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Evaluation and prediction of drug–drug interaction of tegoprazan using physiologically based pharmacokinetic modeling

생리학 기반 약물동태 모델링을 이용한 테고프라잔의 약물–약물 상호작용 평가 및 예측

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Ph.D. Dissertation of Medical Science

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ABSTRACT

Evaluation and prediction of drug–drug interaction of tegoprazan using physiologically based pharmacokinetic modeling

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Introduction: Tegoprazan, a potassium–competitive acid blocker, is a potential substrate of cytochrome P450 (CYP) 3A4. The clinical drug–drug interaction (DDI) studies of tegoprazan conducted so far have been limited to the DDI between tegoprazan and clarithromycin or clarithromycin and amoxicillin. Therefore, further studies may be required to assess the DDI between tegoprazan and other CYP3A4 perpetrators, which can affect both pharmacokinetics (PKs) and pharmacodynamics of tegoprazan by inducing or inhibiting the activity of CYP3A4. Physiologically based pharmacokinetic (PBPK) modeling is an *in silico* mechanistic approach combining the concept of the

anatomical and physiological properties of the human body and the physicochemical and biological properties of a drug to simulate and predict the PK profile of the drug. This study aimed to develop a PBPK model of tegoprazan and to predict the potential of DDI between tegoprazan and CYP3A4 perpetrators.

Methods: A minimal PBPK model with a single adjusted compartment was constructed, reflecting enzyme kinetic elimination, using the SimCYP simulator. The model was refined and verified by comparing the model-predicted PKs of tegoprazan with the observed data from various phase 1 clinical studies including DDI study between tegoprazan and clarithromycin. DDIs between tegoprazan and five CYP3A4 perpetrators (i.e., clarithromycin, ketoconazole, carbamazepine, rifampicin and phenobarbital) were predicted using a validated PBPK model by simulating the change of tegoprazan exposure after multiple doses with or without the perpetrators over a clinically used dose range.

Results: The final PBPK model adequately predicted the biphasic distribution profiles of tegoprazan and DDI between tegoprazan and clarithromycin. All ratios of the predicted-to-observed pharmacokinetic parameters were within 0.5 and 2.0, which met the conventionally accepted criteria. In the DDI simulation, systemic exposure to tegoprazan was expected to increase by about threefold

when co-administered with the maximum recommended dose of clarithromycin or ketoconazole. Meanwhile, tegoprazan exposure was expected to decrease to ~30% when carbamazepine, rifampicin or phenobarbital was co-administered.

Conclusion: The PBPK model of tegoprazan was successfully established and it adequately predicted the DDI between tegoprazan and clarithromycin. Based on the simulation by the PBPK model, the DDI potential should be considered when tegoprazan is used with CYP3A4 perpetrator, because the acid suppression effect of tegoprazan is known to be associated with systemic exposure.

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Keyword : Tegoprazan, CYP3A4, Drug-drug interaction(DDI), Physiologically based pharmacokinetic (PBPK) model

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AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{last}	Area under the concentration-time curve from time 0 to the last observation
CL_{int}	Intrinsic clearance
C_{max}	Maximum plasma concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction
PBPK	Physiologically based pharmacokinetics
PK	Pharmacokinetics
PD	Pharmacodynamics
$t_{1/2}$	Half-life
T_{max}	Time to reach maximum plasma concentration

INTRODUCTION

Tegoprazan is an acid suppression agent for the treatment of patients with acid-related diseases, including gastroesophageal reflux disease, peptic ulcer diseases, and *Helicobacter pylori* infection. The mechanism of acid suppression by tegoprazan is to reversibly inhibit gastric H^+/K^+-ATPase in a potassium-competitive manner [1]. In a phase 1 clinical study, tegoprazan up to 400 mg for a single dose and 200 mg for multiple doses was safe and tolerable for healthy adults, and the systemic exposure to tegoprazan increased in a dose proportional manner [2]. The mean half-life of tegoprazan is reported to be 3.7-6.2 h, and the apparent clearance and volume of distribution are reported to be approximately 17.6 L/h and 107.9 L, respectively [2-4]. The magnitude of acid suppression increases in a dose-dependent manner from 50 mg to 400 mg [2]. The approved dose of tegoprazan for acid-related diseases is 50 mg once daily.

The major metabolic pathway of tegoprazan is the liver, and a negligible amount is excreted via the urine. Both *in vitro* and clinical results have elucidated that tegoprazan is a potential substrate of cytochrome P450 (CYP) 3A4. In an *in vitro* study, ketoconazole, a strong inhibitor of CYP3A4, significantly inhibited the metabolism of tegoprazan in human liver microsomes, while other CYP inhibitors did

not significantly affect the metabolic clearance of tegoprazan. According to the label of tegoprazan, systemic exposure to tegoprazan increases when tegoprazan is co-administered with clarithromycin. Based on the *in vitro* and clinical data, it can be inferred that a drug-drug interaction (DDI) between tegoprazan and CYP3A4 inhibitor may occur. However, the clinical DDI studies of tegoprazan conducted so far have been limited to the DDI between tegoprazan and clarithromycin or clarithromycin and amoxicillin, because tegoprazan is likely to be co-administered with these medications for *Helicobacter pylori* eradication [4]. Considering the substantial prevalence of acid-related diseases, tegoprazan is likely to be administered in combination with various drugs [5, 6]. Therefore, additional studies may be required to assess the DDI between tegoprazan and other CYP3A4 perpetrators, which can affect both pharmacokinetics (PKs) and pharmacodynamics (PDs) of tegoprazan by inducing or inhibiting the activity of CYP3A4. Nevertheless, it could be challenging to conduct clinical studies for all possible cases of DDIs between tegoprazan and CYP3A4 perpetrators.

Physiologically based pharmacokinetic (PBPK) modeling is *in silico* mechanistic modeling combining the concept of the anatomical and physiological properties of the human body and the

physicochemical and biological properties of a drug to simulate and predict the PK profile of the drug. Consequently, PBPK modeling and simulation can be applied to various steps in drug development [7]. The European Medicines Agency and the US Food and Drug Administration (FDA) published guidelines on PBPK modeling and simulation to manage PBPK qualification procedures intended for regulatory submission [8]. The simulation results from the PBPK model can contribute to regulatory decision making from a clinical pharmacology perspective, and the majority of applications of the PBPK approach in drug development have focused on the prediction of the DDIs [9–11]. Therefore, by constructing the PBPK model of tegoprazan, it is able to evaluate the DDI potential of tegoprazan as a substrate of CYP3A4. In other words, it is possible to quantitatively evaluate how the PKs of tegoprazan are altered.

Based on these understandings, the aim of this study was to develop and verify a PBPK model of tegoprazan to predict quantitatively the DDIs between tegoprazan and CYP3A4 inhibitors or inducers, and to establish the DDI–exposure–response relationship of tegoprazan to contribute personalized pharmacotherapy of tegoprazan (**Figure 1**).

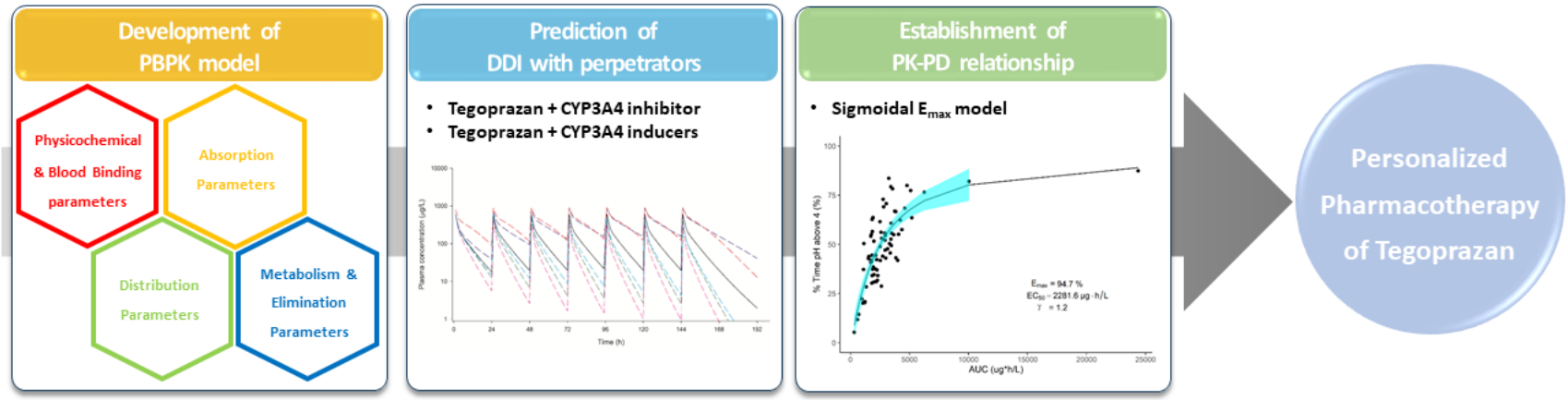


Figure 1. The overall concept of the study.

METHODS

Development of the PBPK model

A PBPK model of tegoprazan was built and verified by both the bottom-up approach using *in vitro* data for maintaining a mechanistic PBPK structure and the top-down approach using clinical PK results for maintaining a descriptive structure (**Figure 2**). The initial PBPK model of tegoprazan was constructed using physicochemical properties (e.g., molecular weight, log P, pKa), *in vitro data* (e.g., permeability, intrinsic clearance), and *in vivo* data (e.g., renal clearance) provided by HK inno.N Corp. (Seoul, Korea). The commercially available software SimCYP simulator v19 (SimCYP Limited, Certara, Sheffield, UK) was used to build the PBPK model and generate the PK simulations. The PBPK model-predicted PK profiles and parameters of tegoprazan were compared with the observed PK profiles and parameters from previously conducted clinical studies [3, 4, 12]. The specific model configuration related to absorption, distribution, and elimination is described below.

