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Quantitative Evaluation of How OATP1B1 and OATP2B1 Genetic Polymorphisms Influence Fexofenadine Pharmacokinetic Variability Using Pharmacometrics

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ABSTRACT

Fexofenadine is widely employed for treating various allergic conditions, yet limited data exist regarding its pharmacokinetic variability and the quantitative determinants influencing it. This study sought to validate previously suggested genetic factors using population pharmacokinetic modeling of fexofenadine and to quantify the genetic contributions affecting its pharmacokinetic diversity. Polymorphisms in the organic-anion-transporting-polypeptides (OATP) 1B1 and 2B1 have been implicated in interindividual differences in fexofenadine disposition; thus, pharmacokinetic modeling was conducted based on oral exposure data stratified by these polymorphisms. The analysis identified OATP1B1 and OATP2B1 as significant covariates influencing apparent clearance (CL/F) and the relationship between volume of distribution (V/F) and CL/F, respectively. Depending on the OATP1B1 genotype, fexofenadine CL/F and average steady-state plasma concentrations varied by as much as 2.17- and 2.20-fold, respectively. Similarly, subjects with different OATP2B1 variants exhibited up to 1.73- and 2.00-fold differences in CL/F and V/F. The ratios of the area under the curve (AUC) after single and multiple doses, along with cumulative AUC ratios, significantly differed across OATP1B1 and OATP2B1 genotype groups. Quantitative modeling outcomes demonstrated that OATP1B1 exerts a stronger influence on fexofenadine pharmacokinetic variability than OATP2B1. Furthermore, based on the established pharmacokinetic–pharmacodynamic model, fexofenadine efficacy varied by approximately 1.25- and 0.87-fold according to OATP1B1 and OATP2B1 polymorphisms, respectively, indicating that OATP1B1 genetic variability may also play a meaningful role in pharmacodynamic responses. Collectively, this population pharmacometric investigation provides a valuable framework for advancing precision medicine approaches to optimize fexofenadine therapy.

Keywords: Genetic polymorphism, Population pharmacometrics, Fexofenadine, OATP2B1, OATP1B1

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Introduction

Fexofenadine is an antihistamine medication commonly prescribed for managing a range of allergic disorders, including hay fever, conjunctivitis, eczema, and urticaria [1]. It is preferred over many other anti-allergic agents because it selectively antagonizes peripheral histamine receptors, which minimizes sedative side effects [2]. Owing to its favorable safety profile and high patient compliance, fexofenadine has been extensively and continuously used in clinical settings [1, 3]. Despite its long-standing clinical use [4], the development of a scientifically supported, quantitative dosing regimen for fexofenadine remains insufficient. In clinical practice, dosing typically follows empirical patterns—such as standard administration of 120 mg once daily or dosage adjustments based on symptom severity—without adequately accounting for interindividual variability [5]. This gap largely stems from the limited research on the pharmacokinetic variability of fexofenadine and the lack of quantitative methods to characterize such differences.

Previous investigations [6, 7] identified fexofenadine as a substrate for organic-anion-transporting polypeptides (OATP) 1B1 and 2B1, and variations in these transporters have been associated with distinct in vivo

pharmacokinetic profiles. The SLCO1B1 and SLCO2B1 genes encode OATP1B1 and OATP2B1, respectively [8]. Notably, polymorphisms such as SLCO1B1 521T>C and SLCO2B1 1457C>T are known to alter transporter function [8], and each single-nucleotide polymorphism has been shown to reduce the transport activity of OATP1B1 and OATP2B1 in vitro [6, 7]. OATP1B1 primarily mediates hepatic clearance [6, 9], whereas OATP2B1 is expressed in the intestinal epithelium and plays a role in drug absorption [7, 10]. Therefore, it is reasonable to expect that genetic variations in these transporters influence fexofenadine's pharmacokinetic behavior. However, earlier studies [6, 7] only described qualitative differences among genotypes without quantifying their impact or validating these polymorphisms as effective pharmacokinetic covariates. As a result, the extent and nature of pharmacokinetic variability associated with OATP1B1 and OATP2B1 genetic variants remain unclear.

Population pharmacokinetic modeling serves as a powerful quantitative approach for optimizing dosage regimens based on interindividual differences [11-13]. Understanding the pharmacokinetic diversity of fexofenadine is clinically important for balancing therapeutic efficacy and safety [14-16]. Continuous exposure to fexofenadine can lead to significant pharmacokinetic variability across individuals, which may result in subtherapeutic levels or adverse effects such as headache, somnolence, dry mouth, nausea, and dizziness. Identifying and quantifying the genetic and physiological factors responsible for this variability could enable clinicians to tailor dosing strategies that maximize efficacy while minimizing side effects.

The objective of this study was to evaluate the influence of OATP1B1 and OATP2B1 polymorphisms as covariates contributing to interindividual pharmacokinetic variability in fexofenadine using a population modeling framework. Additionally, the study aimed to quantify how these genetic variations affect fexofenadine pharmacokinetic diversity. Through this approach, we sought to enhance the precision of fexofenadine therapy by elucidating the sources of variability and providing predictive insight into their quantitative impact. Ultimately, the population pharmacokinetic findings presented here are expected to support evidence-based dosing strategies and advance precision medicine approaches that consider the genetic polymorphisms influencing fexofenadine disposition and response.

Experimental

Research process

This retrospective study was conducted through four sequential stages. First, pharmacokinetic data for fexofenadine were collected from previously published reports [6, 7] that examined its disposition according to OATP1B1 (SLCO1B1 521T>C) and OATP2B1 (SLCO2B1 1457C>T) polymorphisms. These studies provided mean plasma concentrations and standard deviations for each genotype group following oral administration of fexofenadine. Using Web-Plot-Digitizer software (version 4.5), mean values, maximum and minimum standard deviations, and the 25th and 75th percentiles within the standard deviation range were extracted to represent each dataset.

Second, based on these extracted datasets, population pharmacokinetic modeling for fexofenadine was independently constructed and validated for both OATP1B1 and OATP2B1 genotype groups. Third, quantitative comparisons of fexofenadine pharmacokinetics across genotypes were performed using simulations generated from the established models under single- and multiple-dose conditions.

Finally, pharmacodynamic differences between OATP1B1 and OATP2B1 polymorphisms were quantitatively analyzed using a newly derived relationship describing the pharmacodynamic effect as a function of plasma fexofenadine exposure. This relationship was based on a previously developed population pharmacokinetic–pharmacodynamic (PK–PD) model [17], which characterizes fexofenadine's effect on histamine-induced wheal area reduction—a pharmacological marker of its antihistaminic activity [18]. The existing PK–PD model, which had been designed for general populations without genotype-specific covariates, was adapted to evaluate how genetic variability influences pharmacodynamic responses.

The overall research workflow is summarized in **Figure 1**.

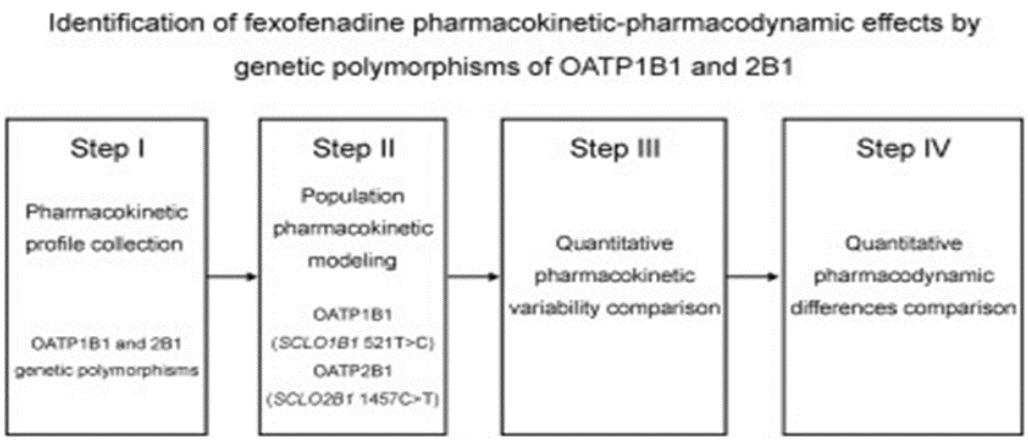


Figure 1. Stepwise workflow of this study. OATP: Organic-Anion-Transporting-Polypeptide.

