European Journal of Drug Metabolism and Pharmacokinetics
https://doi.org/10.1007/s13318-018-0519-1

ORIGINAL RESEARCH ARTICLE

Mechanistic Assessment of the Effect of Omeprazole on the In Vivo Pharmacokinetics of Itraconazole in Healthy Volunteers

Ahmad Y. Abuhelwa[1] · Stuart Mudge[2] · Richard N. Upton[1] · David J. R. Foster[1]

Abstract

Background and Objective SUBA-itraconazole and Sporanox are two oral formulations of itraconazole. Drug–drug interactions with omeprazole have been previously reported; however, mechanistic understanding of the pharmacological and physiological interactions of omeprazole with orally administered itraconazole within a population modeling paradigm is lacking. The objective of this analysis was to mechanistically describe and quantify the effect of omeprazole on the pharmacokinetics of itraconazole and its major metabolite, hydroxyitraconazole from the SUBA itraconazole and Sporanox formulations.

Methods An in vitro–in vivo (IVIV) pharmacokinetic model of itraconazole and hydroxyitraconazole was developed including data from an omeprazole interaction study with SUBA itraconazole. Meta-models of gastric pH for healthy subjects and subjects receiving omeprazole were integrated into the IVIV model to capture omeprazole-mediated gastric pH changes on itraconazole dissolution and absorption.

Results Omeprazole influenced the kinetics of itraconazole through altering the dissolution and absorption due to the pH-dependent solubility of itraconazole, inhibition of efflux transporters, and inhibiting the metabolism of itraconazole and hydroxyitraconazole. The model-predicted population effects of omeprazole on itraconazole from SUBA-itraconazole were to increase the area under the concentration–time curve (AUC_{0-24}) and maximum concentration (C_{max}) by 35 and 31%, respectively, and to decrease AUC_{0-24} and C_{max} from Sporanox by 68 and 76%, respectively.

Conclusion Unlike SUBA itraconazole, which requires basic pH for itraconazole release, the omeprazole-induced pH-mediated reduction in Sporanox dissolution overrides any increased exposure from the drug–drug interaction at hepatic metabolizing enzymes or efflux transporters. The model presented here is the most complete quantitative description of the pharmacokinetics of itraconazole and hydroxyitraconazole currently available.

Key Points

A population in vitro–in vivo pharmacokinetic model was developed to describe and quantitatively predict the differing effect of omeprazole on in vivo itraconazole exposure for the SUBA-itraconazole and Sporanox formulations

Model predictions suggest that omeprazole increases the exposure from SUBA-itraconazole but reduces the exposure from Sporanox

Unlike SUBA-itraconazole, which requires basic pH for itraconazole release from the polymeric matrix, Sporanox is highly dependent on low gastric pH for adequate dissolution and absorption. The significant pH-mediated reduction in dissolution and absorption due to increased gastric pH overrides any increased exposure due to drug–drug interaction at the hepatic metabolizing enzymes or P-gp transporters, resulting in an overall reduced itraconazole and hydroxyitraconazole exposure

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13318-018-0519-1) contains supplementary material, which is available to authorized users.

✉ Ahmad Y. Abuhelwa
ahmad.abuhelwa@mymail.unisa.edu.au

[1] Australian Centre for Pharmacometrics and Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia

[2] Mayne Pharma International, Salisbury South, SA, Australia

Published online: 16 October 2018

1 Introduction

Itraconazole is a broad-spectrum antifungal agent active against a wide range of fungal species. It has been shown to inhibit fungal cytochrome P450 (CYP)-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes [1]. Itraconazole has low water solubility and high intestinal permeability (BCS class II weakly basic drug, pka 3.7) making itraconazole dissolution, which is pH-dependent, the rate-limiting step for oral absorption. Itraconazole is primarily metabolized by human CYP3A4 enzymes to the active metabolite, hydroxyitraconazole. Itraconazole is a substrate of the ATP-dependent efflux transporter P-glycoprotein (P-gp) [2].

