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ARTICLE

Assessing Potential Drug–Drug Interactions Between Dabigatran Etexilate and a P-Glycoprotein Inhibitor in Renal Impairment Populations Using Physiologically Based Pharmacokinetic Modeling

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Plasma concentrations of dabigatran, an active principle of prodrug dabigatran etexilate (DABE), are increased by renal impairment (RI) or coadministration of a P-glycoprotein inhibitor. Because the combined effects of drug–drug interactions and RI have not been evaluated by means of clinical studies, the decision of DABE dosing for RI patients receiving P-glycoprotein inhibitors is empirical at its best. We conducted virtual drug–drug interactions studies between DABE and the P-glycoprotein inhibitor verapamil in RI populations using physiologically based pharmacokinetic modeling. The developed physiologically based pharmacokinetic model for DABE and dabigatran was used to predict trough dabigatran concentrations in the presence and absence of verapamil in virtual RI populations. The population-based physiologically based pharmacokinetic model provided the most appropriate dosing regimen of DABE for likely clinical scenarios, such as drug–drug interactions in this RI population based on available knowledge of the systems changes and in the absence of actual clinical studies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The dosing regimen of dabigatran etexilate for patients with renal impairment receiving concomitant P-glycoprotein inhibitors has yet to be optimized through clinical drug–drug interaction (DDI) studies, which are generally conducted in healthy volunteers.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study explored an appropriate dosing regimen of dabigatran etexilate for renal impairment populations in the presence of the P-glycoprotein inhibitor verapamil using population-based physiologically based pharmacokinetic modeling.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Virtual DDI studies using physiologically based pharmacokinetic modeling revealed that when coadministered with multiple verapamil doses, the optimal dabigatran etexilate dosing varied among populations with healthy renal function and mild and moderate renal impairment.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

☑ Virtual DDI studies through physiologically based pharmacokinetic modeling can help simplify the optimization of dosing regimen for likely clinical scenarios, including DDIs in various renal impairment populations.

Dabigatran etexilate (DABE), a prodrug of dabigatran (DAB), is an oral anticoagulant used for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[1] The prodrug is rapidly converted to the active moiety DAB via two primary intermediated metabolites by carboxylesterase (CES)-2 in the intestine and CES-1/CES-2 in the liver.[2,3] Cytochrome P450 metabolic enzymes play no relevant role in DABE and DAB.[2] Because DAB is extensively excreted in urine,[2] renal impairment prolongs DAB elimination, thereby increasing its plasma concentrations.[4] DABE, but not DAB, is a substrate of the efflux transporter P-glycoprotein (P-gp),[5] which results in poor oral bioavailability (7.2%) because of P-gp–mediated efflux in the intestine.[2] Therefore, concomitant use of DABE with P-gp inhibitors (e.g., amiodarone, quinidine, and verapamil) enhances the exposure to DAB.[5,6] The daily DABE dose should be adjusted in patients with renal impairment or during the coadministration of a P-gp inhibitor. DABE dosing recommendations for such patients vary among the European Union, Japan, and the United States.[7–9] DABE dosing regimens can be considered appropriate when the predicted trough concentrations are within the reported therapeutic

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range (28–210 ng/mL) based on the risk of major bleeding and ischemic stroke/systemic embolism.[10] However, the DABE dosing regimen for patients with renal impairment receiving concomitant P-gp inhibitors has yet to be optimized through clinical drug–drug interaction (DDI) studies, which are generally conducted in healthy volunteers. Although DDI liability may be different among patients with varying degrees of renal impairment,[11] such clinical DDI studies in various renal impairment populations are rarely conducted because of obvious practical and ethical reasons. Therefore, clinicians empirically decide on the dosing regimens for complex DDIs in various renal impairment populations. The lack of specific dosing recommendations for more complex scenarios necessitates clinicians using their previous experience to personalize dosing before or after the start of treatment based on the patient response.[12] It has been argued that the integration of prior knowledge of the system (e.g., attributes associated with renal impairment) together with the knowledge of its pharmacokinetic characteristics through physiologically based pharmacokinetic (PBPK) modeling can help overcome the paucity of clinical data under these circumstances and avoid the undocumented and inconsistent guesswork while treating these vulnerable patients.[13,14]

Virtual DDI studies through PBPK modeling are alternative ways to provide appropriate dosing regimens for likely clinical scenarios, including DDIs in various renal impairment populations.[12,15] PBPK models map complex drug movements in the body to a physiologically realistic compartmental structure using sets of differential equations, including the intercorrelation between physiological parameters (e.g., body weight/liver volume and liver volume/hepatic blood flow).[15] The PBPK model allows for a more accurate prediction of drug disposition, including absorption, distribution, metabolism, and excretion, and enables the quantitative prediction of DDI magnitude. Upon verification, the PBPK model can be applied to various virtual target populations, including patients with renal or hepatic impairments and

Table 1 Summary of input parameters used in the PBPK model for dabigatran etexilate

