20 mg benazepril hydrochloride to CP-B; cilazapril(G) and cilazaprilat(H) following oral 1 mg cilazapril to CP-B; temocapril(I) and temocaprilat(J) following oral 1 mg temocapril hydrochloride to CP-B; oseltamivir(K) and oseltamivir carboxylate(L) following oral 75 mg oseltamivir phosphate to CP-B; flumazenil following intravenous 2 mg/1 min to CP-C(M), 2 mg/5 min to CP-C(N) and CP-B(O); flumazenil(P) following oral 30 mg to CP-C; pethidine following intravenous 0.8 mg/kg,1min(Q), 0.8mg/kg,5min(R), 0.8mg/kg(S,T) pethidine hydrochloride to CP-A(Q,R,S) and CP-B(T), pethidine following oral 0.8 mg/kg pethidine hydrochloride to CP-A(U), 1.6 mg/kg pethidine hydrochloride to CP-A(V) and CP-B(W); remimazolam following intravenous 0.1 mg/kg remimazolam besylate to CP-B(X) and CP-C(Y). Shaded areas indicate the 5% and 95% quantile of simulations derived from 100 virtual individuals. The dashed lines indicate the mean of the simulated profiles. Comparison of the predicted AUC(Z) and C_{max}(Z-1)with observations in healthy subjects and LC patients. Solid, dashed and dotted lines respectively represent unity, 0.8-1.25-fold and 0.5-2-fold errors between observed and predicted data.

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3.3. Prediction of pharmacokinetic profiles for CES1 substrates and their active metabolites following i.v. or oral administration to LC patients using the developed PBPK model

The developed PBPK model, following validation in healthy subjects, was used to predict pharmacokinetic profiles of the selected CES1 substrates and their active metabolites following intravenous or oral administration to 100 virtual LC patients (Figure 3) and their pharmacokinetic parameters were estimated using the mean pharmacokinetic profile derived from 100 simulations (Table S1-S9). The results showed that except oral pethidine, the majority of the drug concentrations in LC patients were well within the 5% and 95% percentiles of pharmacokinetic profiles derived from 100 virtual LC patients. Most of the estimated pharmacokinetic parameters were also within 0.5-2.0-fold of observations (Figure 3), indicating that alterations in pharmacokinetic behaviors of CES1 substrates and their metabolites in LC patients may be predicted using the developed PBPK model.

Extents of pharmacokinetic parameters under liver cirrhosis, AUCR and $C_{max}R$ were also predicted using the estimated pharmacokinetic parameters (Figure 4 and Figure 5). AUC or C_{max} values may come from different clinic reports or different doses, thus, the AUC or C_{max} values were normalized by dose and their mean values were used for estimating AUCR or $C_{max}R$. The results showed that the vast majority of the ratios of predicted AUCR and $C_{max}R$ are close to observed values, with only a few individual values differing significantly, indicating a good prediction. All these show that the PBPK model successfully predicted the pharmacokinetics of the drug in cirrhosis.