Absorption

The advanced dissolution, absorption, and metabolism model was used [13]. The unbound fraction of the drug in enterocytes (fu_{Gut}) and the human jejunum effective permeability ($P_{eff,man}$) were

predicted because these values are not routinely measured (Table 1). The value of fu_{Gut} was predicted using the values of the *in vitro* parameters, such as the octanol:water partition coefficient, the fraction of intracellular water, and other distribution-related parameters. The value of $P_{eff,man}$ was predicted using the parallel artificial membrane permeation assay permeability.

Distribution

A minimal PBPK model with a single adjusted compartment (SAC) was used. The volume of distribution in the steady state was predicted using the method suggested by Rodgers and Rowland, based on the values of the *in vitro* parameters (e.g., tissue neutral lipids, neutral phospholipids, tissue concentrations of acidic phospholipids, extracellular albumin) [14] (Table 1). The parameters for blood flow between the central compartment and SAC (Q) and the volume of SAC (V_{SAC}) were included in the model to reflect the biphasic distribution of tegoprazan. The values of Q, V_{SAC}, and scalar applied to all predicted tissue Kp values (Kp scalar) were estimated to best describe the observed clinical data.

Elimination

The elimination of the PBPK model consisted of enzyme kinetic and renal clearance (Table 1). Intrinsic clearances (CL_{int}) of tegoprazan by various CYPs were determined by an *in vitro* study

that measured the fraction of CL_{int} inhibited by adding inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A to human liver microsomes. Based on the *in vitro* data, an in vitro–to–in vivo extrapolation (IVIVE) approach was used to estimate the *in vivo* CL_{int} by each CYP enzyme [15]. Renal clearance as an additional clearance was used from the result of a single–oral–dose study of tegoprazan 100 mg.

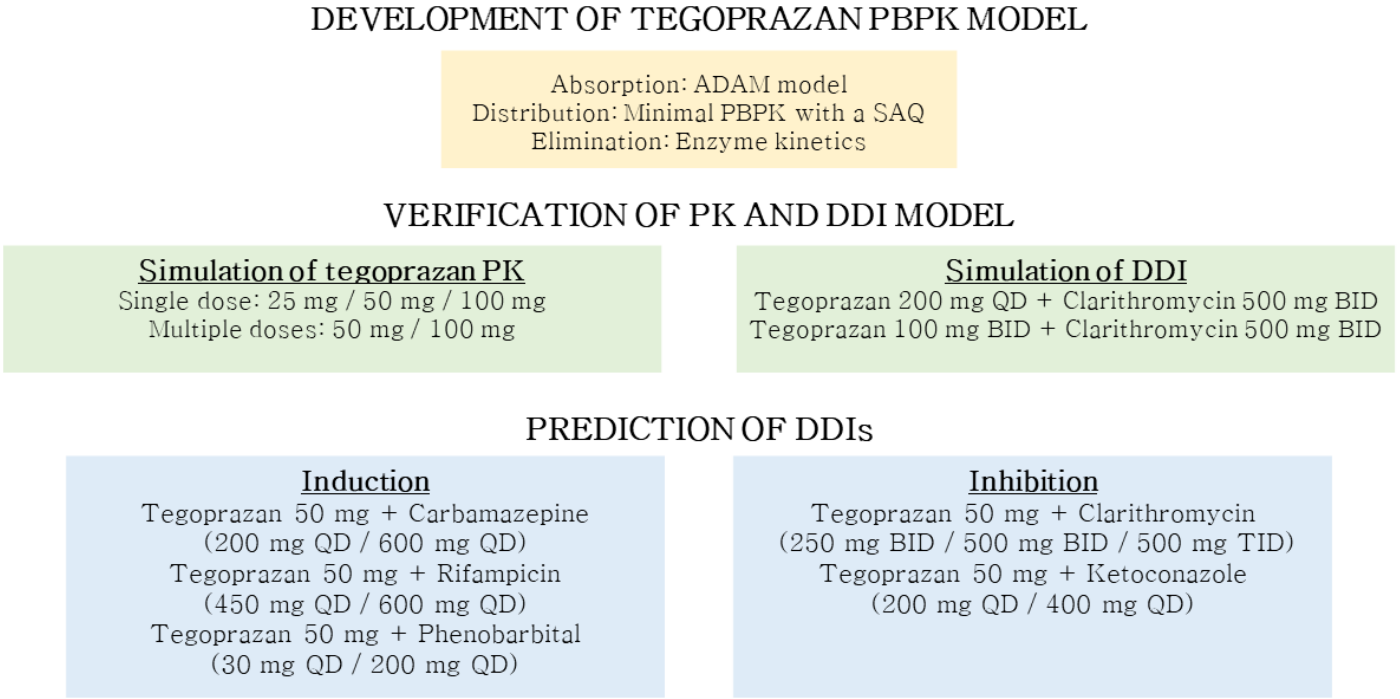


Figure 2. Overview of the tegoprazan physiologically based pharmacokinetic modeling process.

Table 1. The parameter values used for the physiologically based pharmacokinetic model of tegoprazan.

Parameters and models		Value	Source
Physiochemical properties	MW	387.38	Experimental data
	Log P	3	Experimental data
	pKa	Ampholyte pKa 1: 5.2 pKa 2: 12	Experimental data
	B/P	0.868	Experimental data
	fu	0.124	Experimental data
Absorption			
ADAM model			
	fu_{Gut}	0.008	Predicted using method 2 (Rodgers & Rowland, 2007)
	$P_{eff,man}$	12.397	Predicted using PAMPA permeability data
	PAMPA	68.4	Experimental data
Distribution			
Minimal PBPK model + SAC	V_{ss}	1.128	Predicted using method 2 (Rodgers & Rowland, 2007)
	Q	24.4	Estimated
	V_{SAC}	0.66	Estimated
	Kp scalar	0.33	Estimated
Elimination			
	CYP1A2 CL_{int}	2.5	Experimental data
	CYP2C9 CL_{int}	2.6	Experimental data
	CYP2C19 CL_{int}	3.6	Experimental data
	CYP2D6 CL_{int}	2	Experimental data
	CYP3A4 CL_{int}	30.34	Estimated(optimized)
	CL_R	1.31	Experimental data

MW, molecular weight (g/mol); Log P, octanol−water partition coefficient; pKa, acid dissociation constant; B/P, blood/plasma partition ratio; ADAM, advanced dissolution absorption metabolism; fu, faction unbound in plasma; fu_{Gut}, unbound fraction of drug in enterocytes; $P_{eff,man}$, human jejunum effective permeability (10^{-4} cm/s); PAMPA, permeability measured by parallel artificial membrane permeability assay (10^{-6} cm/s); SAC, single adjusted compartment; V_{SAC}, volume of the single adjusted compartment (L/kg); Q, blood flow (L/h); V_{ss}, volume of distribution at steady state (L/kg); Kp, scalar applied to all predicted tissue Kp values; CL_{int}, intrinsic clearance (μL/min/mg protein); CL_R, renal clearance (L/h).

Refinement and verification of the PBPK model

The PBPK model-predicted PK profiles and parameters of tegoprazan were compared with the observed PK profiles and parameters from previously conducted clinical studies. The established PBPK model was verified by applying the predicted values to the clinical PK data from various phase 1 studies conducted with healthy male adults (Table 2). Brief information about the clinical studies are as follows: study 1 (single-dose PK study), a single dose of tegoprazan 25 mg and 50 mg was orally administered; study 2 (food effect study), a single dose of tegoprazan 50 mg was orally administered in both fasted and fed states [12]; study 3 (bioequivalence study of two formulations), a single dose of two different formulations with tegoprazan 100 mg was orally administered [3]; study 4 (multiple-dose PK study), multiple doses of tegoprazan 50 mg and 100 mg were orally administered once daily for 7 days; study 5 (DDI study with clarithromycin), multiple doses of tegoprazan 200 mg were orally administered once daily with or without multiple doses of clarithromycin 500 mg twice daily for 5 days; and study 6 (DDI study with clarithromycin and amoxicillin), multiple doses of tegoprazan 100 mg were orally administered twice daily with or without multiple doses of clarithromycin/amoxicillin 500/1000 mg twice daily for 5 or 7 days [4].

The PBPK model of tegoprazan as a single agent was verified using data from clinical studies of single- and multiple-dose administration of different dosages of tegoprazan (Table 3). To verify the PK predictability of the PBPK model, the model-predicted PK profiles and parameters were compared with the observed PK profiles and parameters measured in clinical studies. The primary PK parameters to be compared were the maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) reflecting systemic exposure. When the observed and predicted PK profiles were similar and the ratios of the predicted-to-observed PK parameters were between 0.5 and 2.0, deciding that the PBPK model was well constructed and the predictability of the PBPK was verified [16].

If the predicted PK profiles and parameters were not close enough to the observed values, the PBPK model was refined by the parameter estimation approach, in which a parameter was optimized with respect to the clinical data [17]. Parameter estimation was conducted using the genetic algorithm method and weighted-least squares as the objective function. Four parameters were simultaneously estimated in the final step of model refinement using the clinical data of single-dose PK study of tegoprazan 50 mg (Table 1). The values of Q and V_{SAC} were estimated to reflect the biphasic

distribution of tegoprazan, and the value of the Kp scalar was estimated because it affected the overall PK profile, especially distribution and clearance. Furthermore, the value of *in vivo* CYP3A4 CL_{int} was also optimized instead of using *in vitro* data, to improve the model fitting to the observed elimination profile. The value of CYP3A4 CL_{int} was one of the most sensitive parameters affecting the PK profile of tegoprazan, considering the results of *in vitro* and clinical studies showing that tegoprazan is mainly metabolized by CYP3A4 and that systemic exposure of tegoprazan increases when a CYP3A4 inhibitor is concomitantly administered.