Input parameter	Initial	Refined	Reference/comments
Molecular weight (g/mol)	627.7	—	5
log *P*	3.80	—	5
Compound type	Diprotic base	—	5
pK_a	4.0 (base), 6.7 (base)	—	5
Blood/plasma ratio	1.26	—	Estimated
Fraction unbound in plasma	0.063	—	Estimated
Absorption			
Model	ADAM	—	—
Fraction of drug unbound in enterocyte	1	—	Simcyp default
$P_{eff,man}$ duodenum (×10^{-4} cm/s)	2.49	0.113	Estimated using Mech P_{eff} model and scaled down (see Methods for details)
$P_{eff,man}$ jejunum I (×10^{-4} cm/s)	6.27	0.206	
$P_{eff,man}$ jejunum II (×10^{-4} cm/s)	4.39	0.144	
$P_{eff,man}$ ileum I (×10^{-4} cm/s)	1.11	0.058	
$P_{eff,man}$ ileum II (×10^{-4} cm/s)	1.11	0.058	
$P_{eff,man}$ ileum III (×10^{-4} cm/s)	1.09	0.057	
$P_{eff,man}$ ileum IV (×10^{-4} cm/s)	1.05	0.055	
$P_{eff,man}$ colon (×10^{-4} cm/s)	0.58	0.0001	
Distribution			
Model	Full PBPK	—	—
V_{ss} (L/kg)	15.16	—	21
Elimination			
HLS9, fu inc	0.69	—	Estimated
HLS9, CES1 K_m (μM)	33.5	—	3
HLS9, CES1 V_{max} (pmol/min/mg)	1,174	19,462	Parameter estimation (see Methods for details)
HLS9, CES1 tissue scalar (liver/intestine)	1.0/0	—	22
HLS9, CES2 K_m (μM)	15.4	—	3
HLS9, CES2 V_{max} (pmol/min/mg)	30.8	9,050	Parameter estimation (see Methods for details)
HLS9, CES2 tissue scalar (liver/intestine)	0.1/0	—	22
Intestinal efflux			
P-gp K_m (μM)	—	38.9	24
P-gp J_{max} (pmol/min/cm^2)	—	146	Optimized using observed data (see Methods for details)

ADAM, advanced dissolution, absorption and metabolism model; CES, carboxylesterase; fu inc, fraction of drug unbound in the incubation; HLS9, human liver S9 fractions; J_{max}, maximum flux; K_a, absorption rate constant; K_m, Michaelis–Menten constant; Mech P_{eff}, mechanistic permeability; PBPK, physiologically based pharmacokinetic model; P-gp, P-glycoprotein; $P_{eff,man}$, the effective permeability in humans; pK_a, negative logarithm of the dissociation constant; V_{max}, maximum rate of metabolism; V_{ss}, volume of distribution at steady state.

pediatric patients. The primary aim of this study was to explore an appropriate dosing regimen of DABE for renal impairment populations in the presence of the P-gp inhibitor verapamil and its metabolite norverapamil using population-based PBPK modeling. We developed a PBPK model for DABE and DAB by incorporating P-gp–mediated intestinal efflux and applied the model to virtual DDI studies between DABE and verapamil in renal impairment populations.

METHODS

Model development

PBPK modeling and simulation were performed using the Simcyp Simulator (version 17.1; Certara, Sheffield, United Kingdom). Virtual populations, assuming varying levels of creatinine clearance (CrCl), were generated by altering physiological parameters, serum creatinine, and glomerular filtration rate range in the preverified population templates within the Simcyp Simulator population library (**Table S1** and **Figure S1**). The DABE/DAB PBPK model was developed using a middle-out approach, which uses an *in vitro* understanding of pharmacokinetic mechanisms (i.e., bottom-up approach) and observed clinical data (i.e., top-down approach; **Tables 1 and 2**).[16] The observed plasma concentration profiles of DABE and DAB were obtained from the literature and digitized using a GetData Graph Digitizer (version 2.26; http://getdata-graph-digitizer.com/).[4–6,17,18]

The DABE compound file was developed using the advanced dissolution, absorption, and metabolism model (i.e., ADAM model) that accounts for regional differences in permeability and P-gp–mediated efflux in the intestine (**Table 1**).[19] Data on physicochemical parameters (molecular weight, the logarithm of the n-octanol:buffer partition coefficient acid/base status, and the negative logarithm of the dissociation constant) were obtained from the literature.[5] The fraction unbound in plasma and the blood/plasma ratio were predicted using physicochemical parameters. In the initial model without P-gp–mediated efflux in the intestine, the effective permeability in humans ($P_{eff,man}$) for DABE was estimated using the mechanistic permeability model, which was developed for predicting the regional passive intestinal permeability of drugs in humans based on the knowledge of regional gut physiology and drug-specific physicochemical parameters.[20] Regional $P_{eff,man}$ values were optimized by the scale-down of values estimated from the mechanistic permeability model when assuming that bioavailability was equivalent to the observed value (7.2%).[2] Drug distribution was modeled using a full-PBPK distribution model that uses a number of time-based differential equations to simulate concentrations in various organ compartments.[21] The CES-1 and CES-2 in the liver were considered as the final steps of the conversion of DABE to DAB, with tissue scalars of 1.0 and 0.1, respectively.[3,22] The Michaelis–Menten kinetic parameters for the conversion of DABE to DAB by CES-1 and CES-2 were obtained from the literature.[3] The maximum rates of metabolism for CES-1 and CES-2 were simultaneously optimized using a parameter estimation module from fitting with observed plasma concentration profiles of DABE and DAB after a single 150-mg oral dose of DABE.[17]