3.4. Sensitivity analysis of model parameters

Plasma concentration-time curve of enalapril and enalaprilat following oral dose(10mg) was exampled for pharmacokinetic sensitivity. Some parameters such as gastrointestinal motility rate (K_t), intestinal absorption (P_{eff}), hepatic arterial blood flow rates (Q_{LA}), portal vein blood flow rates (Q_{PV}), hepatic CES1 activity ($CL_{int,L}$), kidney blood flow rates (Q_K), GFR, $f_{u,b}$ and $f_{u,b,m}$ (free fraction of metabolites in blood) may affects pharmacokinetics of drugs, which were selected for sensitivity analysis. Variations of K_t, P_{eff}, Q_{LA}, Q_{PV}, $CL_{int,L}$ and Q_K were 1/3, 1 and 3-fold. Variation of GFR was 0.5, 1 and 1.5-fold. Variation of $f_{u,b}$ was 0.74, 1 and 1.35-fold for enalapril and $f_{u,b,m}$ was 0.68, 1 and 1.47-fold for enalaprilat. The results (Figure 6) show that these tested parameters affect the pharmacokinetics profile of drugs in varying degrees, their contributions to AUC of enalapril were P_{eff}>K_t>$CL_{int,L}$>Q_{PV}>$f_{u,b}$>GFR>Q_K>Q_{LA}, and to enalaprilat were P_{eff}>K_t>GFR> $CL_{int,L}$>Q_{PV}>$f_{u,b,m}$>Q_K>Q_{LA}. In addition to impairment of liver failure, LC patients were associated with increases in intestinal transit rates, intestinal permeability of drugs, Q_{LA} and $f_{u,b}$ (due to decreases in plasma binding protein levels), decreases in GFR, Q_K, CES1 activity and Q_{PV}, although increases in Q_L were reported in CP-C patients. The contributions of LC-induced alterations in K_t, Q_{PV}, $CL_{int,L}$, P_{eff}, GFR, Q_K and $f_{u,b}$ to plasma concentrations of enalapril and enalaprilat following an oral dose of enalapril maleate(10 mg) to CP-C patients and their integrated effects were also simulated. The results showed that decreases in $CL_{int,L}$ and increases P_{eff} of enalapril increased plasma concentrations of enalapril while the increases in $f_{u,b}$, K_t and decreases in Q_{PV} obviously decreased plasma concentrations of enalapril following an oral dose of enalapril maleate, the net effects were to increase plasma concentrations of enalapril. For enalaprilat, increases in P_{eff} and decreases in GFR, Q_K and Q_{PV} significantly increased plasma concentration profiles of enalaprilat, while decreases in CES1 activity and increases in K_t and $f_{u,b,m}$ of enalaprilat significantly decreased plasma concentrations following oral enalapril maleate. Their net effects were to decrease plasma concentrations of enalaprilat (Figure 6Q and Figure 6R).

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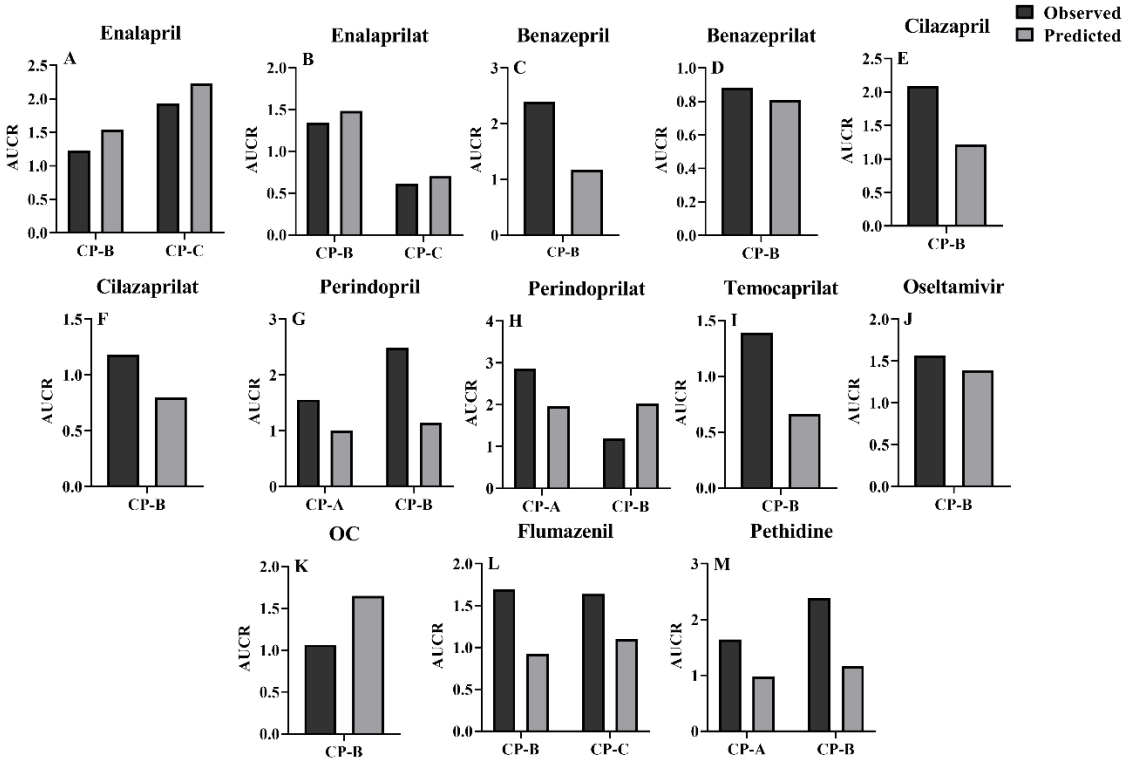

Figure 4. AUCR was calculated from AUC (cirrhotic/healthy) or CL (healthy/cirrhotic) for cirrhotic status and healthy individuals, with the vast majority of parameters in the 0.5-2-fold range. (A) enalapril; (B) enalaprilat; (C) benazepril; (D) benazeprilat; (E) cilazapril; (F) cilazaprilat; (G) perindopril; (H) perindoprilat; (I) temocaprilat; (J) oseltamivir; (K) oseltamivir carboxylate; (L) flumazenil; (M) pethidine. Parameters not reported in the literature were excluded from the calculations; multiple doses were dose-normalized.