After refining and verifying the PBPK model of tegoprazan as a single agent, the DDI between tegoprazan and clarithromycin was finally verified using data from DDI clinical studies. To verify the predictability of the DDI estimated by the PBPK model of tegoprazan, the model-predicted PK profiles, parameters, and fold-increase of parameters were compared with the observed PK data measured in clinical studies (i.e., studies 5 and 6). In the case of study 6, the observed data were generated under the condition of triple administration of tegoprazan, clarithromycin, and amoxicillin. However, it was assumed that co-administration of amoxicillin does not affect the PKs of tegoprazan and clarithromycin because the DDI between tegoprazan and amoxicillin is known to be negligible [4], and

there was a low possibility of a DDI between amoxicillin and clarithromycin, considering the metabolic pathways of both drugs [18, 19]. When simulating the DDI between tegoprazan and clarithromycin, the PBPK model of clarithromycin available in the SimCYP compound file was used.

All simulations for model verification were conducted using the same conditions as those used in the clinical studies, as follows: all subjects were healthy male volunteers aged 19–50 years, and tegoprazan and clarithromycin were both administered in fasted state. The output sampling interval in the SimCYP simulator tool box was set to 0.2 h in all simulations. Every clinical trial simulation was conducted in 10 trials with 10 subjects (total 100 subjects).

Table 2. Summary of information on clinical studies of tegoprazan.

Study No.	Study design	No. of subjects	Dose regimen of tegoprazan	PK sampling time	Reference*
Study 1	Single-dose pharmacokinetic study	12	25 mg / 50 mg single	up to 48 h	NCT03530228
Study 2	Food effect study	12	50 mg single	up to 48 h	NCT03863938
Study 3	Bioequivalence study of two formulations	12	100 mg single	up to 48 h	NCT02995239
Study 4	Multiple-dose pharmacokinetic study	6	50 mg /100 mg QD for 7days	up to 48 h	NCT03009760
Study 5	DDI study with clarithromycin	24	200 mg QD for 5 days	up to 48 h	NCT02052336
Study 6	DDI study with clarithromycin and amoxicillin	24	100 mg BID for 5 days or 7 days	up to 48 h	NCT03011996

QD, once daily; BID, twice daily; DDI, drug-drug interaction. *References are ClinicalTrials.gov Identifier

Table 3. Simulation outline of tegoprazan single- and multiple-dose pharmacokinetic and drug-drug interaction studies.

Tegoprazan	Dose (mg)	Treatment Day	Interacting Drug	Dose (mg)	Treatment Day	Analysis
Single dose	25	1	-	-	-	Pred. versus Obs.
	50	1	-	-	-	Pred. versus Obs.
	100	1	-	-	-	Pred. versus Obs.
Multiple dose	50 QD	7	-	-	-	Pred. versus Obs.
	100 QD	7	-	-	-	Pred. versus Obs.
Multiple dose with interacting drug	200 QD	5	Clarithromycin	500 BID	5	Pred. versus Obs.
	100 BID	5/7*	Clarithromycin	500 BID	7	Pred. versus Obs.
	50 QD	7	Clarithromycin	250 BID	7	Pred.
	50 QD	7	Clarithromycin	500 BID	7	Pred.
	50 QD	7	Clarithromycin	500 TID	7	Pred.
	50 QD	7	Ketoconazole	200 QD	7	Pred.
	50 QD	7	Ketoconazole	400 QD	7	Pred.
	50 QD	7	Carbamazepine	200 QD	7	Pred.
	50 QD	7	Carbamazepine	800 BID	7	Pred.
	50 QD	7	Rifampicin	450 QD	7	Pred.
	50 QD	7	Rifampicin	600 QD	7	Pred.
	50 QD	7	Phenobarbital	30 QD	7	Pred.
	50 QD	7	Phenobarbital	200 QD	7	Pred.

QD, once daily; BID, twice daily; TID, three times a day, Pred., Predicted data; Obs., Observed data. *When tegoprazan was administered alone, tegoprazan was administered for 5 days, while, when tegoprazan was co-administered with clarithromycin, tegoprazan was administered for 7 days.

Table 4. Parameter values related to drug-drug interaction used for the physiologically based pharmacokinetic model for perpetrators.

Perpetrators	Parameters		Value	Mechanisms*
Inhibitors				
Clarithromycin	CYP3A4	K_i	10	Competitive
		fu_{mic}	0.87	inhibition
	CYP3A4	K_{app}	12	Mechanism
		K_{inact}	2.13	based inhibition
		fu_{mic}	1	
Ketoconazole	CYP3A4	K_i	2.5	Competitive
		fu_{mic}	0.87	inhibition
	CYP2C9	K_i	10	Competitive
		fu_{mic}	0.95	inhibition
	CYP3A4	K_i	0.015	Competitive
		fu_{mic}	0.97	inhibition
	CYP3A5	K_i	0.109	Competitive
		fu_{mic}	0.96	inhibition
Inducers				
Carbamazepine	CYP3A4	Ind_{slop}	0.16	Induction
	CYP3A5	Ind_{slop}	0.16	Induction
Rifampicin	CYP1A2	Ind_{max}	2.7	Induction
		$IndC_{50}$	0.1	
	CYP2B6	Ind_{max}	5.04	Induction
		$IndC_{50}$	0.07	
	CYP2C8	Ind_{max}	6.7	Induction
		$IndC_{50}$	0.3	
	CYP2C8	K_i	24.5	Competitive
		fu_{mic}	1	inhibition
	CYP2C9	Ind_{max}	6	Induction
		$IndC_{50}$	0.1	
	CYP2C19	Ind_{max}	5.5	Induction
		$IndC_{50}$	0.45	
	CYP3A4	Ind_{max}	16	Induction
		$IndC_{50}$	0.32	
	CYP3A4	K_i	15	Competitive
		fu_{mic}	1	inhibition
	CYP3A5	Ind_{max}	16	Induction
		$IndC_{50}$	0.32	
Phenobarbital	CYP2C9	Ind_{max}	3.74	Induction
		$IndC_{50}$	68	
	CYP3A4	Ind_{max}	23.4	Induction
		$IndC_{50}$	334.9	

K_i, concentration of inhibitor that support half maximal inhibition (μ M); fu_{mic}, fraction of unbound drug in the *in vitro* microsomal incubation; K_{app}, concentration of mechanism-based inhibitor associated with half maximal inactivation rate (μ M); k_{inact},

inactivation rate of enzyme (1/h); Ind_{max}, maximal fold induction over vehicle; $IndC_{50}$, test compound concentration that supports half maximal induction (μM); Ind_{slop}, slope of the fold induction vs. concentration plot when induction is linear within the range of test compound concentration (1/μM).

*Coefficient of variations for Ind_{slop}, Ind_{max} and $IndC_{50}$ were set to 30, and fraction of unbound drug in the *in vitro* incubation and Hill equation exponent which were the parameters of induction were set to 1.

Prediction of a DDI Potential

A DDI potential between the approved dose of tegoprazan and five potent CYP3A4 perpetrators was simulated using the developed PBPK model of tegoprazan and the PBPK models of clarithromycin, ketoconazole, carbamazepine, rifampicin, and phenobarbital available in the SimCYP compound files (Table 3). The necessary parameters of the perpetrators reflecting induction and inhibition were different based on the mechanism, and the parameter values in the default compound files of inhibitors and inducers were used (Table 4). The dosage regimens of tegoprazan, clarithromycin, ketoconazole, carbamazepine, rifampicin and phenobarbital were selected based on the recommended daily doses on the drug labels. Clarithromycin and ketoconazole are well-known strong CYP3A4 inhibitors, and their maximum recommended daily doses are 500 mg three times a day and 400 mg a day, respectively [20, 21]. Carbamazepine, rifampicin and phenobarbital are well-known CYP3A4 inducers, and their maximum recommended daily doses are 800 mg twice a day 600 mg a day and 200 mg a day, respectively [22-24].

The simulation was conducted using the same conditions as under the conditions of the model verification: all subjects were healthy male volunteers aged 19-50 years, and all drugs were assumed to be administered in fasted state. Tegoprazan PK profiles

were predicted up to 192 h under the assumption that tegoprazan was administered alone or co-administered with perpetrators for 7 days. Every clinical trial simulation was conducted in 10 trials with 10 subjects (total 100 subjects). To evaluate the DDI potential of tegoprazan, the simulated PK profiles, PK parameters, and fold-increase PK parameters of tegoprazan with and without perpetrators were compared. The simulation was conducted using the same conditions as the conditions of model verification: all subjects were healthy male volunteers aged 19-50 years, and all drugs were assumed to be administered in fasted state. Tegoprazan PK profiles were predicted up to 192 h under the assumption that tegoprazan was administered alone or co-administered with perpetrators for 7 days. Every clinical trial simulation was conducted in 10 trials with 10 subjects (total 100 subjects). To evaluate the DDI potential of tegoprazan, the simulated PK profiles, PK parameters, and fold-increase PK parameters of tegoprazan with and without perpetrators were compared.

Establishing PK–PD Relationship

The relationship between the exposure and response of tegoprazan was evaluated with PK and PD data from clinical studies (study 1 and study 2) [2, 12]. The PK and PD parameters representing systemic exposure and response were AUC and the percentage of time of pH greater than or equal to 4, respectively. The PK–PD relationship of tegoprazan was described by the sigmoidal E_{max} model:

$$E = E_0 + \frac{E_{max} \times AUC^{\gamma}}{EC_{50}{}^{\gamma} + AUC^{\gamma}}$$

The 4 parameters of the sigmoidal E_{max} model, including the baseline (E_0), maximum effect (E_{max}), half of the maximum effect (EC_{50}) and the Hill coefficient (γ) were estimated using nonlinear least squares in the R package. The changes in the efficacy of tegoprazan 50 mg depending on the various CYP3A4 perpetrators were estimated using the PK–PD relationship.