Table 2 Summary of input parameters used in the PBPK model for active metabolite dabigatran

Input parameter	Value	Reference/ comments
Molecular weight (g/mol)	471.5	23
log *P*	–2.21	23
Compound type	Ampholyte	23
pK_a	4.4 (acid), 12.4 (base)	23
Blood/plasma ratio	0.69	2
Fraction unbound in plasma	0.65	2
Distribution		
Model	Full PBPK	—
V_{ss} (L/kg)	0.96	2 (see Methods for details)
Elimination		
Renal clearance (L/hour)	7.97	2 (see Methods for details)
Additional systemic clearance (L/hour)	0.97	2 (see Methods for details)

PBPK, physiologically based pharmacokinetic model; pK_a, negative logarithm of the dissociation constant; V_{ss}, volume of distribution at steady state.

The DAB compound file was developed using the physicochemical parameters, fraction unbound in plasma, and blood/plasma ratio obtained from data in the literature (**Table 2**).[23] The drug distribution model was developed using the full-PBPK distribution model, and the predicted volume of distribution at steady state was matched to the observed value (0.96 L/kg) using a tissue-to-plasma partition coefficient scalar of 3.12. Renal clearance and additional systemic clearance were calculated from the intravenous clearance (8.94 L/hour) and urinary excretion ratio (0.892) after a single 5-mg intravenous dose of DAB.[2]

The initial DABE/DAB model was refined using observed clinical data ("Training Sets"; **Table S2**)[2,6] while considering P-gp–mediated efflux in the intestine (**Tables 1 and 2**). The P-gp–mediated efflux was described using the Michaelis–Menten type equation (J_{max}, maximum flux; K_m, Michaelis–Menten constant). The P-gp K_m value for DABE was obtained from the literature.[24] The P-gp J_{max} and regional P_{eff} values were simultaneously optimized by assuming that bioavailability without a P-gp inhibitor and exposure ratio with verapamil were equivalent to observed values (7.2% and 1.54-fold, respectively).[2,6] The $P_{eff,man}$ value in the colon was assumed to be negligibly small because the predominant compound in feces after oral DABE administration was DAB, which exhibited poor intestinal absorption owing to highly polar zwitterionic and hydrophilic natures, and DABE was not found in feces.[2]

Compound files for digoxin, verapamil (and its metabolite norverapamil), and quinidine in the Simcyp compound library were used for PBPK modeling and simulation with minor modifications as described in previous reports (**Table S3**). A digoxin compound file was developed using the mechanistic kidney model module, which accounts for glomerular filtration, passive permeability within all of the tubular segments, and active transport processes within the proximal tubule

segments.[25] The P-gp K_i values (concentration of inhibitor that supports half maximal inhibition) used for norverapamil and quinidine were 0.3 and 0.43 μM, respectively.[26,27]

Model verification

The DABE/DAB PBPK model was verified using the observed DAB concentration data ("Verification Sets"; **Table S2**).[4,6,8,17,18] The characteristics (age, sex distribution, and population/ethnicity) of virtual subjects were matched to those in the clinical trial. Virtual studies were simulated using 10 trials of 10 virtual individuals. The predicted geometric mean values of the exposure parameters and DDI effects were compared with the corresponding observed values except for the use of arithmetic mean values when the observed geometric mean values were not available. The DDI simulations for digoxin were performed in a population representative of healthy volunteers (average values were considered for many parameters).

Virtual DDI studies between DABE and verapamil in renal impairment populations

Virtual DDI studies were simulated using 20 trials of 10 virtual individuals in a population with healthy renal function (CrCl > 80 mL/min) and in populations with mild (CrCl 50–80 mL/min), moderate (CrCl 30–50 mL/min), and severe (CrCl 15–30 mL/min) renal impairment ("Simulation Sets"; **Table S2**). The trial design (age and proportion of females) was replicated as closely as possible to ensure that the characteristics of the virtual subjects were matched to those in a large clinical trial, that is, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial.[1,10] An age range of 59–81 years was used to assume the varying levels of CrCl and to match with the ages in the clinical trial.[1] The virtual subjects received multiple doses of oral DABE in the presence or absence of the P-gp inhibitor verapamil and its metabolite norverapamil. When multiple doses of oral verapamil (120 mg twice a day (b.i.d.) for 5 days) were coadministered, the DABE doses were administered concurrently with or 2 hours before verapamil. The used dosing regimens of DABE and verapamil were same as the previous report, which was a DDI study in healthy volunteers.[6]