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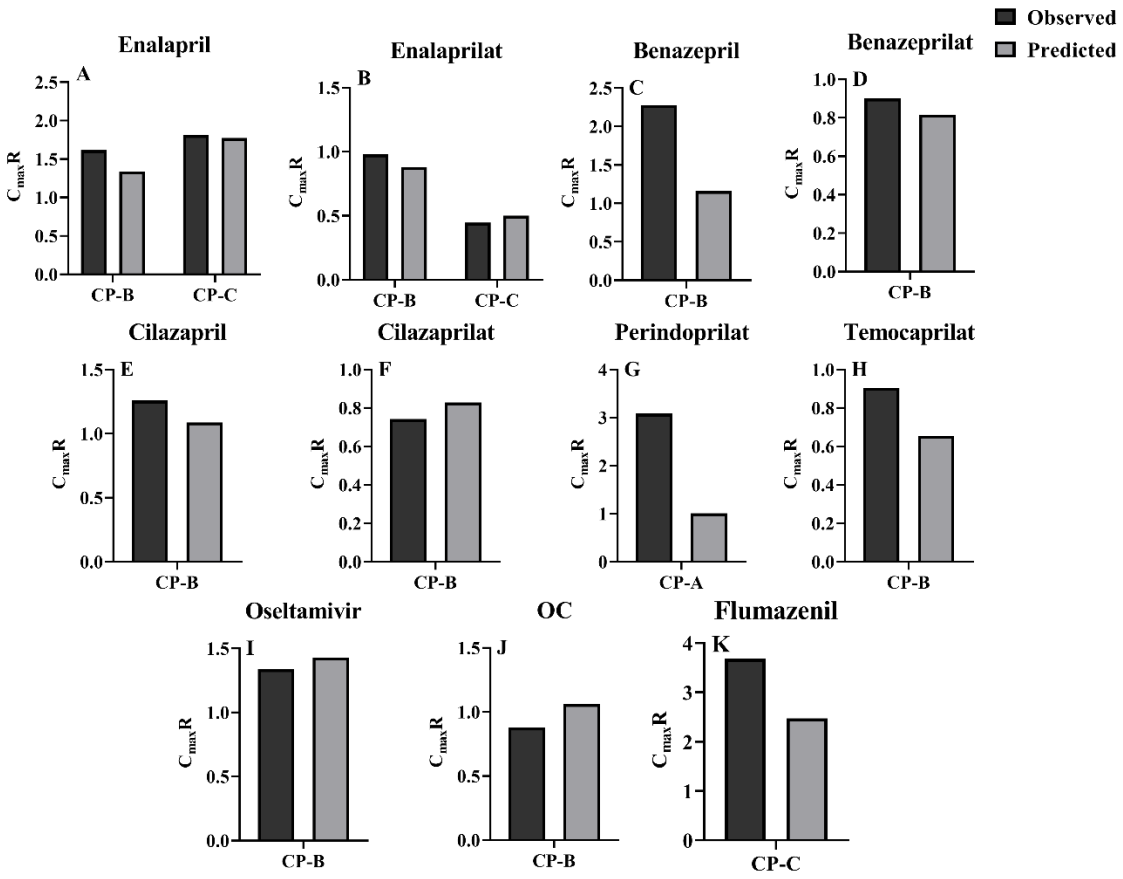

Figure 5. $C_{max}R$ was calculated from C_{max} for cirrhotic status and healthy individuals (cirrhotic/healthy), with the vast majority of parameters in the 0.5-2-fold range. (A) enalapril; (B) enalaprilat; (C) benazepril; (D) benazeprilat; (E) cilazapril; (F) cilazaprilat; (G) perindoprilat; (H) temocaprilat; (I) oseltamivir; (J) oseltamivir carboxylate; (K) flumazenil. Parameters not reported in the literature were excluded from the calculations; multiple doses were dose-normalized.