Population pharmacokinetic modeling

Pharmacokinetic data for fexofenadine in relation to OATP1B1 and OATP2B1 genetic polymorphisms in healthy adults, previously reported by earlier studies [6, 7], served as the foundation for constructing the population pharmacokinetic models in this research. The data regarding OATP1B1 polymorphisms were categorized into SLCO1B1 521T>C genotypes—TT, TC, and CC [6]. For OATP2B1, significant pharmacokinetic differences ($P < 0.05$) were observed between groups carrying the T allele (CT/TT) and non-carriers (CC) of the SLCO2B1 1457C>T variant [7]. All data originated from rigorously controlled clinical trials conducted under approved study protocols, and the physiological characteristics among subjects were consistent, minimizing confounding factors. Model construction and analysis were carried out using a nonlinear mixed-effects modeling approach implemented in Phoenix NLME version 8.3 (Certara Inc., Princeton, NJ, USA). Parameter estimation for the population pharmacokinetic model was performed using the first-order conditional estimation method with extended least squares and η–ε interaction. Individual modeling was initially performed for each genetic subgroup derived from the clinical data associated with OATP1B1 or OATP2B1 polymorphisms.

The modeling procedure comprised two main stages. In the first stage, a structural model was developed to adequately describe plasma fexofenadine concentrations following oral administration across different OATP1B1 and OATP2B1 genotypes. Key structural features—such as the number of compartments, lag time (t_lag) to account for absorption delay, mechanistic representation of the absorption process, and residual/interindividual variability (IIV) models—were systematically explored.

The second stage focused on identifying influential covariates that could explain interindividual differences in fexofenadine pharmacokinetics. Genetic polymorphisms in OATP1B1 and OATP2B1 were assessed as potential covariates, as this retrospective study aimed specifically to quantify their effects on pharmacokinetic variability. Model selection at each stage was guided by statistical criteria, including twice the negative log-likelihood (−2LL), Akaike's Information Criterion (AIC), and goodness-of-fit (GOF) plots. Statistical significance was evaluated using chi-square distribution thresholds ($P < 0.05$), considering changes in degrees of freedom corresponding to parameter adjustments. For instance, a −2LL reduction exceeding 3.84 upon adding a single parameter indicated a statistically significant model improvement.

Polymorphism data for OATP1B1 and OATP2B1 were treated as categorical variables and sequentially incorporated into the IIV of pharmacokinetic parameters using a combination of forward addition and backward elimination procedures. During forward addition, covariates yielding an objective function value (OFV) decrease greater than 3.84 ($P < 0.05$) were retained in the base model. Conversely, during backward elimination, covariates resulting in an OFV increase greater than 6.63 ($P < 0.01$) upon removal were maintained in the final model. Ultimately, the inclusion or exclusion of covariates was stringently judged at a significance level of $P < 0.01$, based on the change in model degrees of freedom.

Model

The developed population pharmacokinetic models for fexofenadine, incorporating OATP1B1 and OATP2B1 genetic polymorphisms, underwent extensive evaluation and validation using both visual and numerical methods in Phoenix NLME and R software (R Foundation, Vienna, Austria). Model validation followed standard practices for population-level pharmacokinetic modeling [11-16]. The validation toolkit included goodness-of-fit (GOF)

diagnostics—such as residual distribution assessment, visual predictive checks (VPC), bootstrapping, and normalized prediction distribution error (NPDE) analyses.

Model simulation

To simulate the population pharmacokinetics of fexofenadine while accounting for genetic variations in OATP1B1 and OATP2B1, the final verified model structure was fixed, and the model parameters were assigned as typical values for each genotype group, stratified categorically according to the genetic polymorphisms of OATP1B1 or OATP2B1. Once the model structure and parameters were fixed, population-level simulations were conducted to assess various exposure conditions influenced by different fexofenadine dosing regimens and frequencies, including multiple-dose scenarios. These simulations were carried out using the Simulation and Prediction modules of Phoenix NLME (Certara Inc., Princeton, NJ, USA). To quantitatively evaluate the intergroup variability in fexofenadine pharmacokinetics predicted for each genetic variant group of OATP1B1 and OATP2B1, representative simulation results were extracted. A total of nine representative outputs were obtained for each group, corresponding to the 5th, 50th, and 95th percentiles of both population prediction ranges and sampling distributions, ensuring representative selection under a normal distribution assumption. The extracted data from each genotype group were further analyzed using non-compartmental analysis (NCA) to derive pharmacokinetic (PK) parameters, enabling quantitative comparison of PK variability among genotypes. The NCA-derived pharmacokinetic parameters included elimination half-life ($t_{1/2}$), maximum plasma concentration (Cmax), time to reach Cmax (Tmax), area under the plasma concentration–time curve (AUC), apparent volume of distribution (V/F), apparent clearance (CL/F), and mean residence time (MRT).

Additionally, a quantitative comparison of fexofenadine pharmacodynamics between different OATP1B1 and OATP2B1 genotypes was performed using a previously established fexofenadine pharmacokinetic-pharmacodynamic (PK-PD) model [17]. This pre-existing model, which predicted antihistamine efficacy based on plasma fexofenadine concentrations in healthy subjects without incorporating covariates, was used to correlate plasma exposure levels (AUC) with pharmacodynamic responses. The degree of therapeutic effect for each genotype was quantified using the area under the effect curve (AUEC) derived from the time–effect profile following fexofenadine administration.

Statistical analysis

Before conducting significance testing among groups, homogeneity of variance was assessed using the F-test. Statistical differences between two groups were analyzed using the Student's t-test, whereas comparisons among three or more groups were performed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. The default significance criterion was set at a P-value of 0.05.

Results and Discussion

Population pharmacokinetic modeling

Using data obtained from previously published pharmacokinetic studies on genetic polymorphisms of OATP1B1 and OATP2B1 [6, 7], a retrospective population pharmacokinetic modeling analysis of fexofenadine was conducted. Both OATP1B1 and OATP2B1 genotype-based population pharmacokinetic models for fexofenadine were best characterized by a one-compartment structure with first-order absorption. When more complex, multi-compartment models were evaluated, the improvement in model fit (reflected by the reduction in −2LL) was not statistically significant relative to the increased number of estimated parameters ($P > 0.05$ and/or $P > 0.01$).

Several alternative absorption models were explored to capture the absorption phase pattern of plasma concentrations, including both non-sequential and sequential dual absorption compartments that considered bioavailability or multiple absorption rate constants, respectively. However, these structures did not yield statistically meaningful improvements in model performance (reduction of −2LL; $P > 0.05$ and/or $P > 0.01$). Moreover, increasing the number of parameters in these complex absorption models reduced interpretability and limited their applicability due to uncertainty in parameter meaning and insufficient experimental data. Therefore, the simplest structural model adequately explained the observed data without unnecessary parameter expansion. Notably, inclusion of an absorption lag time (t_{lag}) led to a statistically significant improvement in model fit only for the OATP2B1 model ($P < 0.05$ and/or $P < 0.01$), while the OATP1B1 model described the data well without incorporating t_{lag}.

The residual unexplained variability for both OATP1B1 and OATP2B1 models was best described using a log-additive error model, which provided the greatest reduction in −2LL (over 90%) while maintaining the same number of estimated parameters compared to other residual error structures. Interindividual variability (IIV) in the pharmacokinetic parameters of fexofenadine was modeled using an exponential error structure defined as:

$$Pi = Ptv \times \exp(\eta i)$$

where ηi represents a random variable for the *i*th individual with a mean of 0 and variance ω^2, Pi is the individual parameter value, and Ptv is the population typical value. Stepwise evaluation confirmed that including IIV for all parameters (K_a, V/F, CL/F, and/or t_{lag}) significantly improved model performance. Omitting IIV from any parameter led to a deterioration in model fit (reduction of −2LL; $P < 0.05$ and/or $P < 0.01$). Here, K_a denotes the first-order absorption rate constant.

Genetic polymorphisms of OATP1B1 and OATP2B1 were examined as potential covariates to explain the observed interindividual variability in fexofenadine pharmacokinetics. Since the original clinical data were stratified by OATP genotype, a key objective of this study was to verify whether these transporter variants accounted for the pharmacokinetic variability between individuals. For OATP1B1, the SLCO1B1 521T>C variant was identified as a significant covariate influencing apparent clearance (CL/F), with model improvement confirmed by forward selection and backward elimination criteria ($P < 0.05$ and $P < 0.01$). However, introducing this polymorphism as a covariate for K_a or V/F did not result in statistically significant enhancement ($P > 0.05$ and/or $P > 0.01$).