RESULTS

Pharmacokinetic predictions of tegoprazan

The final PBPK model of tegoprazan adequately predicted the PK profiles of tegoprazan after single- and multiple-dose administration. The biphasic time-concentration profiles of tegoprazan after single- and multiple-dose administration of tegoprazan were well predicted by the final PBPK model (**Figure 3**). In addition, all ratios of the predicted-to-observed PK parameters, including C_{max} and AUC, were between 0.5 and 2.0, indicating that the model reproduced properly the observed PKs of tegoprazan (**Table 5**). The model-predicted median fraction of tegoprazan metabolized by hepatic CYP enzymes was calculated as 0.92, among which the portion of hepatic CYP3A4 accounted for 0.73.

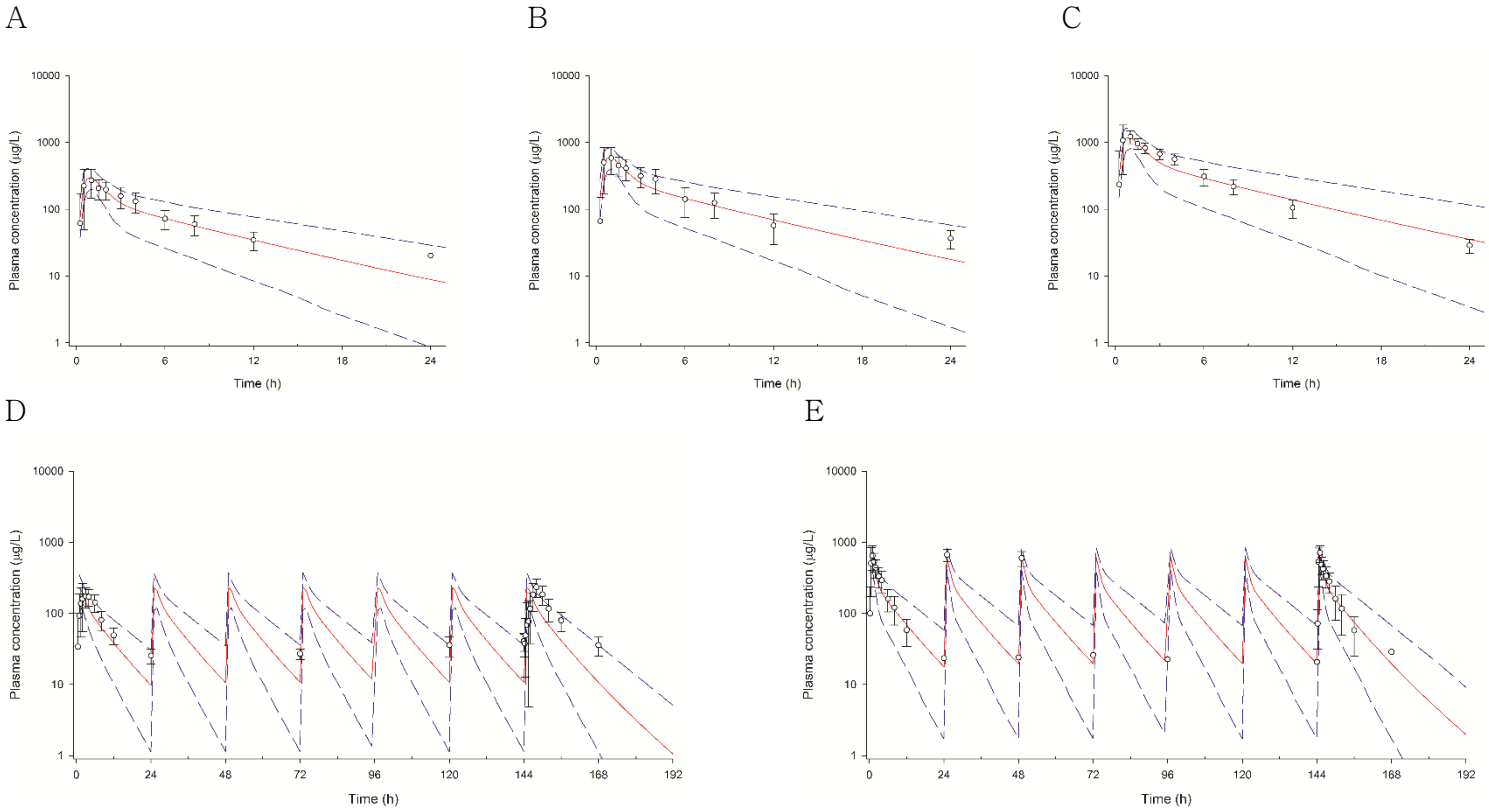


Figure 3. Observed and physiologically based pharmacokinetic–model–predicted plasma concentrations of tegoprazan in healthy subjects after single and multiple oral administration. The open circles and error bars represent the measured concentrations of tegoprazan and the standard deviations, respectively. The solid red lines and the dashed blue lines represent the simulated mean time–concentration profiles and the 5th–95th percentile of the total virtual population, respectively. (A) 25 mg single, (B) 50 mg single, (C) 100 mg single, (D) 50 mg multiple, and (E) 100 mg multiple.

Table 5. A summary of the observed and predicted pharmacokinetic parameters of tegoprazan using the final physiologically based pharmacokinetic model.

Treatment	Dose (mg)	n		T_{max} (h)*		C_{max} (μg/L)			AUC_{inf} or AUC_{τ} (μg·h /L)**		
		Pred.	Obs.	Pred.	Obs.	Pred.	Obs.	R.	Pred.	Obs.	R.
Single oral dose	25	100	12	0.95 [0.50-1.62]	0.75 [0.50-3.00]	310.4	335.6	0.92	1479.4	1340.0	1.03
	50	100	24	0.95 [0.50-1.62]	1.00 [0.50-2.00]	620.6	759.1	0.82	2958.6	2903.0	1.02
	100	100	12	0.95 [0.50-1.62]	1.00 [0.50-1.00]	1241.2	1434.5	0.87	5916.6	5998.1	0.99
Multiple oral doses†	50	100	6	0.94 [0.51-1.59]	1.00 [0.50-1.03]	638.9	842.8	0.76	2969.5	2954.9	1.00
	100	100	6	0.95 [0.50-1.58]	1.25 [0.50-3.00]	1277.6	1149.7	1.11	5929.4	4768.4	1.24

T_{max}, time to reach maximum plasma; C_{max}, maximum plasma concentration; AUC_{inf}, area under the concentration–time curve from time zero to infinity; AUC_{τ}, area under the concentration–time curve from time zero to 24h concentration; Pred., Predicted data; Obs., Observed data; R., Ratio (Pred./Obs.).

Data are presented as the mean. *T_{max} is expressed as the median [range].

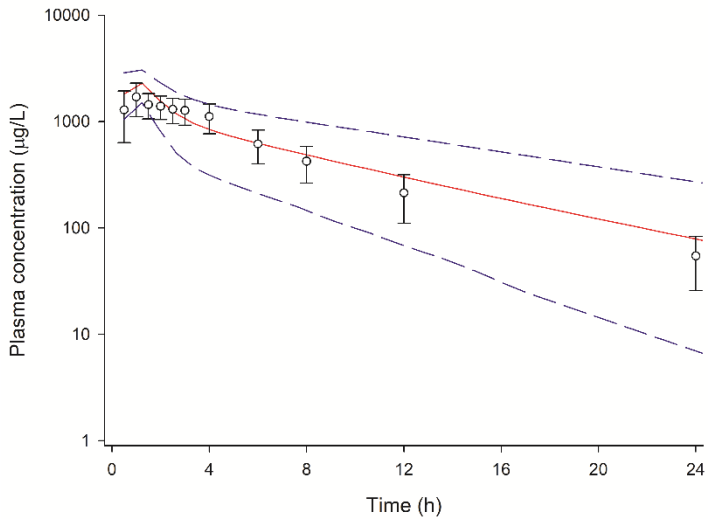
**AUC_{inf} or AUC_{τ} were evaluated followed by single and multiple administration, respectively.

†Multiple oral doses of tegoprazan were administered once daily for 7 days.

Performance of the PBPK Model in Predicting DDI

The final PBPK model also predicted the DDI between tegoprazan and clarithromycin in that the model-predicted PK profiles of tegoprazan when tegoprazan was co-administered with clarithromycin were similar to the observed PK profile (**Figure 4**). The ratios of the predicted-to-observed PK parameters of tegoprazan were all between 0.5 and 2.0 when tegoprazan was administered with clarithromycin (**Table 6**). The model-predicted fold-increase of AUC during a dosage interval (AUC_{τ}) for tegoprazan was similar to the observed value when tegoprazan was administered with clarithromycin; however, the fold-increase of C_{max} for tegoprazan was somewhat under-predicted.