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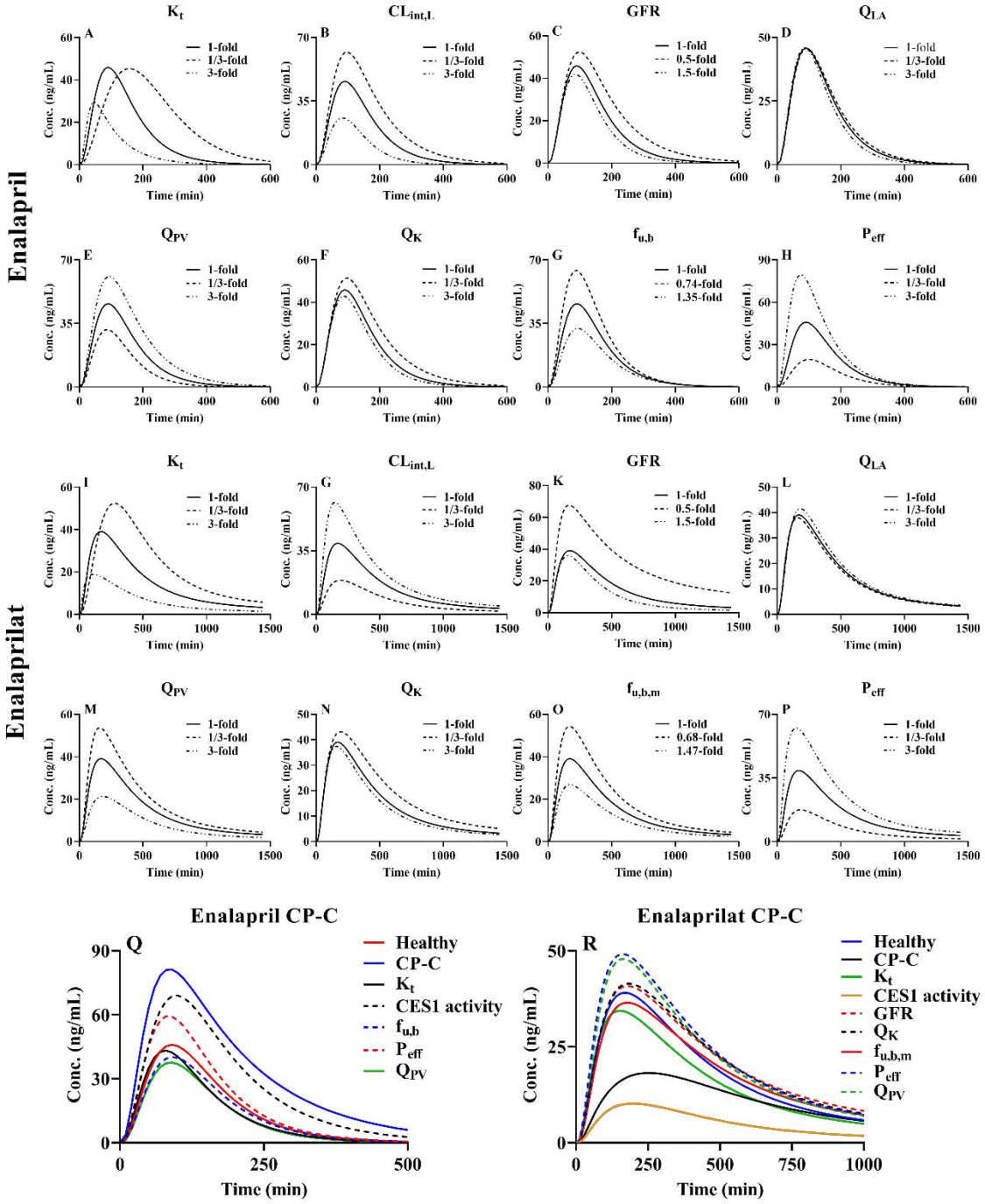