For OATP2B1, the SLCO2B1 1457C>T variant was determined to significantly affect both apparent volume of distribution (V/F) and apparent clearance (CL/F), leading to substantial model improvement ($P < 0.05$ and $P < 0.01$). Furthermore, accounting for covariance between V/F and CL/F by introducing an Omega block considerably enhanced the model fit (over 90% reduction in OFV), consistent with the fact that CL/F is the product of the elimination rate constant (K_e) and V/F. Therefore, including covariance between these parameters was necessary when the same covariate affected both. The final population pharmacokinetic model equations for fexofenadine incorporating these covariates were expressed as follows:

$$V/F = tv_{V/F} \times \exp(\eta_{V/F}) \quad \text{(OATP1B1 model) (1)}$$

$$V/F = tv_{V/F} \times \exp\left[\frac{\mathrm{dV}}{\mathrm{FdSLCO2B1CT}}/\mathrm{TT} \times \left(\frac{CT}{TT} = 1\right)\right] \times \exp(\eta_{V/F}) \quad \text{(OATP1B1 model) (2)}$$

$$\frac{CL}{F} = tv_{V/F} \times [1 + dCL/FdSLCO1B1TC \times (TC = 1)] \times [1 + dCL/FdSLCO1B1CC \times (CC = 1)] \times \exp(\eta_{V/F}) \quad \text{(OATP1B1 model) (3)}$$

$$CL/F = tv_{V/F} \times [1 + dCL/FdSLCO2B1CT/TT \times (CT/TT = 1)] \times \exp(\eta_{V/F}) \quad \text{(OATP2B1 model) (4)}$$

$$K_a = tv_{K_a} \times \exp(\eta K_a) \quad \text{(OATP1B1 and 2B1 models) (5)}$$

$$t_{lag} = tv_{t_{lag}} \times \exp\left(\eta_{t_{lag}}\right) \quad \text{(OATP2B1 model) (6)}$$

In this context, tv denotes the typical values of the model parameters, while dV/FdSLCO2B1 and dCL/FdSLCO2B1 express the extent of correlation between the SLCO2B1 genotypes and the pharmacokinetic parameters V/F and CL/F, respectively; similarly, dCL/FdSLCO1B1 represents the correlation between CL/F and SLCO1B1 genotypes. The finalized fexofenadine population pharmacokinetic model parameters and their estimated values, categorized according to the genetic polymorphisms of OATP1B1 or OATP2B1. The relative standard errors (RSEs) for the typical parameter estimates—V/F, CL/F, Ka, and tlag—were all below 30%, indicating acceptable precision. Moreover, the RSEs for the covariate relationships—dCL/FdSLCO1B1, dV/FdSLCO2B1, and dCL/FdSLCO2B1—were also within 30%, confirming the robustness of the model parameters and the appropriateness of the model structure in capturing the observed data trends.

Model validation

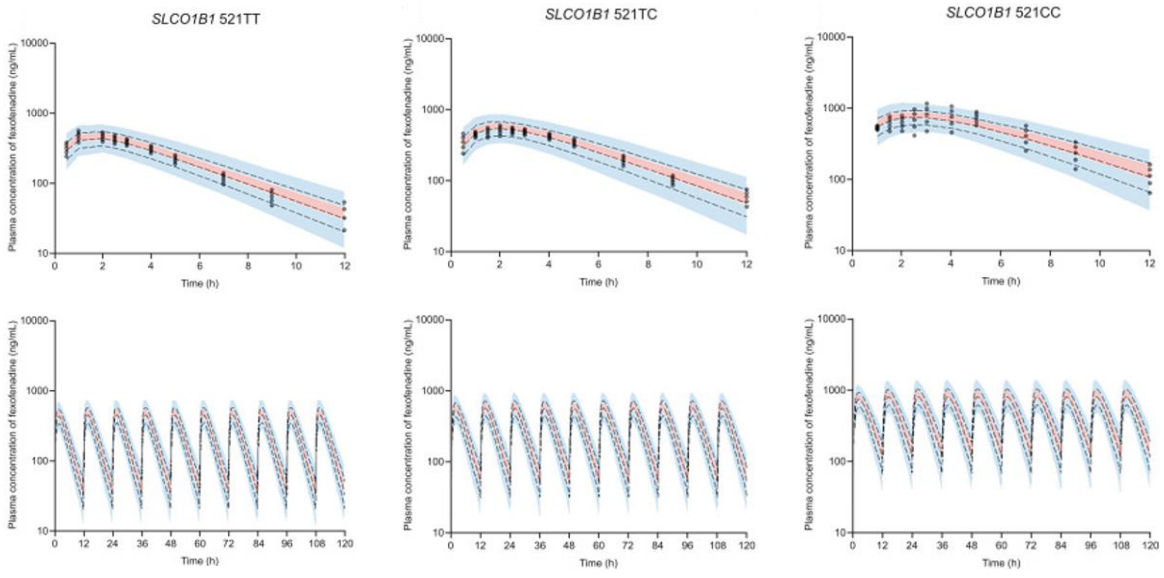
The predicted plasma concentrations, both population-based and individual, corresponded closely with the observed experimental concentrations. The conditional weighted residuals (CWRES) were symmetrically distributed around zero, displaying no systematic bias and remaining within ±4 across predicted concentrations and time points. The quantile–quantile (QQ) plots for CWRES and individual weighted residuals exhibited near-linear symmetry along the x- and y-axes (within ±4), indicating an overall good model fit. These GOF results confirmed that the final population pharmacokinetic models incorporating OATP1B1 and OATP2B1 genetic variability adequately represented the data without graphical inconsistencies.

The bootstrapping analyses further supported the stability of the models. All estimated parameters of the final models fell within the 95% confidence intervals derived from 1,000 bootstrap replicates. Moreover, the parameter estimates differed by less than 10% from the bootstrap medians, reinforcing the robustness and reproducibility of the established models for fexofenadine that accounted for genetic polymorphisms in OATP1B1 and OATP2B1.

The normalized prediction distribution error (NPDE) analyses also validated model performance. The differences between predicted and observed fexofenadine concentrations followed a normal distribution, as evidenced by QQ plots and histograms confirming normality. NPDE values over time and predicted concentrations were symmetrically centered around zero (within ±4), further demonstrating good predictive accuracy.

Visual predictive checks (VPCs) stratified by SLCO1B1 521T > C genotypes after a single 180 mg oral dose of fexofenadine **(Figure 2)** revealed that more than 90% of observed concentrations fell within the 95% confidence interval (CI) of the model predictions. Similarly, for SLCO2B1 1457T allele groups after a single 60 mg dose **(Figure 3)**, over 90% of observed data points were contained within the respective 95% CIs. The VPCs illustrated clear genotype-dependent differences in fexofenadine exposure: plasma concentrations increased and persisted longer as the SLCO1B1 521 genotype transitioned from TT to TC to CC, reflecting the model's identification of OATP1B1 polymorphism as a significant covariate influencing CL/F. Conversely, individuals carrying the SLCO2B1 1457T allele exhibited lower plasma fexofenadine levels, consistent with the covariate effects of OATP2B1 polymorphism on V/F and CL/F.

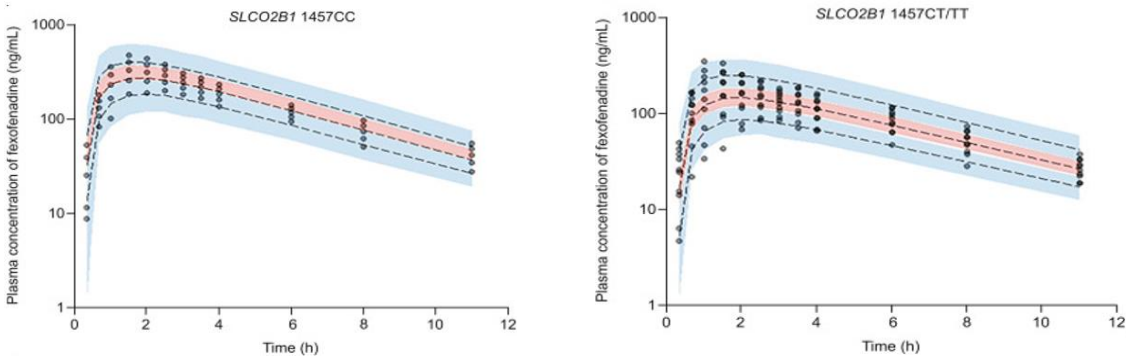
Overall, these validation results collectively demonstrated that the finalized fexofenadine population pharmacokinetic models were robust, well-calibrated, and biologically consistent, effectively characterizing the influence of OATP1B1 and OATP2B1 genetic polymorphisms without notable structural deficiencies.



a) b) c)