Pharmacokinetic profiles of DAB were characterized by trough concentrations (C_{trough}) immediately before the administration of the last dose (the day 5 morning dose). The C_{trough} values are presented as the median and/or 10th/90th percentiles of all 20 trials. The simulated C_{trough} values were compared with the observed data calculated using the dose-normalized DAB concentration obtained from the clinical trial.[10] The DABE dosing regimens were considered appropriate when the predicted 10th/90th percentiles of C_{trough} were within the reported therapeutic range (28–210 ng/mL).[10]

RESULTS

Simulation of concentration–time profiles after the administration of DABE alone in healthy volunteers

The DABE/DAB PBPK model reproduced observed plasma concentration–time profiles of DABE and DAB after a single 150-mg dose of DABE in healthy volunteers (**Figure 1a**). The geometric mean values of the predicted area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) were within twofold of the observed values ($AUC_{0-\infty}$, 837 vs. 899 ng·hour/mL; C_{max}, 79 vs. 110 ng/mL).[17] The model was also verified by other clinical pharmacokinetic data after a single DABE dose ($AUC_{0-\infty}$, 893 vs. 854 ng·hour/mL; C_{max}, 76 vs. 99 ng/mL).[6] The model recovered observed plasma concentration–time profiles of DAB after a multiple DABE dose (150 mg b.i.d.): the arithmetic mean values of the predicted AUC over the dosing time (AUC_{τ}), peak concentration (C_{peak}), and C_{trough} were within twofold of the observed values (AUC_{τ}, 990 vs. 1,120 ng·hour/mL; C_{peak}, 119 vs. 167 ng/mL; C_{trough}, 45 vs. 59 ng/mL; **Figure 1b**).[18]

Prediction of P-gp–mediated DDIs in healthy volunteers

The PBPK models for the P-gp inhibitors verapamil (and norverapamil) and quinidine were verified using the digoxin PBPK model (**Table 3**). The predicted DDI effects (DDI/control) between digoxin and the P-gp inhibitors were consistent with observed effects.[28,29]

The DABE/DAB PBPK model reproduced observed plasma concentration–time profiles of DAB following a single 150-mg dose of DABE 1 hour after verapamil (120 mg b.i.d.) in healthy volunteers (**Figure 1c**).[6] The predicted DDI effects between DABE and verapamil were consistent with the observed effects (AUC ratio, 1.54 vs. 1.54; C_{max} ratio, 1.57 vs. 1.63; **Table 3**).[6] The predicted DDI effects between DABE and quinidine were also consistent with the observed effects (AUC ratio, 1.48 vs. 1.53; C_{max} ratio, 1.48 vs. 1.56; **Table 3**).[8] Moreover, the model recovered the observed plasma concentration–time profiles of DAB following a single 150-mg dose of DABE 2 hours before verapamil (120 mg b.i.d.) in healthy volunteers (**Figure 1d**).[6] The predicted AUC ratio when DABE was administered 2 hours before verapamil was within twofold of the observed effects (1.31 vs. 1.18), although the predicted C_{max} ratio was slightly overestimated relative to the observed effects (1.28 vs. 1.12).[6]

Simulation of concentration–time profiles after the administration of DABE alone in renal impairment populations

The DABE/DAB PBPK model recovered the observed plasma concentration–time profiles of DAB following a single 150-mg dose of DABE in a healthy renal function population and in mild, moderate, and severe renal impairment populations (**Figure 1e–h**).[4] The arithmetic mean values of the predicted $AUC_{0-\infty}$ and C_{max} were within twofold of the observed values in the healthy renal function population ($AUC_{0-\infty}$, 991 vs. 901 ng·hour/mL; C_{max}, 75 vs. 85 ng/mL) and in the mild ($AUC_{0-\infty}$, 1,727 vs. 1,580 ng·hour/mL; C_{max}, 84 vs. 109 ng/mL), moderate ($AUC_{0-\infty}$, 2,447 vs. 2,470 ng·hour/mL; $C_{max,}$ 92 vs. 138 ng/mL), and severe ($AUC_{0-\infty}$, 4,130 vs. 6,150 ng·hour/mL; C_{max}, 108 vs. 205 ng/mL) renal impairment populations.[4]

Virtual DDI studies between DABE and verapamil in renal impairment populations

Virtual DDI studies between DABE and verapamil in renal impairment populations were conducted using the DABE/