Figure 6. Sensitivity analysis of enalapril and enalaprilat following oral 10 mg enalapril maleate. Enalapril: (A) K_t; (B) $CL_{int,L}$; (C) GFR; (D) Q_{LA}; (E) Q_{PV}; (F) Q_K; (G) $f_{u,b}$; (H) P_{eff}; $f_{u,b}$ varies by 0.74-fold and 1.35-fold and GFR varies by 0.5-fold and 1.5-fold; the rest are varied by 1/3-fold and 3-fold. Enalaprilat: (I) K_t; (J) $CL_{int,L}$; (K) GFR; (L) Q_{LA}; (M) Q_{PV}; (N) Q_K; (O) $f_{u,b,m}$; (P) P_{eff}. Where $f_{u,b,m}$ varies by 0.68-fold and 1.47-fold. Individual contributions of LC-induced alterations in K_t, CES1 activity, GFR, $f_{u,b}$, P_{eff}, Q_K and Q_{PV} to plasma concentrations of enalapril(Q) and enalaprilat(R) following oral 10 mg enalapril maleate to LC patients and their integrated effects.

4. Discussion

Hepatic CES1 mediates the inactivation of direct-acting drugs or activation of some prodrugs, most of whose active metabolites are mainly eliminated via kidney. In addition to impairment of liver function, LC patients are also associated with alterations in organ blood flow, decreases in plasma

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protein levels, increases in intestinal permeability of drugs and impairment of renal functions, commonly affecting pharmacokinetics of CES1 substrate drugs and their metabolites. The main contributions of the study were to successfully develop a semi-PBPK model involving intestinal absorption, hepatic metabolism and renal excretions to simultaneously predict pharmacokinetic profiles of nine CES1 substrates (six prodrugs and three direct-acting drugs) in both healthy subjects and LC patients. Most clinic observations were within 5%-95% quantiles of simulations derived from 100 virtual subjects. Most of the estimated AUC and C_{max} were also within 0.5-2.0-fold of observations.

The extent of LC-induced alterations in plasma exposure of CES1 substrates and their metabolites were also assessed using AUCR and $C_{max}R$. It was found that although most of the clinically observed plasma concentrations for the tested agents were within 5%-95% quantiles of simulations, poor predicted AUCR or $C_{max}R$ were found in benazepril, temocaprilat, perindopril and perindoprilat. The predicted AUCR values of flumazenil and pethidine were less than the clinic observations. Benazepril and temocaprilat belong to highly bound compounds, whose $f_{u,b}$ values were 0.03 and 0.025, respectively. In general, obtaining an accurate plasma binding measurement for highly bound compounds is difficult[144]. In addition to CES1, UGTs also mediate perindopril metabolism[100]. Which isoenzyme of UGT was involved in metabolism of perindopril was not identified. In the simulation, it was assumed that LC-induced alterations in $CL_{int,\,UGT}$ of perindopril were similar to that of metoprolol[101]. LC patients by different etiologies show different amounts of hepatic CES1. In addition to CES1, other enzymes also mediate metabolism of flumazenil[142]. Pethidine is co-metabolized by CES1 and CYP2B6[49,98]. Several reports have demonstrated extensive interindividual variability in the expression of CYP2B6[145] and CES1[98]. All may be reasons leading to these differences between the predicted and the observed AUCR values, which need further investigation.

In general, LC-induced impairments of hepatic CES1 activity increase plasma exposure of CES1 substrates, but sensitivity analysis showed that the increases in plasma concentrations of CES1 substrates under LC patients were only partly attributed to impairment of hepatic CES1. The increases in intestinal permeability of drugs were also observed in LC patients, contributing to increased plasma exposures of CES1 substrates. In contrast, LC-induced increases in intestinal transit rate and decreases in plasma binding protein and Q_{PV} obviously decreased plasma exposure of CES1 substrates, which partly attenuated the increases in plasma exposures of CES1 substrates by liver cirrhosis. Metabolites of the tested CES1 substrates are eliminated via kidney. The decreases in plasma exposure of metabolites induced by impairment of hepatic CES1 activity were also partly attenuated by LC-induced alterations in GFR and Q_K. Even under some conditions, levels of the metabolites are increased rather than decreased due to impairment of renal function. For example, AUC values of perindoprilat in CP-A and CP-B patients were obviously higher than those in healthy humans, the observed AUCR values were 2.89 and 1.2, respectively, which were near to predictions (1.97 in CP-A patients and 2.03 in CP-B patients). These findings may partly explain clinical findings that although liver cirrhosis obviously increases plasma levels of enalapril and perindopril, but the magnitude of serum ACE lowering effects by the two drugs was fairly comparable between LC patients and healthy humans[14,118,119].