Sporanox and SUBA-itraconazole are two itraconazole oral capsule formulations each employing different formulation strategies to address the solubility limitation of itraconazole. Sporanox (Janssen Pharmaceuticals, Inc.), in which a layer of solid itraconazole is sprayed on onto a sugar sphere core, requires an acidic gastric pH for adequate dissolution and absorption [3]. The SUBA-itraconazole capsule (Mayne Pharma, Inc., Salisbury South, South Australia, Australia), is a novel formulation in which itraconazole is presented as a solid dispersion of microparticles within a pH-dependent polymeric matrix. The polymeric matrix dissolves at intestinal (pH ~ 6) rather than gastric pH, resulting in substantially enhanced oral bioavailability compared to Sporanox [4, 5].

Population pharmacokinetic models of SUBA-itraconazole and Sporanox have been progressively developed by Abuhelwa et al. [3–5]. The continued developments include the addition of a pH-dependent dissolution model for Sporanox and SUBA-itraconazole to allow in vitro–in vivo (IVIV) correlation of pH-dependent dissolution and oral absorption [3], meta-analysis models of gastric and intestinal pH and transit times and their variability to inform the in vitro dissolution rate of SUBA-itraconazole and Sporanox [6, 7], and the addition of a first-pass metabolism model and revision of non-linear kinetics incorporating literature data for intravenously administered itraconazole [5]. The latter comprehensive population IVIV pharmacokinetic model described the first-pass metabolism, absolute bioavailability and the relative roles of first-pass metabolism, absorption, and dose and food effects for Sporanox and SUBA-itraconazole.

Omeprazole is an orally administered proton pump inhibitor (PPI) most commonly used for treatment of peptic ulcer, gastroesophageal reflux disease (GORD), reflux esophagitis and Zollinger–Ellison syndrome [8]. Omeprazole irreversibly inhibits H + /K + -ATPase and suppresses basal and stimulated gastric acid secretions. The inhibitory effect of omeprazole on gastric acid secretion may last for 2–3 days after single-dose administration and increases upon daily administration for up to 5 days, after which a plateau is reached [9]. Omeprazole is primarily metabolized by CYP3A4 and CYP2C9 enzymes and is a substrate and inhibitor of P-gp efflux transporters [10].

Drug–drug interactions of omeprazole with various drugs have been reviewed previously [11, 12]. However, mechanistic understanding of the pharmacological and physiological interactions of omeprazole with orally administered itraconazole, especially within a population modeling paradigm is lacking.

The objectives of this study were to (1) develop an updated version of the previously published IVIV pharmacokinetic model [5] by including pharmacokinetic data from the drug–drug interaction study of omeprazole with SUBA-itraconazole capsules and new single- and multi-dose clinical data for SUBA-itraconazole and Sporanox; and (2) provide a mechanistic understanding and quantitative assessment of the effect of omeprazole on the in vivo pharmacokinetics of itraconazole and hydroxyitraconazole from SUBA-itraconazole and Sporanox formulations.

2 Methods

2.1 Study Data Used in the Analysis

Data used in the analysis included single- and multi-dose intravenous and oral pharmacokinetic data used in the previously published model [5] in addition to new oral pharmacokinetic data for SUBA-itraconazole 65 mg and Sporanox 100 mg capsules. The previously published model included intravenous itraconazole and hydroxyitraconazole data extracted from the literature (a total of nine cohorts providing a total of 356 extracted mean concentrations of itraconazole and hydroxyitraconazole and randomized crossover design oral pharmacokinetic studies comparing Sporanox with SUBA-itraconazole in healthy volunteers (seven clinical trials providing 24,965 plasma concentrations from 238 subjects) [5].