A



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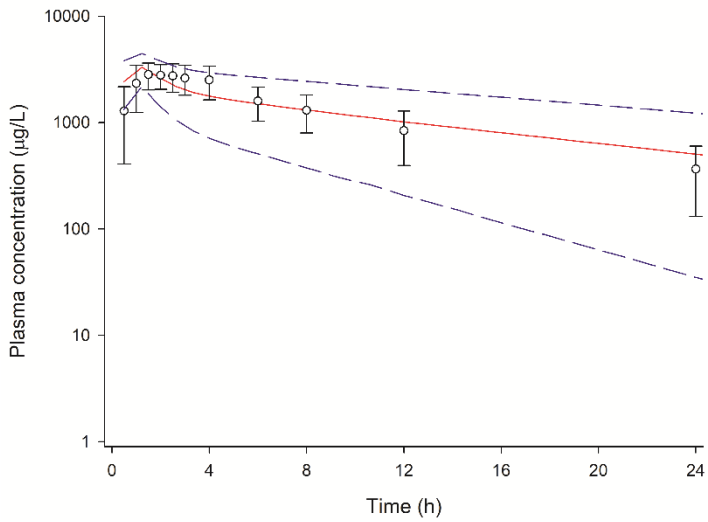

Figure 4. Observed and physiologically based pharmacokinetic–model–predicted plasma concentrations of tegoprazan following multiple oral administration of tegoprazan with and without clarithromycin. The open circles and error bars represent the measured concentrations of tegoprazan and the standard deviations, respectively. The solid red lines and the dashed blue lines represent the simulated mean time–concentration profiles and the 5th–95th percentile of the total virtual population, respectively. (A) Tegoprazan alone and (B) tegoprazan with clarithromycin.

Table 6. A summary of observed and predicted pharmacokinetic parameters of tegoprazan when co-administered with clarithromycin or clarithromycin/amoxicillin.

Treatment	n		T_{max} (h)*		C_{max} (μg/L)			AUC_{τ} (μg·h /L)		
	Pred.	Obs.	Pred.	Obs.	Pred.	Obs.	R.	Pred.	Obs.	R.
T 200 mg QD†	100	24	0.95 [0.50–1.58]	1.00 [0.50–4.00]	2554.8	1868.6	1.37	11838.9	10817.6	1.09
T 200 mg QD + C 500 mg BID†	100	24	1.04 [0.55–1.62]	1.50 [1.00–4.00]	3491.4	3096.0	1.13	28881.4	27796.4	1.04
T 100 mg BID††	100	20	0.95 [0.51–1.55]	1.30 [0.50–6.00]	1411.3	1018.4	1.39	5921.6	5955.9	0.99
T 100 mg BID + C 500 mg BID + A 1000 mg BID†††	100	20	1.03 [0.55–1.55]	2.50 [1.00–3.00]	2268.2	2285.6	0.99	14897.5	16045.0	0.93

T, tegoprazan; C, clarithromycin; A, amoxicillin; QD, once daily; BID, twice daily; T_{max}, time to reach the maximum plasma concentration; C_{max}, maximum plasma concentration; AUC_{τ}, area under the concentration–time curve from time zero to 24 h concentration; Pred., predicted data; Obs., observed data; R., Ratio (Pred./Obs.).

Data are presented as the mean. *T_{max} is expressed as the median [range].

†Tegoprazan 200 mg once daily without or with clarithromycin 500 twice daily was administered for 5 days.

††Tegoprazan 100 mg twice daily for 4 days and tegoprazan 100 mg once daily on day 5 were administered.

†††Tegoprazan 100 mg twice daily with amoxicillin 1000 mg/clarithromycin 500 mg twice daily for 6 days and tegoprazan 100 mg once daily with amoxicillin 1000 mg/clarithromycin 500 mg once daily on day 7 were administered.

Table 7. Fold increase of systemic exposure of tegoprazan when co-administered with clarithromycin or clarithromycin/amoxicillin.

Treatment	Fold-increase			
	Pred. $C_{max\,R}$	Obs. C_{maxR}	Pred. AUC_R	Obs. AUC_R
T 200 mg QD + C 500 mg BID†	1.37	1.66	2.44	2.57
T 100 mg BID + C 500 mg BID + A 1000 mg BID††	1.61	2.24	2.52	2.69

T, tegoprazan; C, clarithromycin; A, amoxicillin; QD, once daily; BID, twice daily; C_{maxR}, ratio of increased maximum plasma concentration; AUC_R, ratio of increased area under the concentration-time curve from time zero to 24h; Pred., Predicted data; Obs., Observed data.

*T_{max} is expressed as median [range].

†Tegoprazan 200 mg once daily without or with clarithromycin 500 twice daily was administered for 5 days.

††Tegoprazan 100 mg twice daily with amoxicillin 1000 mg/clarithromycin 500 mg twice daily for 6 days and tegoprazan 100 mg once daily with amoxicillin 1000 mg/clarithromycin 500 mg once daily on 7th day were administered.

DDI potential of tegoprazan

Systemic exposure to tegoprazan was expected to increase significantly when it was co-administered with the maximum recommended daily dose of clarithromycin or ketoconazole. In particular, the elimination profile of tegoprazan was continuously changed during multiple administrations with clarithromycin. However, when tegoprazan was co-administered with rifampicin, it was expected that tegoprazan elimination would gradually increase with multiple administrations, resulting in a decrease in systemic exposure (**Figure 5**). It was predicted that the $AUC_{\tau,ss}$ of tegoprazan would increase by approximately three times when tegoprazan 50 mg was administered with clarithromycin 500 mg three times a day or with ketoconazole 400 mg once a day for 7 days. Conversely, the $AUC_{\tau,ss}$ was predicted to decrease to approximately 30% when tegoprazan 50 mg was administered with rifampicin 600 mg once a day for 7 days (**Table 8**).

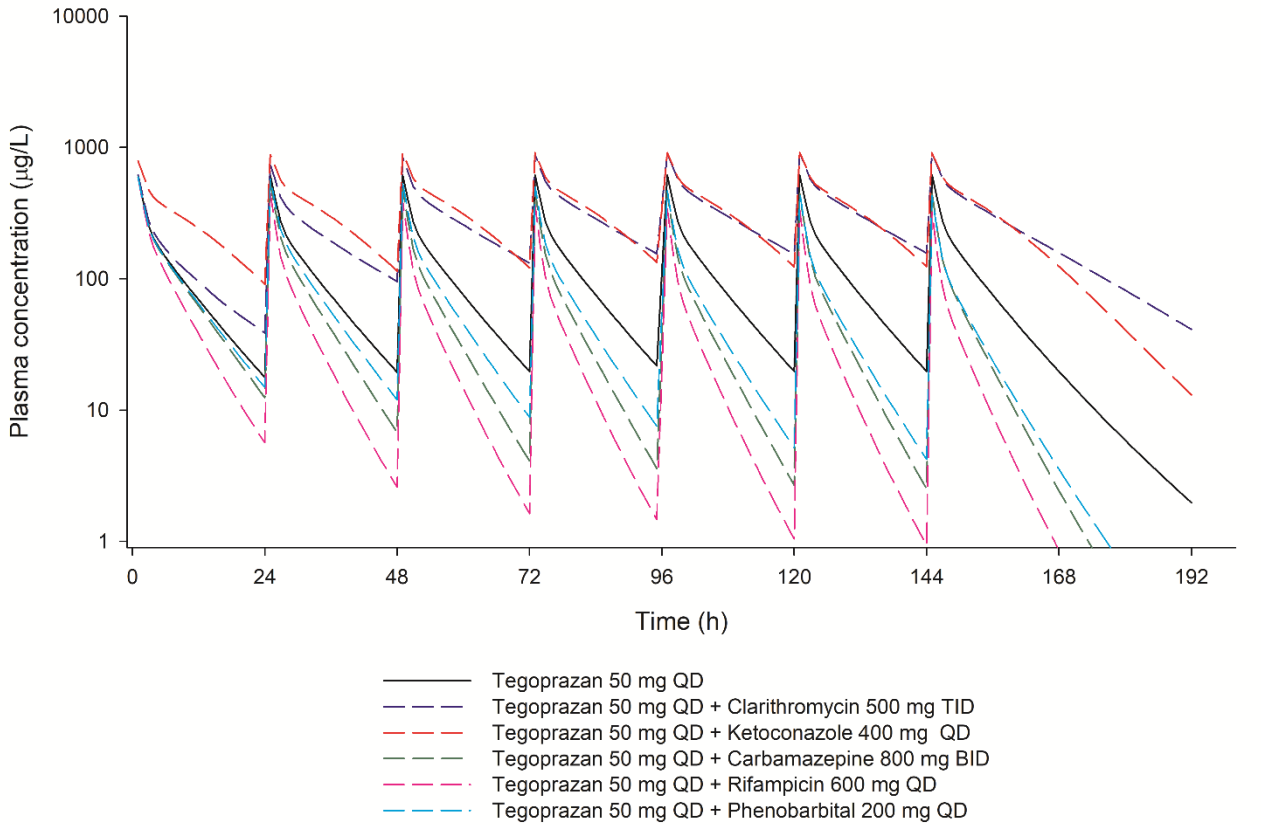

Figure 5. Physiologically based pharmacokinetic model–predicted plasma concentrations of tegoprazan when tegoprazan 50 mg was administered alone or with various CYP3A4 perpetrators for 7 days.

Table 8. Prediction of systemic exposure changes of tegoprazan 50 mg with co-administration of perpetrator for 7 days using the final physiologically based pharmacokinetic model.

Perpetrator	Predicted C_{max} (μg/L)	Predicted AUC_{τ} (μg·h /L)	Predicted fold-increase	
			C_{maxR}	AUC_R
Clarithromycin 250 mg BID	768.67	4896.31	1.20	1.63
Clarithromycin 500 mg BID	887.78	7455.77	1.40	2.57
Clarithromycin 500 mg TID	933.45	8356.44	1.47	2.96
Ketoconazole 200 mg QD	905.80	7633.19	1.44	2.84
Ketoconazole 400 mg QD	936.16	8382.80	1.49	3.14
Carbamazepine 200 mg QD	591.9	2374.81	0.93	0.82
Carbamazepine 800 mg BID	472.67	1400.02	0.74	0.50
Rifampicin 450 mg QD	367.79	931.72	0.57	0.31
Rifampicin 600 mg QD	353.70	873.51	0.55	0.29
Phenobarbital 30 mg QD	593.39	2473.85	0.93	0.83
Phenobarbital 200 mg QD	456.72	1431.28	0.71	0.47

QD, once daily; BID, twice daily; TID, three times a day. C_{max}, maximum plasma concentration; AUC_{τ}, area under the concentration-time curve from time zero to 24h; C_{maxR}, ration of increased maximum plasma concentration; AUC_R, ratio of increased area under the concentration-time curve from time zero to 24h.