Figure 2. Visual predictive check (VPC) plots stratified by SLCO1B1 genotypes after a single oral dose of 180 mg fexofenadine (upper panel) and pharmacokinetic profiles after repeated oral administrations of 180 mg fexofenadine (lower panel; 12-hour intervals for 10 consecutive doses). The panels correspond to (a) SLCO1B1 521TT, (b) SLCO1B1 521TC, and (c) SLCO1B1 521CC genotypes. The observed plasma concentrations following oral dosing are shown as dots. Black dashed lines represent the model-predicted 95th, 50th, and 5th percentiles of concentration values. The blue-shaded areas indicate the 95 percent

confidence intervals (CIs) for the predicted 5th and 95th percentiles, while the red-shaded regions show the 95 percent CIs for the predicted 50th percentile. Abbreviations: T= thymine; C= cytosine.



a) b)

Figure 3. Visual predictive check (VPC) plots stratified by SLCO2B1 genotypes following a single oral dose of 60 mg fexofenadine, showing (a) SLCO2B1 1457CC and (b) SLCO2B1 1457CC/TT groups. Observed plasma concentrations after oral administration are indicated by dots. The model-predicted 95th, 50th, and 5th percentiles are represented by black dashed lines. Blue-shaded areas denote the 95 percent confidence intervals (CIs) for the predicted 5th and 95th percentiles, whereas red-shaded regions represent the 95 percent CIs for the predicted 50th percentile. Abbreviations: C, cytosine; T, thymine.

Model simulation-based pharmacokinetic comparison

Model simulation was conducted to assess how changes in pharmacokinetic parameter values varied with OATP genotypes, which acted as influential covariates in the finalized fexofenadine population pharmacokinetic model. Using non-parametric simulation based on the single-dose VPC outcomes, the plasma concentration–time profiles of multiple fexofenadine doses were estimated according to SLCO1B1 521T > C genotypes **(Figure 2)**. Consistent with the single-dose findings, simulated results demonstrated that mean fexofenadine plasma concentrations during repeated dosing increased and persisted longer as the SLCO1B1 521T > C genotype shifted from TT to TC to CC **(Figure 2)**. Quantitative pharmacokinetic parameters derived from single- and multiple-dose simulations stratified by OATP1B1 polymorphisms are provided in **Tables 1 and 2**, respectively. Statistically significant differences among SLCO1B1 521T > C genotypes were observed for Cmax, AUC, V/F, CL/F, and MRT ($P < 0.05$).

A graphical summary of significant inter-genotype comparisons **(Tables 1 and 2)** is shown in **Figure 4**. As reflected in the VPC outcomes, $AUC_{0-\infty}$, Cmax, and MRT increased markedly ($P < 0.05$), whereas CL/F declined as the genotype transitioned from TT to TC to CC. The magnitude of quantitative variation among OATP1B1 genotypes ranged from approximately 0.46- to 2.20-fold, indicating that steady-state mean plasma concentrations could differ by as much as 2.20 times across genotypes. Although changes in the mean accumulation ratio (R) were modest (1.00–1.03-fold) and not statistically significant, a slight increasing trend was noted from TT to TC to CC, with the AUC ratio being significantly higher in the SLCO1B1 521CC group. These results suggest that the SLCO1B1 521T > C polymorphism contributes to increased plasma accumulation of fexofenadine during repeated dosing, particularly in individuals carrying the CC genotype.

Table 1. Pharmacokinetic parameter estimates for each genotype group derived from the population pharmacokinetic model predictions, incorporating OATP1B1 polymorphism as a covariate following a single oral 180 mg dose of fexofenadine. The parameters were calculated based on predicted concentration percentiles (5th, 50th, 95th) and their respective confidence intervals (5%, 50%, 95%), corresponding to population proportions across prediction ranges (e.g., 5th−5 percent, 5th−50 percent, 5th−95 percent, 50th−5 percent, 50th−50 percent, 50th−95 percent, 95th−5 percent, 95th−50 percent, and 95th−95 percent).

Parameters	***SLCO1B1* 521T > C genotypes**		
	TT	**TC**	**CC**
$t_{1/2}$ (h)	2.45 ± 0.27	2.52 ± 0.26	2.83 ± 0.46
t_{max} (h)	2.00 ± 0.00	2.00 ± 0.00	2.50 ± 0.25*

c_{max} (ng/mL)	450.17 ± 124.22*	561.64 ± 154.96*	770.89 ± 214.36*
AUC_{0-t} (h·ng/mL)	2502.56 ± 833.74*	3315.74 ± 1100.37*	5258.51 ± 1721.99*
$AUC_{0-\infty}$ (h·ng/mL)	2633.93 ± 918.31*	3519.09 ± 1228.25*	5792.42 ± 2101.14*
V/F (L)	259.19 ± 58.86*	200.51 ± 49.72*	134.78 ± 26.29*
CL/F (L/h)	75.87 ± 26.26*	56.93 ± 20.18*	34.86 ± 12.80*
MRT (h)	4.44 ± 0.30*	4.73 ± 0.34*	5.62 ± 0.54*
R value [a]	1.04 ± 0.01	1.04 ± 0.01	1.06 ± 0.03

a R value meant the accumulation ratio and was calculated by the following formula:

$\frac{1}{1-e^{-k\times\tau}}$In the formula, k and τ represent the elimination rate constant of fexofenadine and the dosing interval (as 12 h) for multiple exposures, respectively.

* $P < 0.05$ between *SLCO1B1* 521TT, TC, and CC groups. T: thymine; C: cytosine; $t_{1/2}$: half-life; c_{max}: peak plasma concentration; t_{max}: time to reach c_{max}; AUC: area under the time-plasma concentration curve; V/F: volume of distribution; CL/F: clearance; MRT: mean residence time.

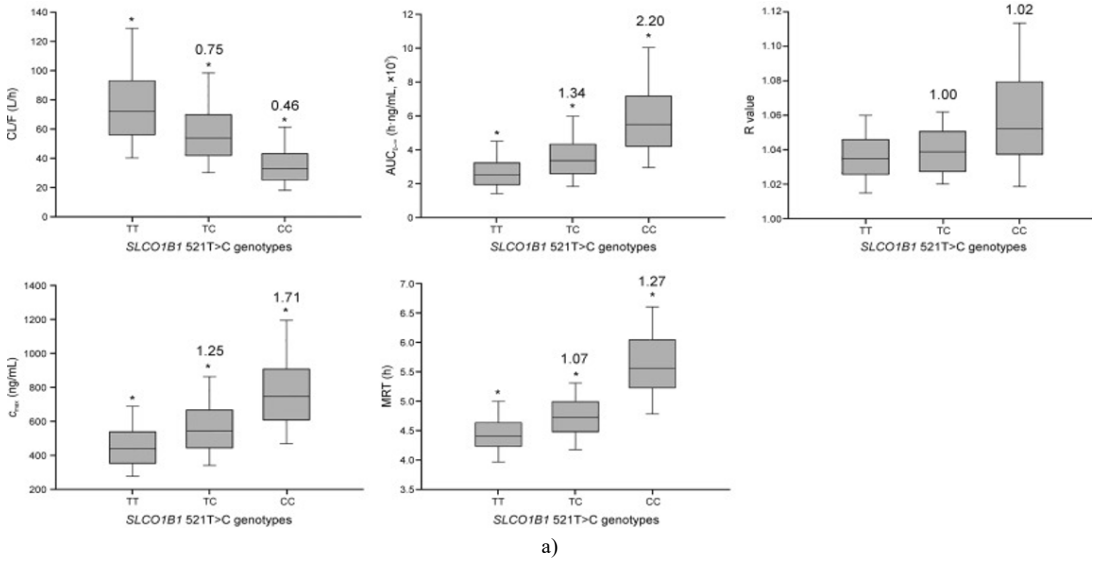
Table 2. Pharmacokinetic parameter estimates for each genotype group obtained from population pharmacokinetic model predictions, incorporating the organic-anion-transporting-polypeptide 1B1 (OATP1B1) genetic polymorphism as a covariate, following repeated oral administrations of 180 mg fexofenadine (10 doses at 12-hour intervals). The calculations were based on predicted concentration percentiles (5th, 50th, and 95th) and corresponding confidence interval (CI) ranges (5 percent, 50 percent, and 95 percent), expressed as combinations of population proportions within each prediction range (5th−5 percent, 5th−50 percent, 5th−95 percent, 50th−5 percent, 50th−50 percent, 50th−95 percent, 95th−5 percent, 95th−50 percent, and 95th−95 percent). The 5th, 50th, and 95th values represent the mean predicted percentiles of concentration for each genotype group, while the 5 percent, 50 percent, and 95 percent values indicate the mean 95% CI ranges corresponding to each percentile.