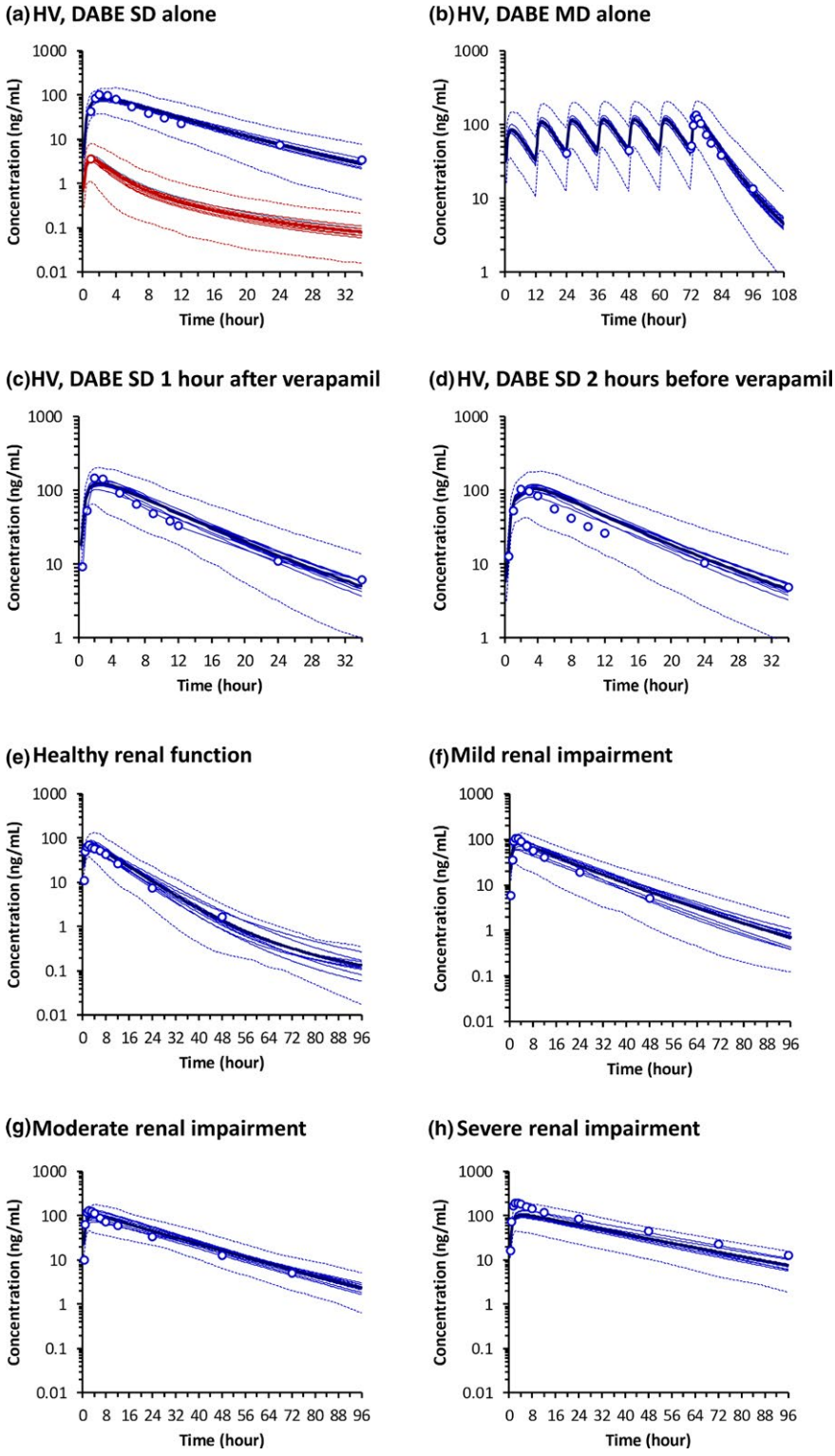

Figure 1 Simulated and observed plasma concentration–time profiles of dabigatran etexilate (DABE; *red*) and dabigatran (DAB; *blue*) after a single oral dose (SD) or multiple doses (MD) of 150 mg DABE. (**a**) DABE SD alone in healthy volunteer (HV), (**b**) DABE MD alone in HV, (**c**) DABE SD 1 hour after verapamil (MD) in HV, (**d**) DABE SD 2 hours before verapamil (MD) in HV, and (**e**) DABE SD alone in the population with healthy renal function (creatinine clearance (CrCl) >80 mL/min) and in the populations with (**f**) mild (CrCl 50–80 mL/min), (**g**) moderate (CrCl 30–50 mL/min), and (**h**) severe (CrCl 15–30 mL/min) renal impairment. Simulation results are presented as the means of all 10 trials (heavy lines), 10 individual trials (thin lines), and 5th and 95th percentiles (dashed lines). Observed data extracted from the literature[4,6,17,18] are presented as the means (open circles).

Table 3 Observed and simulated exposure ratio of digoxin and dabigatran etexilate in drug–drug interactions with P-glycoprotein inhibitors

	Digoxin–inhibitor interactions						Dabigatran etexilate–inhibitor interactions					
			Observed		Simulated				Observed		Simulated	
Inhibitor	Digoxin dosing schemes	Inhibitor dosing schemes	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio	Dabigatran etexilate dosing schemes	Inhibitor dosing schemes	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio
Training set												
Verapamil	0.25 mg, b.i.d.	80 mg, t.i.d.	1.50	1.44	1.53	1.44	150 mg, single dose 1 hour after verapamil dose	120 mg, b.i.d.	1.54	1.63	1.54	1.57
Verification set												
Quinidine	0.25 mg, q.d.	200 mg, q.d.	1.77	1.75	1.64	1.71	150 mg, single dose	200 mg, every 2 hours	1.53	1.56	1.48	1.48
Verapamil	—	—	—	—	—	—	150 mg, single dose 2 hours before verapamil dose	120 mg, b.i.d.	1.18	1.12	1.31	1.28

Data are presented as the geometric mean. AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration; q.d., once a day; b.i.d., twice a day; t.i.d, three times a day.