PK-PD relationship of tegoprazan

The values of E_{max}, EC_{50} and γ were estimated as 94.7 %, 2881.6 μg·h /L and 1.2, respectively (**Figure 6**). The value of E_0 was fixed as 0 when the other values were estimated, because the estimated value of E_0 was negative, which could not reflect the physiological characteristics of the gastric pH. The mean percentages of the time of pH greater than or equal to 4 were calculated with the sigmoidal E_{max} model and simulated AUC from the final PBPK model (**Figure 7**). When tegoprazan 50 mg was administered alone, the mean percentage of time of pH greater than or equal to 4 was 51.8. The mean percentages of time of pH greater than or equal to 4 were 75.5, 76.9, 32.8, 21.5 and 31.9 when tegoprazan 50 mg was administered with clarithromycin, ketoconazole, carbamazepine, rifampicin, and phenobarbital, respectively.

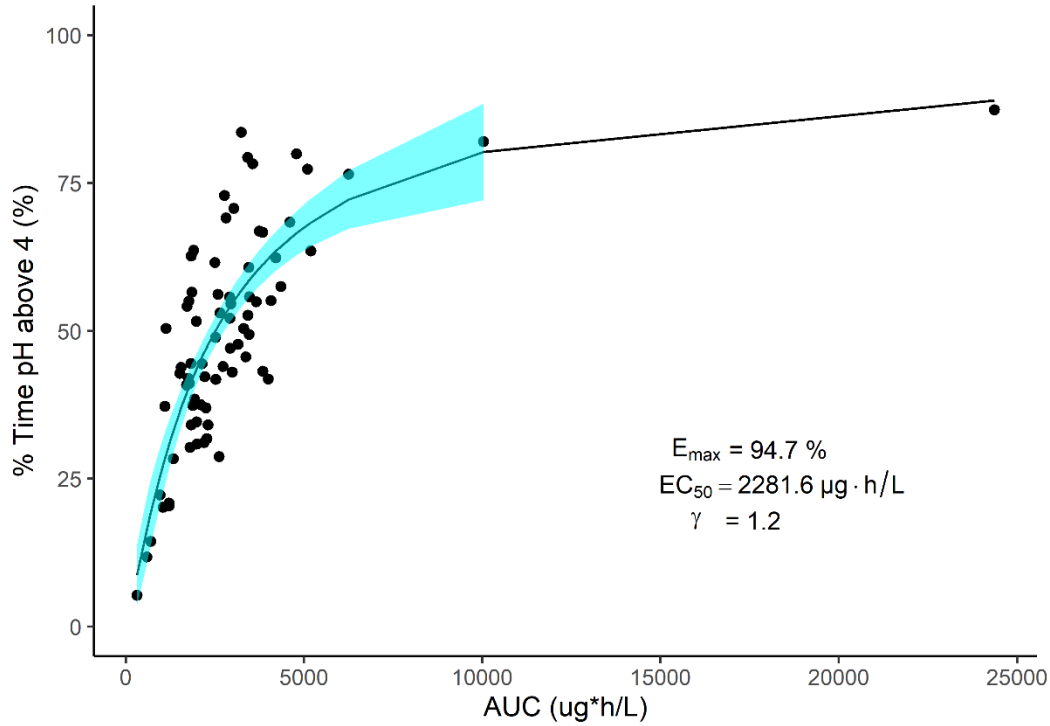

Figure 6. Pharmacokinetic pharmacodynamic relationships of tegoprazan described by a sigmoidal E_{max} model.

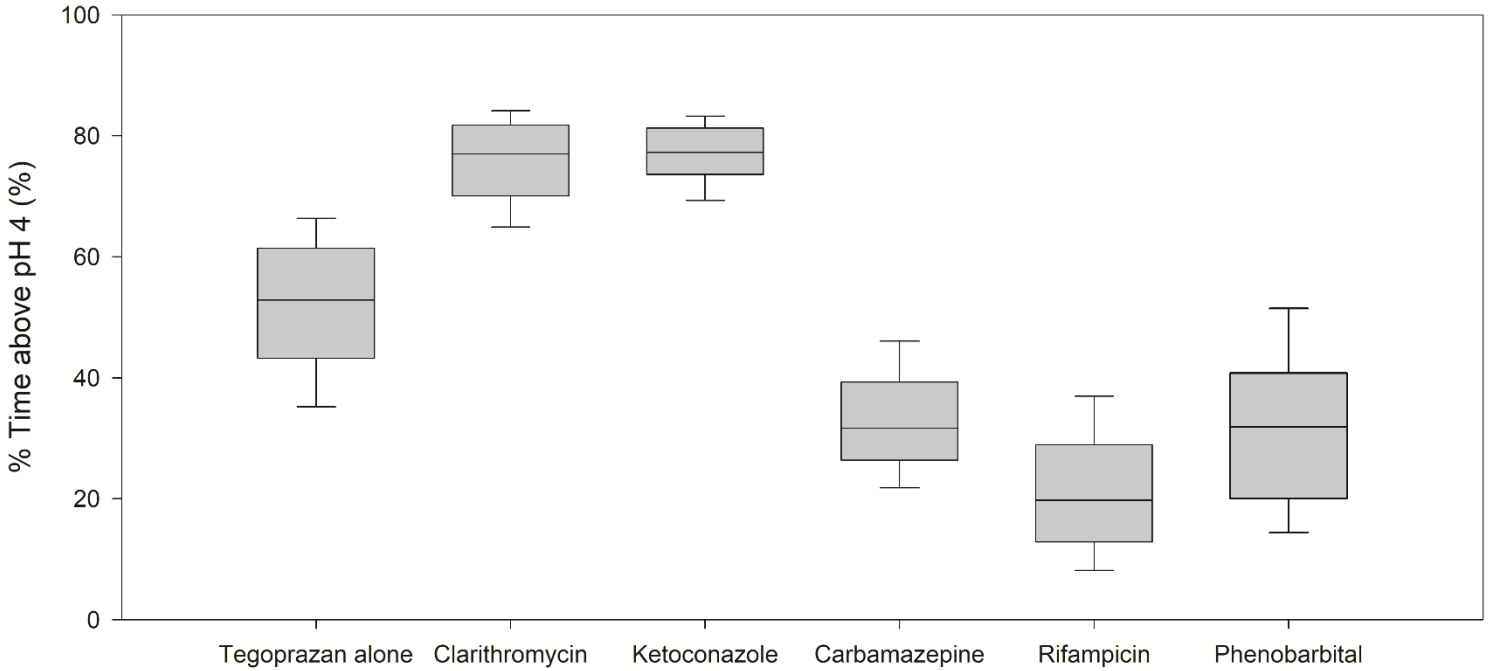

Figure 7. Physiologically based pharmacokinetic model–predicted the percentage of time of pH greater than or equal to 4 when tegoprazan 50 mg was administered alone or with various CYP3A4 perpetrators for 7 days.

DISCUSSION

In this study, the first PBPK model of tegoprazan for predicting DDIs by comprehensively applying physicochemical and PK properties of tegoprazan was conducted with absorption, distribution, metabolism, and elimination data. Because tegoprazan shows dose proportional PKs, the PKs of tegoprazan could be predicted well in various dose strengths with single- and multiple-dose administration [2]. The tegoprazan PBPK model properly implemented the previously reported PKs of tegoprazan. The overall time-concentration profiles and PK parameter predictions were similar to the clinical data under various dosing conditions (**Figure 3** and **Table 5**). For example, the predicted exposure indices (i.e., C_{max} and AUC) for single or repeated administration of tegoprazan were consistent with the results reported in previous clinical studies, satisfying the 2-fold criteria that is commonly used in IVIVE prediction [16]. The predicted range of time to reach C_{max} was also comparable with the observed range in each trial [2-4, 12, 25]. In addition, the mean apparent clearance (i.e., AUC/dose) was predicted to be 17.5 L/h when tegoprazan was administered alone and it decreased to 6.4 L/h by the co-administration of clarithromycin, which is similar to the results of the DDI study between tegoprazan and clarithromycin (17.7 L/h and 6.6

L/h, respectively) [4]. The clinical data used for model verification covered all dose ranges and regimens from previously reported clinical trials. Therefore, it was considered that the developed PBPK model is robust and can be used to predict the PKs of tegoprazan as well as the DDI potentials by CYP3A4 perpetrators.

Tegoprazan is mainly metabolized by the liver, especially CYP3A4, and the administration of tegoprazan with clarithromycin triggers an increase in systemic exposure to tegoprazan because clarithromycin inhibits the activity of CYP3A4 [4]. The metabolic effects of other CYP enzymes, such as CYP1A2, CYP2C9, CYP2C19, and CYP2D6, on tegoprazan were not significant in *in vitro* studies (in-house data). Information about intrinsic clearance by CYP3A4 and other CYP enzymes was reflected in the final PBPK model, mechanistically enabling the prediction of DDIs. In DDI simulation results, the mean predicted total clearance was 16.0 L/h when tegoprazan was administered alone, but it decreased to 9.6 and 5.7 L/h when co-administered with clarithromycin or ketoconazole, respectively. In addition, when tegoprazan was administered with carbamazepine, rifampicin or phenobarbital, the total clearance increased to 36.3, 47.0 and 36.1 L/h, respectively. Along with these changes in total clearance by DDIs, the predicted hepatic CYP3A4 fraction metabolizing tegoprazan was changed from approximately 70%

to 10% and 90% by the co-administration of CYP3A4 inhibitors (i.e., ketoconazole or clarithromycin) and inducers (i.e., carbamazepine, rifampicin, or phenobarbital), respectively.