Parameters	***SLCO1B1* 521T > C genotypes**		
	TT	**TC**	**CC**
$t_{1/2}$ (h)	1.97 ± 0.63	1.84 ± 0.25	2.09 ± 0.46
t_{max} (h)	1.84 ± 0.29	1.93 ± 0.15	2.39 ± 0.31*
c_{max} (ng/mL)	470.17 ± 137.78*	593.83 ± 175.80*	846.32 ± 268.89*
$AUC_{108-120}$ (h·ng/mL)	2633.14 ± 917.84*	3518.62 ± 1227.54*	5793.46 ± 2100.82*
$AUC_{108-\infty}$ (h·ng/mL)	2750.95 ± 1013.51*	3671.18 ± 1324.20*	6231.77 ± 2445.98*
V/F (L)	191.14 ± 36.08*	145.23 ± 62.91*	92.15 ± 14.61*
CL/F (L/h)	73.41 ± 26.55*	54.89 ± 19.87*	32.98 ± 12.94*
MRT (h)	4.35 ± 0.34*	4.54 ± 0.23*	5.27 ± 0.42*
$c_{SS,mean}$ (ng/mL) [a]	219.49 ± 76.53*	293.26 ± 102.35*	482.70 ± 175.10*
AUC ratio [b]	1.04 ± 0.02	1.04 ± 0.01	1.07 ± 0.03*

[a] cSS,mean represents the average steady-state plasma concentration of fexofenadine.

[b] The AUC ratio denotes the comparison between single- and multiple-dose exposures of fexofenadine, calculated as $AUC_{108-\infty}$ (from multiple dosing) divided by $AUC_{0-\infty}$ (from a single dose).

*P < 0.05 indicates significant differences among the SLCO1B1 521TT, TC, and CC genotypes. Abbreviations: T, thymine; C, cytosine; $t_{1/2}$, elimination half-life; Cmax, maximum plasma concentration; Tmax, time to reach Cmax; AUC, area under the plasma concentration–time curve; V/F, apparent volume of distribution; CL/F, apparent clearance; MRT, mean residence time.



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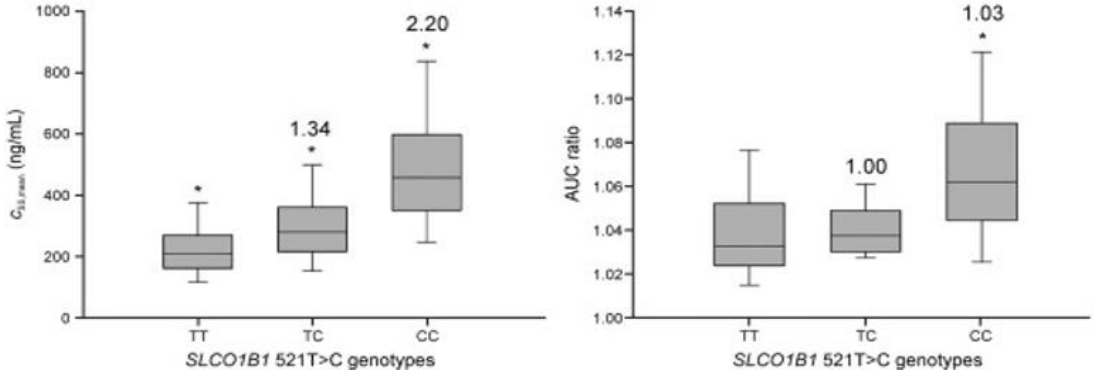

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Figure 4. Pharmacokinetic parameter estimates for each genotype group were derived from population pharmacokinetic model predictions of 5th−5 percent, 5th−50 percent, 5th−95 percent, 50th−5 percent, 50th−50 percent, 50th−95 percent, 95th−5 percent, 95th−50 percent, and 95th−95 percent (percentage of total population−percentage in range). These results were obtained from the visual predictive check (VPC) of the fexofenadine population pharmacokinetic model that incorporated organic-anion-transporting-polypeptide 1B1 (OATP1B1) genetic polymorphism as a covariate, following (a) a single oral administration and (b) repeated oral dosing (180 mg, every 12 h for 10 doses). The numerical values displayed above each bar in the figure represent the ratio of the mean parameter values for each genotype group relative to the mean of the SLCO1B1 521TT group. $P < 0.05$ indicates statistically significant differences among the SLCO1B1 521TT, TC, and CC groups. Abbreviations: T, thymine; C, cytosine; CL/F, apparent clearance; AUC, area under the plasma concentration–time curve; R value, accumulation ratio; Cmax, maximum plasma concentration; MRT, mean residence time; CSS, mean, mean steady-state plasma concentration of fexofenadine.

The OATP2B1 genetic polymorphism model was simulated at the same 180 mg dosage to enable a quantitative comparison with the OATP1B1 model. Specifically, the simulation was performed by scaling up the model originally developed from the 60 mg dose dataset, leveraging previously reported dose linearity of fexofenadine pharmacokinetics across the 10–800 mg range [18]. The resulting VPC simulations for both single and multiple 180 mg exposures, accounting for OATP2B1 polymorphisms, are illustrated in **Figure 5**. The model showed that individuals carrying the SLCO2B1 1457T allele had consistently lower average plasma fexofenadine concentrations compared with non-carriers. Quantitative pharmacokinetic outcomes derived from single- and multiple-dose simulations stratified by OATP2B1 genotypes are summarized in **Tables 3 and 4**, respectively.
During the single-dose simulation, significant genotype-related differences ($P < 0.05$) were observed in all pharmacokinetic parameters except Tmax. However, under multiple dosing conditions, statistically significant differences were limited to $t_{1/2}$, Cmax, and MRT. A comparative summary of parameters showing significant genotype effects is provided in **Figure 6**. Following single oral administration, subjects with the SLCO2B1

1457CT/TT genotype exhibited significantly lower $AUC_{0-\infty}$ and Cmax values ($P < 0.05$) compared with non-carriers, accompanied by increased CL/F, V/F, and R values. The magnitude of quantitative variation between OATP2B1 genotype groups ranged from approximately 0.54- to 2.00-fold, and the mean steady-state plasma concentration differed by as much as 0.61 times between genotypes. Furthermore, the mean R and AUC ratios exceeded 1 in both carriers and non-carriers of the SLCO2B1 1457C > T variant, indicating that repeated fexofenadine exposure leads to measurable plasma accumulation across all genotype groups.

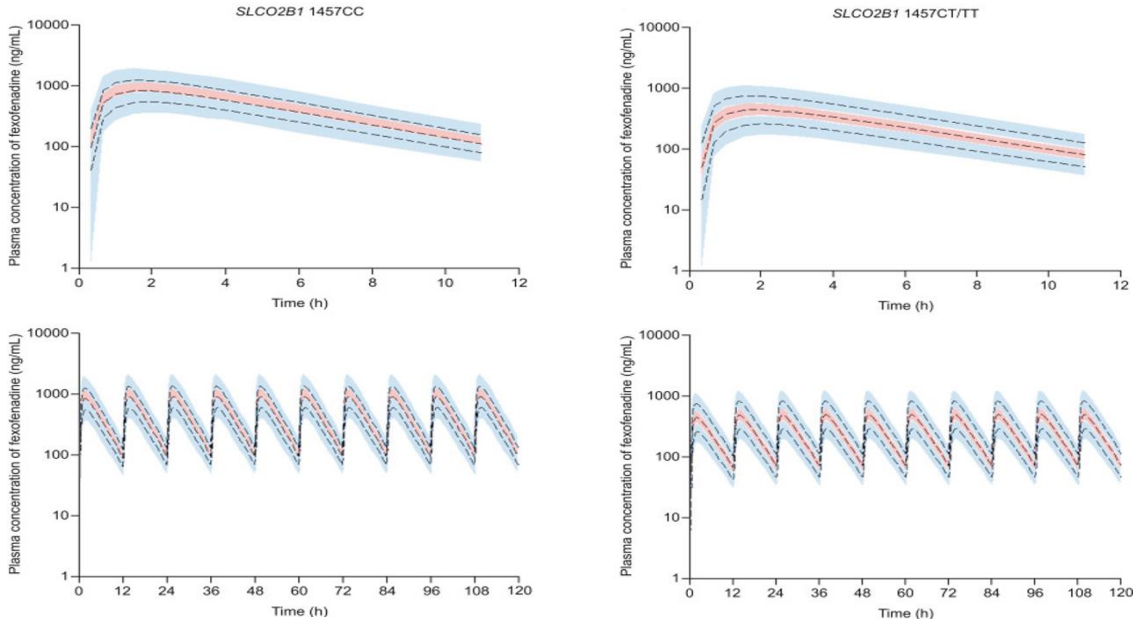


Figure 5. Stratified visual predictive check (VPC) outcomes based on SLCO2B1 genetic polymorphisms following a single 180 mg oral administration of fexofenadine (upper panel) and pharmacokinetic profiles after repeated 180 mg oral doses (lower panel; 12-hour intervals, 10 doses): (a) SLCO2B1 1457CC and (b) SLCO2B1 1457CT/TT genotypes. The predicted plasma concentration percentiles (95th, 50th, and 5th) are indicated with black dashed lines. The 95 percent confidence intervals (CIs) corresponding to the 5th and 95th predicted percentiles are displayed as blue shaded areas, whereas those for the 50th percentile are shown as red shaded areas. C denotes cytosine; T denotes thymine.