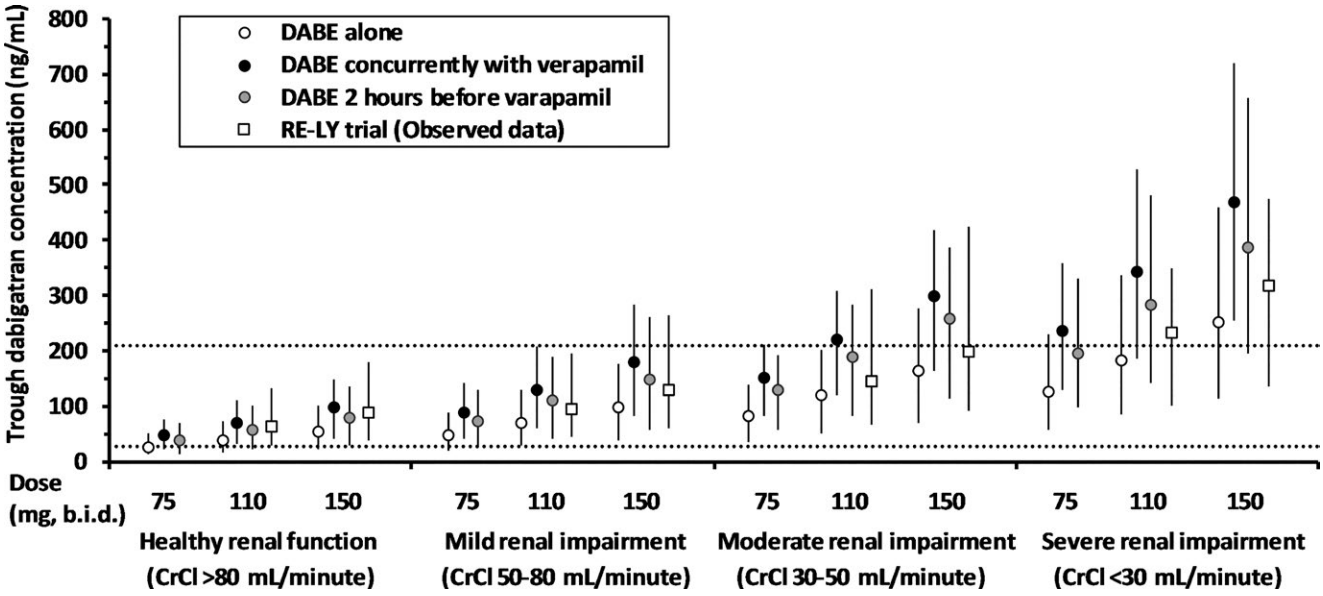

Figure 2 Simulated and observed trough dabigatran concentrations after multiple dose (75, 110, or 150 mg b.i.d.) of dabigatran etexilate (DABE) without, concurrently with, or 2 hours before verapamil in the population with healthy renal function (creatinine clearance (CrCl) >80 mL/min) and the populations with mild (CrCl 50–80 mL/min), moderate (CrCl 30–50 mL/min), and severe (CrCl 15–30 mL/min) renal impairment. Virtual studies were simulated using 20 trials of 10 virtual individuals. Data are presented as the medians and 10th/90th percentiles of all 20 trials. Observed concentrations were calculated using dose-normalized concentrations extracted from the literature (Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial).[10] Lower and upper dotted lines indicate 28 ng/mL with 50% increase in the risk of ischemic stroke or systemic embolism and 210 ng/mL with a doubled risk of major bleeding, respectively. b.i.d., twice a day.

DAB PBPK model (**Figure 2**). The standard (150 mg b.i.d.) and reduced (75 or 110 mg b.i.d.) doses of DABE were used in simulations to investigate an appropriate dosing regimen for achieving the 10th/90th percentiles of C_{trough} within the therapeutic range.[10] The predicted C_{trough} values were close to the observed data obtained from the RE-LY Trial, which included patients with the coadministration of P-gp inhibitors.[10] Predicted 10th/90th percentiles of C_{trough} values in the absence of verapamil were within the therapeutic range when 150 mg b.i.d. DABE was administered to the mild renal impairment population (37–177 ng/mL) and 110 mg b.i.d. to the moderate renal impairment population (51–203 ng/mL), but these were slightly below the lower limit of the therapeutic range when 150 mg b.i.d. DABE was administered to the healthy renal function population (23–100 ng/mL). For the severe renal impairment population, the predicted values of C_{trough} exceeded the upper limit of the therapeutic range even when a reduced

dose of 75 mg b.i.d. DABE was administered in the absence of verapamil (57–229 ng/mL).