One advantage of PBPK modeling in predicting DDI is that the phenomenon of DDI can be interpreted mechanistically because the PBPK model is generally constructed based on various concepts of DDI, such as competitive inhibition and mechanism-based drug interaction. Especially, prediction of the effect of CYP3A4 perpetrators on the PKs of the substrate using the PBPK approach has been widely researched, and the PBPK-predicted and observed DDIs related to CYP3A4 metabolism are highly consistent [26, 27]. Another advantage of PBPK modeling in predicting DDI is the ability to generate PK profiles for various dosages for which clinical DDI have not been tested. Although clinical DDI studies were performed only for tegoprazan 100 mg and 200 mg, the DDI could be predicted for the approved tegoprazan dose of 50 mg using the simulation based on the PBPK model in this study. It is known that the ability of a potassium-competitive acid blocker (P-CAB) such as tegoprazan to suppress acid is correlated with the PKs [2, 28]. Therefore, by using the PBPK model of tegoprazan constructed in this study, the DDIs between tegoprazan and CYP3A4 perpetrators can be predicted without the need for unnecessary clinical studies and the results of

the prediction might be considered by clinicians when making decisions about prescribing tegoprazan with possible interacting drugs.

According to the guidelines for clinical drug interaction studies released by the FDA, a strong perpetrator refers to an inhibitor or an inducer that increases the AUC of a substrate by ≥5-fold or decreases the AUC of a substrate by ≥80%, respectively [29]. In this study, ketoconazole, clarithromycin, carbamazepine, rifampicin and phenobarbital were selected as CYP3A4 perpetrators because these drugs are well-known strong CYP3A4 perpetrators and are widely applied to PBPK modeling and simulation for predicting DDI [20-22, 30]. In the simulation for predicting DDI potential, the duration of administration of tegoprazan and CYP3A4 perpetrator was set to 7 days, since it is known that CYP3A4 enzymes can be induced or inhibited sufficiently by administering these drugs for 7 days [21, 22]. Consequently, by simulating a scenario where tegoprazan was co-administered with CYP3A4 perpetrators at the maximum recommended daily dose, the changes of the tegoprazan PK profiles in the worst-case scenario could be predicted.

Based on the definition from the guideline, a moderately sensitive substrate is a drug whose AUC increases 2- to <5-fold when a strong index inhibitor is co-administered [29]. Accordingly,

tegoprazan is considered a moderately sensitive substrate of CYP3A4 because the AUC of tegoprazan increases by up to about three times when ketoconazole or clarithromycin is co-administered. Moreover, the AUC of tegoprazan decreases to approximately 30% when carbamazepine, rifampicin, or phenobarbital is co-administered. Therefore, if tegoprazan is administered along with potential CYP3A4 perpetrators, a clinician might consider the potential DDI and refer to the simulation results.

The predicted ratio of increased AUC was similar to the observed values in both DDI studies, while the fold increase for C_{max} seems to have been under-predicted (Table 7). The under-estimated fold increase for C_{max} might be due to the variability in the data observed in clinical studies, considering that the values of C_{max} after multiple administration were lower than those after single administration. A possible reason for the decrease in C_{max} after multiple doses is the pH-dependent change in the absorption of tegoprazan, that is, the C_{max} of tegoprazan might be reduced after multiple administrations due to augmented gastric pH caused by tegoprazan itself. In previous studies, when tegoprazan was administered with food, a decreased C_{max} was observed with a delayed time to reach C_{max}, which was explained by an increase in gastric pH as food dilutes the H^+ concentration in the stomach [12, 31]. Because pH-dependent

absorption was not reflected in the PBPK model, the difference between the observed and predicted C_{max} might have occurred. However, despite the under-predicted fold increase of C_{max}, the magnitude of acid suppression can be inferred using AUC because the acid suppression ability of P-CAB is correlated with AUC rather than C_{max} [2, 28].

When tegoprazan was administered with CYP3A4 perpetrators at the maximum recommended daily dose, the induction and inhibition profiles of CYP3A4 for tegoprazan were different based on the characteristics of the induction and inhibition mechanism (**Figure 5**). It takes time for endogenous enzymes to be fully induced because the transcription and translation of the enzyme is required [32]. Therefore, systemic exposure to tegoprazan is gradually reduced when tegoprazan is administered with CYP3A4 inducers. In the case of CYP enzyme inhibition, co-administration of tegoprazan and ketoconazole resulted in a rapid CYP3A4 inhibition profile, while co-administration with clarithromycin resulted in a gradual CYP3A4 inhibition profile. The phenomenon of a gradual CYP3A4 inhibition profile might be caused by the fact that clarithromycin simultaneously acts as an inhibitor as well as a substrate of CYP3A4. Indeed, the mechanism-based inhibition of clarithromycin as a CYP3A4 perpetrator and substrate was reflected in the compound file of

clarithromycin available in SimCYP and implemented in the simulations for predicting DDIs between tegoprazan and clarithromycin [33].

The PBPK model could be applied for the prediction of human PK during the early clinical development stage in addition to the prediction of DDI.[34] The PBPK model of tegoprazan could be used as a reference for constructing a PBPK model of other P-CABs in the developing stage. Parameters of absorption, distribution, metabolism and elimination can be generated from *in vitro* and *in vivo* preclinical studies. Although it is difficult to validate the constructed PBPK model only with preclinical data, the PBPK model of tegoprazan can be used for decision making during the developmental stage of P-CAB.

One of the limitations in developing the PBPK model of tegoprazan in this study is that the predictability of DDIs of tegoprazan with ketoconazole and CYP3A4 inducers was not verified since clinical DDI studies on tegoprazan and such drugs were not conducted. Nevertheless, since the predictability of the DDI between tegoprazan and clarithromycin was verified, it is considered that the model reflecting tegoprazan as a substrate of CYP3A4 would reasonably have predicted DDIs between tegoprazan and other CYP3A4 perpetrators. Another limitation of the PBPK model is that

the properties of tegoprazan as a substrate of transporters or perpetrators of CYP enzymes were not reflected in the PBPK model. According to the result of the clinical study aiming to determine whether tegoprazan inhibits OATP1B1, tegoprazan showed no inhibitory effect on OATP1B1 and the parameter was not reflected in the final model [35]. Some P-CABs, such as vonoprazan, potentially inhibit CYP2C19 at clinical doses [36], while the inhibitory activity of tegoprazan against CYP2C19 was not evaluated through a clinical study. If the additional data are generated through either *in vitro* or clinical studies and reflected in the model, the PBPK model of tegoprazan could be refined more sophisticatedly. The other limitation of the PBPK model is that the model is not able to represent the change in gastric pH over time caused by the compound itself. Therefore, the prediction of the C_{max} could be under-estimated compared to the AUC after multiple administrations, and pH-dependent absorption of tegoprazan is not reflected in the model. However, this limitation is a minor defect, considering that the overall PK profile and acid suppression ability of tegoprazan are barely influenced by the characteristics of pH-dependent absorption.

The efficacy of tegoprazan affected by CYP3A4 perpetrators could be predicted by using the PBPK model-predicted PK and PK-PD relationship of tegoprazan established by a sigmoidal E_{max} model,

because it is known that the efficacy of P-CAB to suppress gastric acid is correlated with its systemic exposure [2, 28]. Based on the PK-PD relationship, the efficacy of tegoprazan is expected to increase by up to maximum 1.5-fold when co-administered with the maximum recommended dose of a CYP3A4 inhibitor, and decreased by up to 40 % when co-administered with the maximum recommended dose of CYP3A4 inducer. Although the sigmoidal E_{max} model established in this study had a limitation in that the value of the baseline was fixed at 0, the efficacy of tegoprazan might be valid in the range of AUC from 316.0 to 24361.6 μg·h /L, which was calculated from tegoprazan 25 to 400 mg.

The PKs of tegoprazan has been investigated previously in various dosage ranges, and its DDI with clarithromycin and food effect studies have also been performed [2-4, 12, 25]. However, there are still many aspects of the PKs of tegoprazan that has not been identified mechanistically and clinically. It is impossible to conduct clinical trials for all scenarios to determine the PK properties of tegoprazan in an infinite number of clinical situations. In this regard, the tegoprazan PBPK model developed in this study helps to mechanistically simulate PK properties and DDI potentials for various dosing regimens with CYP enzyme perpetrators, without having to conduct clinical trials. In addition, the information simulated using the

model can be used as evidence for appropriate drug therapy in clinical settings. This study focused on the DDI potential of CYP3A4 enzyme perpetrators, as tegoprazan is known to be primarily metabolized by CYP enzymes and is expected to be affected by CYP3A4 inhibitors. Although changes in the PKs of tegoprazan by clarithromycin have been reported in clinical trials [4], the doses used in the trials did not reflect the approved dose, and other situations, including the effect of CYP3A4 inducers on the PKs of tegoprazan, have not been identified. In this study, by developing a tegoprazan PBPK model, it is suggested that caution be used when using tegoprazan with potent CYP3A4 inhibitors or inducers. The model also successfully predicted the metabolic profile of tegoprazan mechanistically, accounting for changes in the fraction metabolized by each CYP enzyme when tegoprazan was administered alone or in combination with CYP enzyme perpetrators. These results deepen the understanding of tegoprazan PKs, especially in terms of elimination aspects. The tegoprazan model presented in this study can be used as a basic model for the development of more sophisticated models to predict the pH-dependent absorption pattern of tegoprazan, food effects, or the effects of other perpetrators on metabolic enzymes and transporters.