Table 3. Pharmacokinetic parameters estimated for each SLCO2B1 genotype group using population pharmacokinetic model predictions for 5th−5 percent, 5th−50 percent, 5th−95 percent, 50th−5 percent, 50th−50 percent, 50th−95 percent, 95th−5 percent, 95th−50 percent, and 95th−95 percent (percentage of total population−percentage within range). These results were derived from the VPC of the fexofenadine population pharmacokinetic model that incorporated organic-anion-transporting-polypeptide 2B1 (OATP2B1) genetic polymorphism as a covariate following a single oral dose of 180 mg fexofenadine. The 5th, 50th, and 95th indicate the predicted concentration percentiles, while 5 percent, 50 percent, and 95 percent represent the corresponding percentile confidence interval (CI) ranges.

Parameters	***SLCO2B1* 1457C > T genotypes**	
	CC	**CT/TT**
$t_{1/2}$ (h)	2.92 ± 0.13	3.38 ± 0.14*
t_{max} (h)	1.72 ± 0.26	1.83 ± 0.25
c_{max} (ng/mL)	930.28 ± 474.74	503.06 ± 283.14*
AUC_{0-t} (h·ng/mL)	5110.29 ± 2500.48	2984.28 ± 1615.63*
$AUC_{0-\infty}$ (h·ng/mL)	5617.20 ± 2708.82	3408.37 ± 1807.09*
V/F (L)	166.90 ± 88.34	334.45 ± 197.19*
CL/F (L/h)	38.89 ± 18.44	67.35 ± 36.20*
MRT (h)	5.13 ± 0.20	5.82 ± 0.27*

R value [a]	1.06 ± 0.01	1.09 ± 0.01*

a R value meant the accumulation ratio and was calculated by the following formula:

$\frac{1}{1-e^{-k\times\tau}}$In the formula, k and τ represent the elimination rate constant of fexofenadine and the dosing interval (as 12 h) for multiple exposures, respectively.

* $P < 0.05$ between *SLCO2B1* 1457CC and CT/TT groups. T: thymine; C: cytosine; $t_{1/2}$: half-life; c_{max}: peak plasma concentration; t_{max}: time to reach c_{max}; AUC: area under the time-plasma concentration curve; V/F: volume of distribution; CL/F: clearance; MRT: mean residence time.

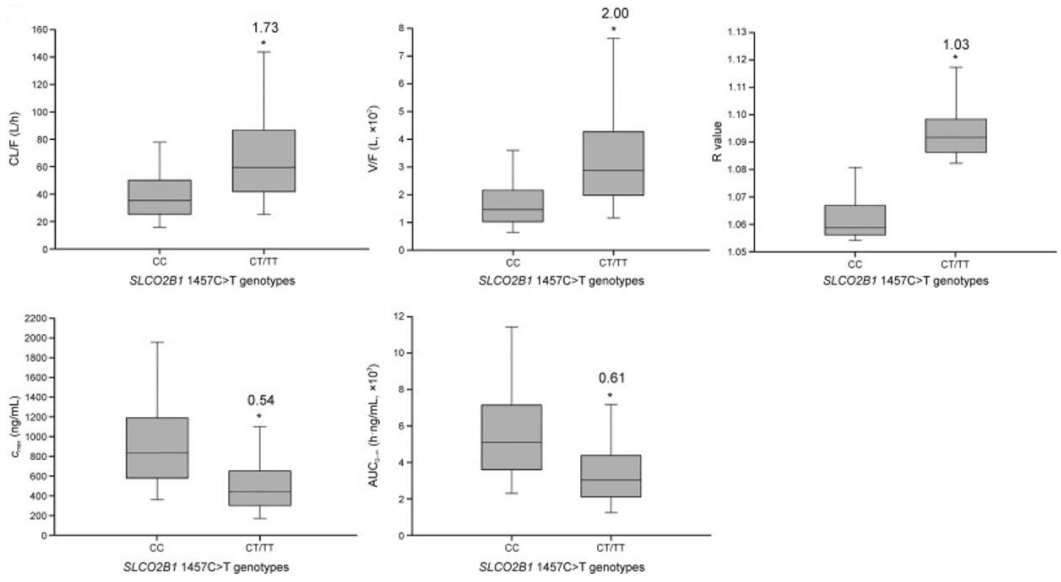
Table 4. Pharmacokinetic parameter estimates for each genotype group were obtained through population pharmacokinetic simulations corresponding to 5th−5 percent, 5th−50 percent, 5th−95 percent, 50th−5 percent, 50th−50 percent, 50th−95 percent, 95th−5 percent, 95th−50 percent, and 95th−95 percent (percentage of total population−percentage within range). These results were derived from the visual predictive check (VPC) of the fexofenadine population pharmacokinetic model incorporating the organic-anion-transporting-polypeptide 2B1 (OATP2B1) genetic polymorphism as a covariate, following repeated oral administration of 180 mg fexofenadine at 12-hour intervals for 10 doses. The 5th, 50th, and 95th denote the predicted concentration percentiles for each group, while 5 percent, 50 percent, and 95 percent indicate the corresponding percentile confidence interval (CI) ranges.

Parameters	***SLCO2B1* 1457C > T genotypes**	
	CC	**CT/TT**
$t_{1/2}$ (h)	2.92 ± 0.13	3.38 ± 0.14∗
t_{max} (h)	1.72 ± 0.22	1.79 ± 0.22
c_{max} (ng/mL)	994.91 ± 501.28	556.11 ± 309.22*
$AUC_{108-120}$ (h·ng/mL)	5615.91 ± 2706.02	3408.81 ± 1806.76
$AUC_{108-\infty}$ (h·ng/mL)	6038.29 ± 2873.34	3785.38 ± 1971.53
V/F (L)	154.15 ± 79.85	297.87 ± 170.51
CL/F (L/h)	35.94 ± 16.66	60.01 ± 31.29
MRT (h)	5.14 ± 0.19	5.79 ± 0.26*
$c_{SS,mean}$ (ng/mL) [a]	468.10 ± 225.74	284.03 ± 150.59
AUC ratio [b]	1.08 ± 0.01	1.12 ± 0.01*

[a] cSS,mean represents the average steady-state plasma concentration of fexofenadine.

[b] The AUC ratio indicates the comparison between single- and multiple-dose exposures to fexofenadine, determined using the formula: AUC108−∞ (for multiple doses)/AUC0−∞ (for a single dose).

∗ P < 0.05 denotes a statistically significant difference between the SLCO2B1 1457CC and CT/TT genotype groups. T: thymine; C: cytosine; t1/2: elimination half-life; cmax: maximum plasma concentration; tmax: time to reach cmax; AUC: area under the plasma concentration–time curve; V/F: apparent volume of distribution; CL/F: apparent clearance; MRT: mean residence time.