Plasma DAB concentrations were simulated in the presence of a multiple dose of verapamil (**Figure 2**). For the healthy renal function population, the predicted 10th/90th percentiles of C_{trough} were 43 to 149 and 28 to 136 ng/mL after 150 mg b.i.d. DABE was administered concurrently with and 2 hours before verapamil, respectively, which produced DAB concentrations within the therapeutic range. The predicted 10th/90th percentiles of C_{trough} in the healthy renal function population were below the lower limit of the therapeutic range (21–100 ng/mL) when 110 mg b.i.d. DABE was administered 2 hours before verapamil and within the therapeutic range (31–109 ng/mL) when administered concurrently with verapamil. The predicted 10th/90th percentiles of C_{trough} in the mild renal impairment population exceeded the upper limit of the therapeutic range when 150 mg b.i.d. DABE was administered concurrently with and 2 hours before verapamil (82–282 and 57–260 ng/mL, respectively) and were within the therapeutic range when 110 mg b.i.d. DABE was administered concurrently with and 2 hours before verapamil (60–206 and 42–190 ng/mL, respectively). The predicted 10th/90th percentiles of C_{trough} in the moderate renal impairment population exceeded the upper limit of the therapeutic range when 110 mg b.i.d. DABE was administered concurrently with and 2 hours before verapamil (121–307 and 83–283 ng/mL, respectively) and were within the therapeutic range when 75 mg b.i.d. DABE was administered concurrently with and 2 hours before verapamil (82–209 and 57–193 ng/mL, respectively). The median predicted C_{trough} in the severe renal impairment population exceeded the upper limit of the therapeutic range when 75 mg b.i.d. DABE was administered concurrently with verapamil (234 ng/mL).

DISCUSSION

This study provides valuable data that were lacking thus far concerning the optimization of DABE dosing regimens in renal impairment populations who are not routinely assessed as part of clinical DDI studies. The DABE/DAB PBPK model was used to predict the DDI effect between DABE and the P-gp inhibitor verapamil in populations with renal impairment. Virtual DDI studies using PBPK modeling revealed that when coadministered with multiple verapamil doses, the optimal DABE dosing varied among populations with healthy renal function and mild and moderate renal impairment. Specifically, the moderate renal impairment population required a two-stage reduction (75 mg b.i.d.) of the DABE dose when coadministered with multiple verapamil doses, suggesting that a one-stage reduction (110 mg b.i.d.) of the DABE dose was not enough to decrease the risk of major bleeding. The present study demonstrates that the population-based PBPK model can provide the most appropriate dosing regimen of DABE for likely clinical scenarios, including DDIs in this renal impairment population based on available knowledge of the systems changes and in the absence of actual clinical studies.

The DABE/DAB PBPK model was used to predict P-gp–mediated DDIs (**Figure 2**). The accurate prediction of P-gp–mediated DDIs in the intestine can be achieved using more appropriate parameters for permeability and P-gp–mediated efflux in the intestine. Therefore, the values of regional $P_{eff,man}$ and P-gp J_{max} in the intestine were optimized using observed clinical data of bioavailability and exposure ratio with the P-gp inhibitors verapamil and its metabolite norverapamil.[2,6] The model successfully predicted DDIs between DABE and the P-gp inhibitors, such as verapamil and norverapamil, and quinidine in healthy volunteers (**Table 3**). The previous PBPK modeling for DABE and DAB was performed using a static approach in which the effective inhibitor concentration is kept unchanged.[30] The static approach is unlikely to simulate plasma DAB concentration profiles when the dosing time of verapamil shifts from that of DABE, although DDI between DABE and verapamil could be minimized if DABE was administered 2 hours prior to verapamil.[6] Our DABE/DAB PBPK model in conjunction with the verapamil/norverapamil PBPK model could predict the DDI effect when DABE was administered 2 hours before verapamil (**Table 3**). The P-gp inhibitory effect of norverapamil is important for estimating the P-gp–mediated DDI effect when the dosing time of verapamil shifts from that of DABE. The P-gp K_i value for norverapamil used in the verapamil/norverapamil PBPK model was 0.3 μM as determined based on the literature,[26] because in the preliminary study, the default value (0.04 μM) in the Simcyp compound library overestimated the P-gp–mediated DDI effect when DABE was administered 2 hours before verapamil. Thus, these PBPK models can be used to investigate P-gp–mediated DDIs in various scenarios.

The DABE/DAB PBPK model could recover plasma concentration–time profiles of DAB in renal impairment populations (**Figure 1f–h**). The renal excretion of DAB in the model, which was defined using the typical renal clearance for healthy male volunteers, predicted DAB elimination from the body in virtual renal impairment populations generated assuming varying levels of CrCl. The model fulfilled the twofold criterion for the difference between the observed and predicted exposure parameters: the predicted values of $AUC_{0-\infty}$ were in agreement with the observed values, but the C_{max} values were underestimated regardless of the CrCl values in our populations. This underestimation of C_{max} was attributed to difference in the volume of distribution between the early and terminal phases of DAB distribution based on the evidence of a multiexponential decrease in DAB concentration after intravenous administration.[2] Owing to the incorporation of distribution volume in the terminal phase, the DABE/DAB PBPK model accurately recovered C_{trough} values of DAB after the repeated administration of DABE because of the accurate prediction in the elimination phase (**Figure 1b**). Moreover, the predicted C_{trough} values in each renal impairment population were also close to observed data obtained from the RE-LY Trial.[10] These findings suggest that this PBPK model can be used for virtual DDI studies in renal impairment populations. The predicted DAB concentration profile in the severe renal impairment population was underestimated when compared with the observed profile, although the predicted exposure parameters were within twofold of the observed values (**Figure 1h**). The metabolic enzyme activity and transporter function are suppressed in chronic renal failure most likely because of the accumulation of uremic toxins.[31] This underestimation in severe renal