Plasma levels of the direct-acting drugs flumazenil, pethidine and remimazolam following administration to LC patients were also successfully simulated. Although the observed AUCR values of remimazolam in LC patients could not be calculated due to lack of the observed pharmacokinetic parameters in LC patients, it was contrasted to our expectation that the predicted AUCR values in CP-B patients and CP-C patients were 0.77 and 0.62, which may be explained by the fact that the increased plasma concentration by impairment of hepatic CES1 may be attenuated by increases in hepatic arterial blood flow and increases in $f_{u,b}$ (Figure S2).

However, the study also has some limitations. The predictions for healthy subjects were based on “ideal” healthy subjects (body weight assumed to be 70 kg) without considering gender, body weight, race and gene variance of CES1. Genetic variation in CES1 also affects pharmacokinetics of the CES1 substrates[98]. During the simulation in LC patients, LC patients were considered “ileal” CP-A, CP-B or CP-C patients without considering LC etiology, gender and race. It was reported that

the amount of CES1 protein in hepatitis C cirrhotic patients was about 1.47-fold of the alcoholic cirrhosis[146]. Similarly, it was reported that flumazenil might improve memory in alcoholic cirrhotic patients but not in nonalcoholic cirrhotic patients[147].

5. Conclusions

The developed PBPK model may successfully be applied simultaneously to predict the pharmacokinetics of CES1 substrate drugs and their active metabolites in healthy subjects and LC patients.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1: Observed and predicted values of AUC_{0-t} and C_{max} of enalapril and enalaprilat following oral enalapril maleate to healthy (HT) subjects and liver cirrhosis patients. Table S2: Observed and predicted values of AUC_{0-t} and C_{max} of benazepril and benazepril following benazepril hydrochloric to healthy(HT) subjects and cirrhosis. Table S3: Observed and predicted values of AUC_{0-t} and C_{max} of cilazapril following oral cilazapril to healthy(HT) subjects and LC patients. Table S4: Observed and predicted values of AUC_{0-t} and C_{max} of perindopril following oral perindopril tert-butylamine to healthy(HT) subjects and LC patients. Table S5: Observed and predicted values of AUC_{0-t} and C_{max} of temocapril and temocaprilat following oral temocapril hydrochloride to healthy (HT) subjects and LC patients. Table S6: Observed and predicted values of AUC_{0-t} and C_{max} of oseltamivir and oseltamivir carboxylate (OC) following oral oseltamivir phosphate to healthy (HT) subjects and cirrhosis. Table S7: Observed and predicted values of AUC_{0-t} (μg×h/mL) or CL(L/min) and C_{max}(ng/mL) of flumazenil to healthy(HT) subjects and LC patients. Table S8: Observed and predicted values of AUC_{0-t}(μg×h/mL) or CL(L/min) and C_{max}(ng/mL) of pethidine following oral and intravenous pethidine HCL to healthy (HT) subjects and LC patients. Table S9: Observed and predicted values of AUC_{0-t} of remimazolam following intravenous remimazolam besylate to healthy (HT) subjects and LC patients. Figure S1: The observed(points) and predicted(lines) plasma concentrations of the tested CES1 substrates and their active metabolites following intravenous or oral administration to healthy subjects. Benazepril(A) and benazeprilat(B) following oral 10 mg benazepril hydrochloride; cilazapril(D,F) and cilazaprilat(C,E,G,H) following oral 1.25, 2.5, 5, 10 mg cilazapril; oseltamivir(I) and oseltamivir carboxylate(J) following oral 150 mg oseltamivir phosphate; flumazenil following intravenous 10 mg/1 min(K) and 10mg/10min(L); pethidine following intravenous 50 mg/1min(M), 25mg/1min(N), 0.8mg/kg,1min(O) and 0.8mg/kg,5min(P) pethidine hydrochloride and oral 25 mg(Q), 0.8mg/kg(R) pethidine hydrochloride; remimazolam following intravenous 0.05(S), 0.075(T), 0.2(U), 0.3(V), 0.4(W)mg/kg remimazolam besylate. Shaded areas indicate the 5% and 95% quantile of simulations derived from 100 virtual individuals. The dashed lines indicate the mean of the simulated profiles. Figure S2: Contributions of alterations in $f_{u,b}$, CES1 activity, Q_{LA} and Q_{PV} by LC to plasma concentrations of remimazolam following 10.4mg(CP-B, A) and 8.2mg(CP-C, B) to healthy human and LC patients.

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