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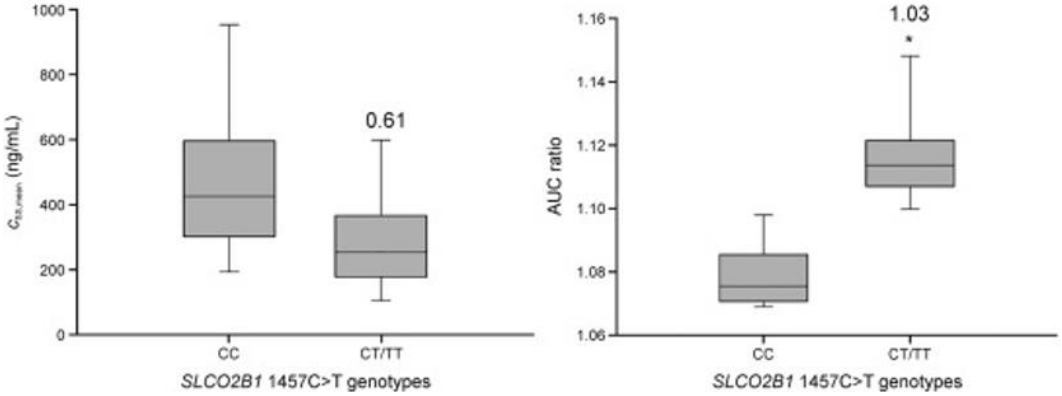

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Figure 6. Pharmacokinetic parameter estimates for each genotype group were obtained using population pharmacokinetic simulations at 5th−5 percent, 5th−50 percent, 5th−95 percent, 50th−5 percent, 50th−50 percemt, 50th−95 percent, 95th−5 percent, 95th−50 percent, and 95th−95 percent (percentage of total population−percentage within range). These values were derived from the visual predictive check (VPC) of the fexofenadine population pharmacokinetic model that incorporated the organic-anion-transporting-polypeptide (OATP) 2B1 genetic polymorphism as a covariate, following (a) single-dose or (b) multiple-dose (180 mg every 12 h for 10 doses) oral administration of fexofenadine. The ratios displayed above each bar represent the mean values of each genotype group relative to the mean value of the SLCO2B1 1457CC group. ∗ $P < 0.05$ indicates statistically significant differences between SLCO2B1 1457CC and CT/TT genotypes. C: cytosine; T: thymine; CL/F: apparent clearance; V/F: apparent volume of distribution; R value: accumulation ratio; cmax: maximum plasma concentration; AUC: area under the plasma concentration–time curve; cSS, mean: mean steady-state plasma concentration of fexofenadine.

Model simulation-based pharmacodynamic comparison

The population pharmacokinetic model constructed in this study was further utilized to perform a quantitative pharmacodynamic comparison of fexofenadine across OATP1B1 and OATP2B1 genotype populations. This required establishing a quantitative link between plasma exposure levels of fexofenadine (influenced by genetic polymorphisms of OATP1B1 and OATP2B1) and its pharmacological efficacy. Consequently, a new correlation model describing the relationship between AUEC (area under the effect–time curve) and plasma AUC (area under the concentration–time curve) was developed, based on previously reported pharmacokinetic–pharmacodynamic data for fexofenadine [17]. Through simulation, the correlation between AUC and AUEC was quantified as a function of dose variation, referencing the established pharmacokinetic–pharmacodynamic framework of fexofenadine [17]. In this context, AUC reflects the extent of systemic drug exposure, whereas AUEC represents the cumulative efficacy over time.

Figure 7 illustrates the AUC–AUEC relationship determined in this study, which was most accurately described using the Weibull model. The complete inclusion of all data points within the 95% confidence and prediction intervals demonstrated the robustness and reliability of the established correlation model in predicting quantitative fexofenadine efficacy. The Weibull model was selected due to its high flexibility, enabling it to effectively capture various data distributions, including skewed, nonlinear, and symmetric patterns [19]. The observed nonlinear relationship between AUC and AUEC across different fexofenadine doses was appropriately characterized by this model. The optimized equations and parameter estimates for the AUC–AUEC correlation model are summarized in **Table 5**, showing low relative standard errors (RSE < 2%) and parameter means fully contained within their respective 95% confidence intervals. Furthermore, the model's Akaike Information Criterion (AIC) value was low (11.49), and the correlation coefficient reached 1.00, confirming an excellent fit between the observed and modeled data.

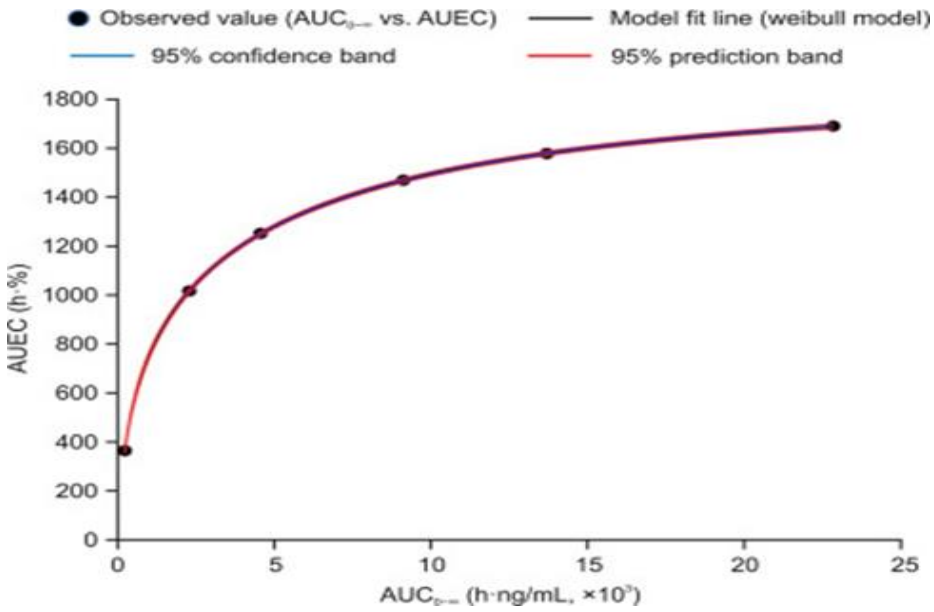

Figure 7. Correlation plot illustrating the relationship between the area under the plasma concentration–time curve ($AUC_{0-\infty}$) and the area under the effect–time curve (AUEC), as determined from the developed fexofenadine population pharmacokinetic–pharmacodynamic model. In this context, the pharmacodynamic effect represents the antihistaminic response elicited by fexofenadine.

Table 5. The Weibull model [a] and parameter values between $AUC_{0-\infty}$ and area under the effect curve (AUEC) estimated using the established fexofenadine population pharmacokinetic-pharmacodynamics model.

Parameters	Mean ± standard error	Relative standard error (%)	95% CI
A	1846.55 ± 6.15	0.33	1820.08–1873.01
B	2028.31 ± 18.23	0.90	1949.85–2106.77
C	0.03 ± 0.00	0.75	0.02–0.03
D	0.45 ± 0.01	1.52	0.43–0.48
AIC	11.49	–	–
Correlation coefficient	1.00	–	–

[a] Weibull model: $y = A - Bx \exp(-C \times x^D)$, where x indicates $AUC_{0-\infty}$, y indicates AUEC, A indicates the asymptote parameter, B indicates scale parameter, C indicates curve growth-rate parameter, and D indicates the shape parameter.
−: no data; AUC: area under the time-plasma concentration curve; CI: confidence interval; AIC: Akaike's information criterion.

Table 6 presents the predicted AUEC values corresponding to the OATP1B1 and OATP2B1 genetic polymorphisms, calculated using the established fexofenadine population pharmacokinetic models in combination with the AUC–AUEC correlation model developed in this study. The AUEC estimates were obtained through interpolation within the prediction range defined by the AUC–AUEC correlation curve. After a single fexofenadine dose, the AUC-based AUEC values in plasma varied by approximately 1.25-fold for OATP1B1 and 0.87-fold for OATP2B1 genotypes. Similarly, under multiple-dose conditions at steady state, these differences were 1.25-fold and 0.89-fold, respectively. These findings indicate that the extent of fexofenadine exposure—and consequently, drug efficacy—varies notably depending on the OATP1B1 or OATP2B1 genetic variants. Specifically, in the SLCO1B1 521T > C polymorphism, progressive loss of the T allele (TT → TC → CC) was associated with a substantial rise in plasma fexofenadine concentration **(Tables 1 and 2)**, leading to an estimated increase in efficacy of up to 1.25-fold. Conversely, for the SLCO2B1 1457C > T polymorphism, the markedly lower plasma levels of fexofenadine observed in T-allele carriers compared to non-carriers **(Table 3)** corresponded to an estimated 0.87-fold reduction in efficacy.

Table 6. Area under the effect curve (AUEC) values for each organic anion transporting polypeptide (OATP) genotype, calculated from the $AUC_{0-\infty}$–AUEC correlation model derived using the established fexofenadine population pharmacokinetic–pharmacodynamic framework. The estimated AUEC values were based on mean

$AUC_{0-\infty}$ (for single-dose exposure) and $AUC_{108-\infty}$ (for multiple-dose exposure) predictions obtained from population pharmacokinetic models that incorporated OATP genetic polymorphisms as covariates.