CONCLUSION

The final PBPK model of tegoprazan as a substrate of CYP3A4 was successfully established and adequately predicted the DDI between tegoprazan and clarithromycin. Using this model, the PKs of tegoprazan can be mechanistically predicted, and the DDI potential under various clinical conditions can be predicted. Consequently, as a valid model, the PBPK model of tegoprazan developed through this study can be applied to evidence-based dosing strategies by clinicians.

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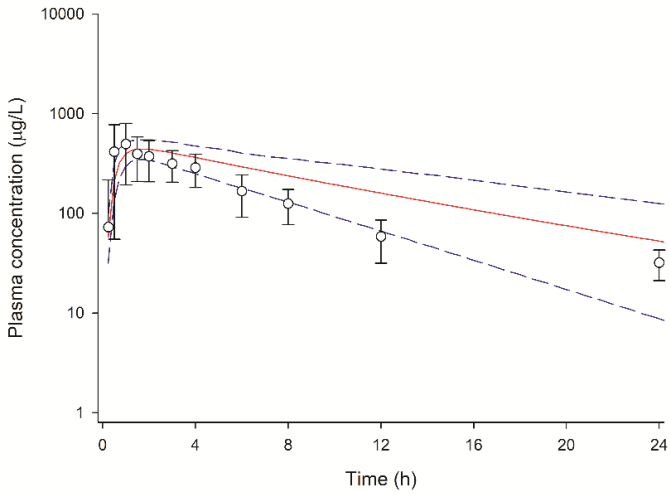
APPENDIX

A



B

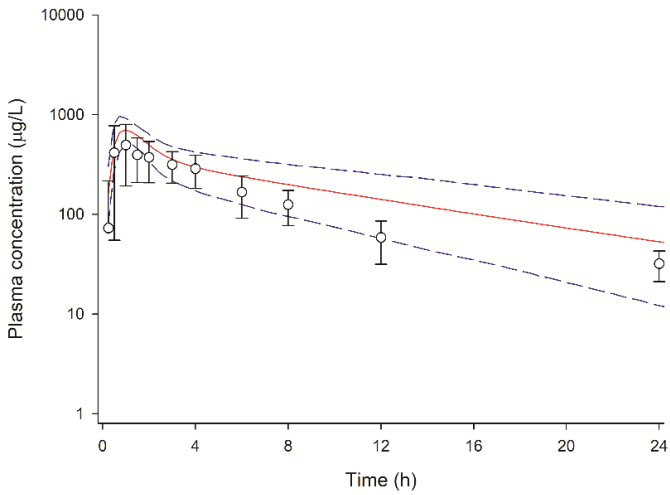


Figure 1A. Development of physiologically based pharmacokinetic model of tegoprazan. (A) Parameters of single adjusted compartment, blood flow and intrinsic clearance of CYP3A4 were not estimated. (B) Parameter of intrinsic clearance of CYP3A4 was not estimated. The open circles and error bars represent the measured concentrations of tegoprazan and the standard deviations, respectively. The solid red lines and the dashed blue lines represent the simulated mean time–concentration profiles and the 5th-95th percentile of the total virtual population, respectively.

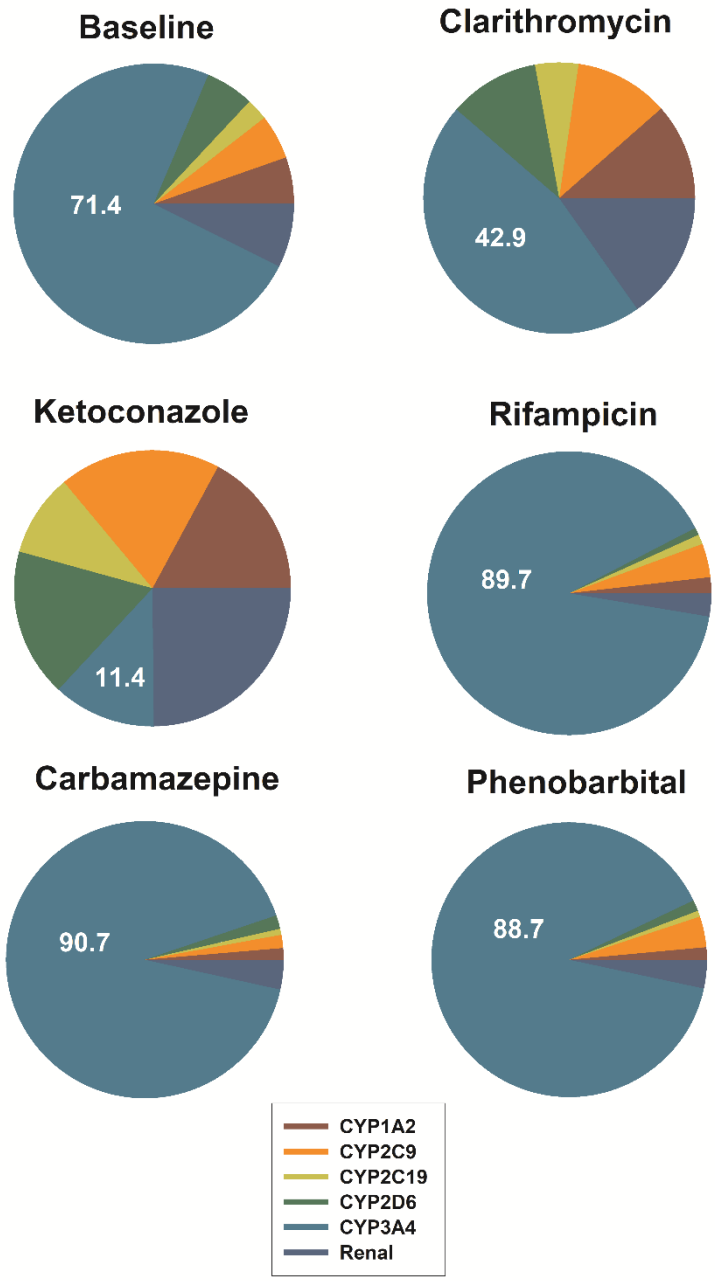


Figure 2A. Mean fractions of metabolism and excretion in relation to the systemic clearance of tegoprazan when tegoprazan 50 mg was administered alone or with various CYP3A4 perpetrators for 7 days.

국문 초록

서론: 칼륨 경쟁적 위산 분비 차단제인 테고프라잔은 CYP3A4 의 잠재적 기질이다. 테고프라잔의 약물-약물 상호작용 임상시험은 제한적이다. 지금까지 수행된 테고프라잔의 약물-약물 상호작용 임상시험은 테고프라잔과 클라리스로마이신 또는 클라리스로마이신 및 아목시실린 간 약물-약물 상호작용 연구로 제한되었다. 따라서, 테고프라잔과 CYP3A 의 활성을 유도하거나 억제하여 테고프라산의 약동학 및 약력학 모두에 영향을 미칠 수 있는 CYP3A4 가해약물 사이의 약물-약물 상호작용을 평가하기 위한 추가 연구가 필요할 수 있다. 생리학적 기반 약물동태(PBPK) 모델링은 인체의 해부학적 및 생리학적 특성과 약물의 물리화학적 및 생물학적 특성의 개념을 통합하여 약물의 약동학 양상을 시뮬레이션하고 예측하기 위한 *in silico* 기계론적 접근법이다. 본 연구의 목적은 테코프라잔의 생리학 기반 약물동태 모델을 개발하고 테코프라잔과 CYP3A4 가해약물 사이의 약물-약물 상호작용 가능성을 평가하는 것이다.

방법: SimCYP 시뮬레이터를 사용하여 효소 역학 제거를 반영하는 단일 조정 구획을 가진 최소 PBPK 모델을 구축하였다. 본 모델은 모델을 통해 예측된 테고프라잔의 약동학과 테고프라잔과 클라리스로마이신 사이의 약물-약물 상호작용연구를 포함한 다양한 1 상 임상시험을 통해 얻어진 관찰값을 비교하여 개선되고 검증되었다. 검증된 PBPK 모델을 이용한 테고프라잔의 노출 변화를 시뮬레이션하여 테고프라잔과 5 개의

CYP3A4 가해약물(클라리스로마이신, 케토코나졸, 카바마제핀, 리팜피신 및 페노바비탈) 사이의 약물-약물 상호작용을 예측하였다.

결과: 최종 PBPK 모델은 테고프라잔의 이중 분포 양상 및 테고프라잔과 클라리스로마이신 사이의 약물-약물 상호작용을 적절하게 예측하였다. 예측 대비 관측된 약동학 파라미터의 모든 비는 0.5 와 2.0 사이였으며, 이는 일반적인 허용 기준을 충족하였다. 약물-약물 상호작용 시뮬레이션에서, 테고프라잔의 전신 노출은 최대 권장 용량의 클라리스로마이신 또는 케토코나졸 병용 투여 시 약 3 배 증가할 것으로 예상되었다. 한편, 카바마제핀, 리팜피신 또는 페노바비탈 병용 투여 시 테고프라잔의 노출은 최대 30%까지 감소할 것으로 예상되었다.

결론: 테고프라잔의 PBPK 모델은 성공적으로 구축되었고 본 모델은 테고프라잔과 클라리스로마이신 사이의 약물-약물 상호작용을 적절하게 예측하였다. 테고프라잔의 위산 억제 효과가 전신 노출과 관련이 있는 것으로 알려져 있기 때문에, PBPK 모델을 통한 시뮬레이션 결과를 바탕으로 테고프라잔을 CYP3A4 가해약물과 병용 투여 시 약물-약물 상호작용 가능성을 고려해야 한다.

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주요어 : 테고프라잔, CYP3A4, 약물-약물 상호작용, 생리학 기반

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