New pharmacokinetic data from 5 clinical studies became available since the last published model. A summary of the design and dosing schedule of all oral pharmacokinetic studies used in the current analysis is provided in Table 1, a summary of demographic characteristics in Table 2, and a summary of the pharmacokinetic sampling times in individual studies in Table S1 of the supplementary material. Of the new clinical studies, there were four multi-dose studies comparing the pharmacokinetics of SUBA-itraconazole 65 mg capsule with Sporanox 100 mg capsule in the fed and fasted states (studies MPG012, MPG013, MPG015, MPG017) and an omeprazole drug interaction study (MPG016) comparing the pharmacokinetics of a single dose

Table 1 Clinical studies used for model development

Study	Number of subjects	Single/multiple	Treatment periods per subject	SUBA-itraconazole daily doses per subject	Sporanox daily doses per subject	Sporanox source	Fed (yes/no)	Fasted (yes/no)	Replicate design (yes/no)
HGN007	36	Single	4	1 × 50 mg/2 periods	1 × 100 mg/2 periods	UK	Y	Y	N
HGN008	48	Single	4	1 × 50 mg/2 periods	1 × 100 mg/2 periods	UK	Y	N	Y
MPG009	52	Single	4	1 × 65 mg/2 periods	1 × 100 mg/2 periods	USA	Y	Y	N
10850702	24	Single	4	1 × 50 mg/1 period 2 × 50 mg/1 period	1 × 100 mg/1 period 2 × 100 mg/1 period	USA	N	Y	Y
10850703	36	Single	4	1 x 50 mg/2 periods	1 × 100 mg/2 periods	USA	Y	Y	N
MPG016	29	Single	2	2 × 65 mg/1 period 2 × 65 mg with 40 mg omeprazole/1 period	NA	NA	N	Y	N
10850705	24	Multiple	2	2 × 50 mg q.d x 15 days/1 period	2 × 100 mg q.d × 15 days/1 period	USA	Y	N	N
10850706	24	Multiple	2	2 × 50 mg b.i.d × 15 days/1 period	2 × 100 mg b.i.d × 15 days/1 period	USA	Y	N	N
MPG012	22	Multiple	2	2 × 65 mg q.d × 15 days/1 period	2 × 100 mg q.d ×15 days/1 period	USA	Y	N	N
MPG013	15	Multiple	2	2 × 65 mg t.i.d × 3 days and q.d on day 4/1 period	2 × 100 mg t.i.d × 3 days and q.d on day 4/1 period	USA	Y	N	N
MPG015	16	Multiple	2	2 × 65 mg b.i.d × 15 days/1 period	2 × 100 mg b.i.d × 15 days/1 period	USA	Y	N	N
MPG017	20	Multiple	2	2 × 65 mg b.i.d × 15 days/1 period	NA	NA	Y	Y	N

All studies were conducted by Mayne Pharma International, Salisbury South, South Australia, Australia

All studies were randomized cross-over design studies with 1, 2 or 4 treatment periods per subject

q.d once daily, *b.i.d* twice daily, *t.i.d* three times daily

of 2 × SUBA-itraconazole 65 mg capsules with and without co-administration of multiple daily doses of 40 mg of omeprazole delayed-release capsule (Sandoz, Inc.) under fasted conditions.

All studies presented in Table 1 were conducted by Mayne Pharma International, Salisbury South, South Australia, Australia, in accordance with the ICH Guidelines for Good Clinical Practice [13], the Declaration of Helsinki on the ethical conduct of medical research [14], and applicable regulatory requirements. Each subject provided written informed consent before study participation. There were no exclusions or corrections to the supplied data prior to analysis. All available subjects and data points were included in the analysis. Subjects with partial data were included in the analysis where possible. Overall, the model presented here included data from a total of 11 studies of 340 subjects receiving SUBA-itraconazole or Sporanox and providing a total of 36,069 plasma concentrations, with an average of 106 observations per subject.