Exposures	Predicted AUEC for OATP1B1 (h×%)			Predicted AUEC for OATP2B1 (h×%)	
	TT	TC	CC	CC	CT/TT
Single dose	1065.48	1163.73	1328.94	1319.04	1152.91
Multiple dose	1080.22	1178.02	1352.30	1342.26	1188.35

T: thymine; C: cytosine; AUC: area under the time-plasma concentration curve.

Effects of OATP1B1 and OATP2B1 on Fexofenadine Pharmacokinetic–Pharmacodynamic Variability

This study employed a retrospective modeling approach based on segmental pharmacokinetic data stratified by OATP1B1 or OATP2B1 genetic polymorphisms. Consequently, constructing a model that simultaneously accounts for both OATP1B1 and OATP2B1 polymorphisms was limited, as the available experimental data [6, 7] only allowed analysis for each transporter individually. Therefore, separate models were developed for each genetic polymorphism to identify which transporter exerts a greater influence on inter-individual variability in fexofenadine pharmacokinetics and pharmacodynamics. Comparatively, OATP1B1 polymorphisms had a more pronounced impact on fexofenadine pharmacokinetics than OATP2B1, as the variation in AUC and steady-state mean plasma concentration for OATP1B1 genotypes was up to 2.20-fold, whereas for OATP2B1 it was only 0.61-fold **(Figures 4 and 6)**. Similarly, in AUEC predictions based on the AUC–AUEC correlation model, OATP1B1 polymorphisms produced a 1.25-fold difference compared to 1.13–1.14-fold for OATP2B1. Thus, OATP1B1 and OATP2B1 genetic variations are likely the primary and secondary determinants, respectively, for precision dosing of fexofenadine.

The selection of OATP1B1 and OATP2B1 as significant covariates for CL/F in these models indicates a heterogeneous interplay between the two transporters in determining systemic clearance. Although both are homologous transporters using fexofenadine as a substrate, their predominant expression sites differ: OATP1B1 in the liver and OATP2B1 in the intestine [9, 20]. This suggests a combined effect on systemic clearance through OATP2B1-mediated intestinal absorption and OATP1B1-mediated hepatic elimination.

The fexofenadine population pharmacokinetic models developed in this study were adequately described by a one-compartment structure, using plasma concentration data up to 12 hours after a single oral dose. The pharmacokinetic data stratified by OATP1B1 or OATP2B1 polymorphisms [6, 7] were limited to this 12-hour timeframe, and post-12-hour concentrations were not available. Therefore, modeling focused exclusively on the first 12 hours after dosing.

OATP2B1, primarily expressed in the gastrointestinal tract, directly influences oral absorption of fexofenadine [20]. Incorporating inter-individual variability (IIV) and accounting for tlag related to OATP2B1 polymorphisms significantly improved the physiological relevance of the absorption phase in the model. The sparsity of absorption-phase data for OATP2B1 also supported the utility of including tlag in IIV.

In the models, OATP1B1 (SLCO1B1 521T > C) and OATP2B1 (SLCO2B1 1457C > T) polymorphisms were included as covariates for CL/F and V/F, but not for tlag or Ka. This indicates that differences in fexofenadine pharmacokinetics between genotypes are primarily driven by changes in clearance and volume of distribution. Specifically, OATP1B1 polymorphisms, expressed in the liver, majorly affect hepatic clearance by mediating fexofenadine uptake into hepatocytes [6]. In contrast, OATP2B1 polymorphisms are associated with intestinal clearance and influence the volume of distribution by affecting fexofenadine absorption from the gastrointestinal tract. Overall, OATP1B1 and OATP2B1 polymorphisms are key determinants of inter-individual variability in CL/F and V/F, explaining observed differences in plasma fexofenadine concentrations.

While previous reports [21] suggested that ABCB1 (P-glycoprotein) polymorphisms may contribute to fexofenadine pharmacokinetic variability, the evidence remains controversial. Some studies observed inter-individual differences in fexofenadine pharmacokinetics based on ABCB1 variants (2677G > T/A, 3435C > T) [21], whereas others did not [22]. Additionally, Dickens *et al*. [23] reported that ABCB1 polymorphisms (1236C > T, 2677G > T/A, 3435C > T) do not significantly affect P-gp function for fexofenadine, limiting their suitability as covariates. Consistently, our prior work [17] found ABCB1 variants were not significant predictors of fexofenadine pharmacokinetic variability. Therefore, this study focused on OATP1B1 and OATP2B1 as more specific determinants. Nonetheless, other factors influencing inter-individual variability—such as ABCC gene-encoded multidrug resistance-associated proteins (MRP2, MRP3, MRP4)—may warrant future investigation [24].

Recent studies [17] indicated that demographic factors were not significant contributors to fexofenadine pharmacokinetic variability, likely because the analyses were conducted in healthy adults with limited inter-individual variability. Accordingly, demographic factors were not included in this study due to limited clinical data [6, 7] and previous findings [17].

In the pharmacokinetic observations stratified by SLCO2B1 1457C > T polymorphisms [7], cmax was lower in the CT/TT group compared to the CC group, although plasma concentrations were more consistent **(Figure 3)**. Similarly, in the established model, cmax and AUC were significantly ($P < 0.05$) reduced in the CT/TT group relative to the CC group, whereas CL/F, t1/2, and MRT were higher **(Table 3)**. Therefore, despite the lower overall plasma exposure in the SLCO2B1 1457CT/TT group following the same fexofenadine dose, relative accumulation after multiple doses could be higher. This suggests that reduced fexofenadine uptake in SLCO2B1 1457CT/TT significantly decreases AUC and increases CL/F, but the elimination rate of absorbed drug is slower in the CT/TT group. In other words, OATP2B1 polymorphisms appear closely linked to the initial gastrointestinal absorption phase of fexofenadine, influencing the extent of absorption (intestinal clearance) rather than the absorption rate.

For OATP2B1 polymorphisms, no significant differences in AUC, V/F, or CL/F were observed between SLCO2B1 1457CC and CT/TT groups during simulations of multiple fexofenadine doses, unlike the single-dose scenario **(Tables 3 and 4)**. This indicates that the impact of OATP2B1 diminishes with repeated dosing, as reflected by the lack of significant difference in steady-state mean plasma concentrations **(Table 4)**. Conversely, pharmacokinetic differences among SLCO1B1 521TT, TC, and CC groups persisted in multiple-dose simulations, reinforcing the relatively dominant influence of OATP1B1 polymorphisms on inter-individual fexofenadine pharmacokinetic variability.

The effect of plasma exposure on fexofenadine efficacy for each OATP1B1 or 2B1 genotype group was quantified using the AUC–AUEC correlation model developed in this study. However, this model was derived from pharmacokinetic–pharmacodynamic data without incorporating covariates for inter-individual variability, meaning the AUEC estimates **(Table 6)** reflect predicted pharmacodynamic differences solely based on OATP genetic polymorphisms. Future studies should investigate additional covariates influencing fexofenadine pharmacodynamic variability, as individuals may respond differently to the same plasma exposure due to variations in target receptor sensitivity.

This study relied on limited clinical data [6, 7], as very few reports provide human fexofenadine concentration profiles alongside OATP1B1 and 2B1 genotyping. Despite this, the modeling results offer a scientific foundation and guidance for future large-scale clinical trials. Moreover, because the study was based on healthy volunteers, it is uncertain whether the established effects of OATP1B1 and 2B1 apply to patient populations. Future clinical studies in disease groups such as chronic allergic conditions or liver cirrhosis will be necessary to confirm these findings. Additionally, further research should explore pharmacokinetic–pharmacodynamic interactions between fexofenadine and concomitant medications.

Overall, this study provides valuable data to support more effective clinical use of fexofenadine and represents a step toward precision medicine, as it quantitatively clarifies the influence of OATP1B1 and 2B1 on inter-individual pharmacokinetic variability, which had not been clearly documented previously.

Conclusion

This research presents a population pharmacokinetic model of fexofenadine that incorporates genetic polymorphisms of OATP1B1 and 2B1. Using simulation approaches, the established models enabled quantitative comparisons of fexofenadine pharmacokinetics across different OATP1B1 and 2B1 genotypes. The findings highlight that OATP1B1 and 2B1 genetic factors are currently the most influential determinants of inter-individual variability in fexofenadine pharmacokinetics, indicating that these polymorphisms should be considered when designing dosing regimens. This work provides a critical foundation for personalized fexofenadine therapy and precision medicine, while also addressing previous gaps by delivering quantitative insights into the drug's pharmacokinetic variability.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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