impairment population may be attributed to the decrease of the intestinal P-gp–mediated efflux in the actual patients because intestinal P-gp activity is decreased in rats with chronic renal failure.[31]

Virtual DDI studies between DABE and verapamil through PBPK modeling were conducted in virtual renal impairment populations, which revealed that when the standard dose (150 mg b.i.d.) of DABE was administered, the predicted 90th percentiles of C_{trough} for both mild and moderate renal impairment populations in the presence of verapamil exceeded the upper limit of the therapeutic range regardless of the dosing time of verapamil (**Figure 2**). The predicted C_{trough} values within the therapeutic range were provided when 110 mg b.i.d. and 75 mg b.i.d. were administered for mild and moderate renal impairment populations, respectively, in the presence of verapamil (**Figure 2**). These results suggest that, when coadministered with a multiple verapamil dose, one-stage (110 mg b.i.d.) and two-stage (75 mg b.i.d.) reductions of the DABE dose are required for mild and moderate renal impairment populations, respectively, if DABE is administered 2 hours before the verapamil dose when possible. The US Food and Drug Administration has approved the two-stage reduced dose of 75 mg b.i.d. in patients with moderate renal impairment only when coadministered with the strong P-gp inhibitors dronedarone or systemic ketoconazole, which is contraindicated in the European Union.[7,9] The use of P-gp inhibitors, including verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor, does not require DABE dose adjustment in the United States.[9] The DABE dose of 110 mg b.i.d. is considered in the European Union and Japan when DABE is administered to patients with either moderate renal impairment or coadministration of a moderate P-gp inhibitor,[7,8] whereas the recommended dosing is not provided for patients with both of these factors. The difference in dosing recommendations among the European Union, Japan, and the United States can be attributed to the lack of information regarding the optimization of DABE dosing in renal impairment populations, which are not routinely assessed as part of clinical DDI studies. Furthermore, the population with healthy renal function may not require the reduced DABE dose when coadministered with a multiple verapamil dose because the predicted C_{trough} values were within the therapeutic range (**Figure 2**). The DABE dose should not be administered 2 hours before the verapamil dose when a one-stage reduced DABE dose was administered to the population with healthy renal function with the coadministration of verapamil because the subtherapeutic DAB concentration might be provided in a part of the population. Moreover, the predicted 90th percentile of C_{trough} in the severe renal impairment population exceeded the upper limit of the therapeutic range even when the two-stage reduced DABE dose was administered in both the presence and absence of verapamil, suggesting a twofold risk of major bleeding in some patients.

Our study has several limitations for the model verification and applicability of the current study. First, the predictive performance of the DABE PBPK model was not directly verified using plasma DABE concentration data for renal impairment and P-gp–mediated DDI because the observed data were not available. The changes in the bioavailability of DABE could be reflected in the plasma DAB concentrations, which were used in model verification, because most of absorbed DABE is rapidly converted to DAB prior to systemic circulation, and DAB is not a substrate of P-gp.[2,5] Second, DAB has a more simple elimination primarily through renal excretion with no contribution of P-gp–mediated active renal tubular secretion.[2,5] In case of drugs with more complex elimination such as both renal and hepatic eliminations and both passive glomerular filtration and active renal tubular secretion. The PBPK modeling and simulation used for complex DDI scenarios need to be further verified because renal failure could also affect hepatic metabolism and transporter function.[31]

In conclusion, the DABE/DAB PBPK model was used to predict the DDI effect between DABE and the P-gp inhibitor verapamil in renal impairment populations. Virtual DDI studies between DABE and the P-gp inhibitor verapamil through PBPK modeling provided the most appropriate DABE dosing in renal impairment populations coadministered with verapamil. The population-based PBPK model can help simplify the optimization of dosing regimen for likely clinical scenarios that cannot be observed during drug development.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website. (www.psp-journal.com)

Figure S1. Distributions of creatinine clearance in populations with healthy renal function (A) and mild (B), moderate (C), and severe (D) renal impairments.
Table S1. Input values of renal function for the populations used in virtual studies.
Table S2. Summary of input parameter used for models of digoxin, verapamil, norverapamil, and quinidine.
Table S3. Trial design for virtual studies using a PBPK model of dabigatran etexilate and dabigatran.
Supplementary Material S1. Dabigatran etexilate compound file.
Supplementary Material S2. Dabigatran compound file.

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