Table 2 Demographic characteristics of study population in single versus multi-dose studies

Demographic	Single-dose studies	Multi-dose studies	All studies
n	224	116	340
Age (years)	34.9 (34, 18–59)	38.5 (36.5, 19–67)	36.1 (35.5, 18–67)
Weight (kg)	75.9 (75.7, 47.4–110.7)	82.4 (83.2, 53.5–109.5)	78.1 (78, 47.4–110.7)
Height (cm)	173.6 (174.9, 147.7–198.1)	174.4 (174.9, 155–198.1)	173.9 (174.9, 147.7–198.1)
Body mass index(kg/m^2)	25 (25.4, 18–30)	26.9 (27.3, 18.3–32.7)	25.7 (25.9, 18–32.7)
Sex (male:female)	162:62	77:39	239:101
Race (white:black/african:american/other)	155:39:30	37:53:26	192:92:56
Ethnicity (hispanic:not hispanic)	16:208	5:111	21:319

All values calculated as mean (median, range) unless stated otherwise

n is the number of subjects

Overall, 11.43% of the itraconazole and 16.47% of the hydroxyitraconazole data were missing. The missing data were primarily below the lower limit of quantitation (LLOQ) and occurred primarily at the beginning or the end of the observation period. Models accounting for LLOQ-censored data using the YLO and M3 methods investigated previously by Abuhelwa et al. [4, 5] and were found to be characterized by unreliable minimization and covariance step status and therefore LLOQ observations were excluded a priori from the dataset (M1 method).

2.2 Software

Modeling was performed using a Dell® Power Edge R910 server with 4 × 10 core Xeon 2.26 Ghz processors running Windows Server 2008 R2 Enterprise 64-bit. Log-transformed plasma concentrations were used for pharmacokinetic modeling. Model development employed non-linear mixed-effect modeling using NONMEM (Version 7.3; ICON Development Solutions, Ellicott City, MD, USA) [15] with the Wings for NONMEM (version 7.3, Auckland, New Zealand) interface and IFort compiler [16]. All models were coded using the ADVAN13 subroutine and fit using FOCE-I method. Importance sampling was used to assess the precision of the estimated parameters. Processing NONMEM output and generating plots were conducted with the R Software (Vienna, Austria) Version 3.1.1 or later [17] using ggplot2, plyr, and scales packages [18–20] and associated dependencies.

2.3 Population Model Development

2.3.1 Updating the Population IVIV Pharmacokinetic Model

The same structural model of the previously published model [5] was used as a base model for the full available datasets and all model parameters were re-estimated. Briefly, the previously published model integrated meta-models of gastrointestinal (GI) pH and GI transit time in healthy subjects and in vitro dissolution models of Sporanox and SUBA-itraconazole with the absorption and disposition kinetics of itraconazole and hydroxyitraconazole from Sporanox (100 mg) and SUBA-itraconazole (50 mg) studies. A schematic diagram of the population pharmacokinetic model is presented in Fig. 1. Hydroxyitraconazole clearance was described by Michaelis–Menten elimination kinetics and itraconazole clearance was described by a mixed inhibition model that allowed hydroxyitraconazole concentrations to inhibit the clearance of itraconazole, assuming hydroxyitraconazole undergoes further metabolism by the same metabolizing enzymes of itraconazole [5].

The updated 'base model' was then used for screening of covariates other than those included in the previously published model. Covariates were evaluated for statistical significance using a stepwise covariate modelling of forward addition and backward elimination [21]. The statistical criteria for retaining a covariate in the model were $p < 0.005$ during forward addition and $p < 0.001$ for backward elimination. Potential significant covariates were identified by visualizing plots of covariates versus between-subject variability of parameter estimates. Covariates included in the previously published model were tested if they retained significance in the updated model by removing each one at a time and observing the objective function value (OFV). An increase in OFV of 10.8 units indicated that a single covariate retained significance and therefore stayed in the final model.

2.3.2 Omeprazole and Gastric pH

Meta-models describing fed and fasted GI pH and GI transit time were integrated to the IVIV pharmacokinetic model to capture the effect of these physiological variables on drug release and pharmacokinetics and can be referred to in the previous publication [5]. In the current analysis, a gastric pH model for healthy subjects receiving omeprazole 40 mg was

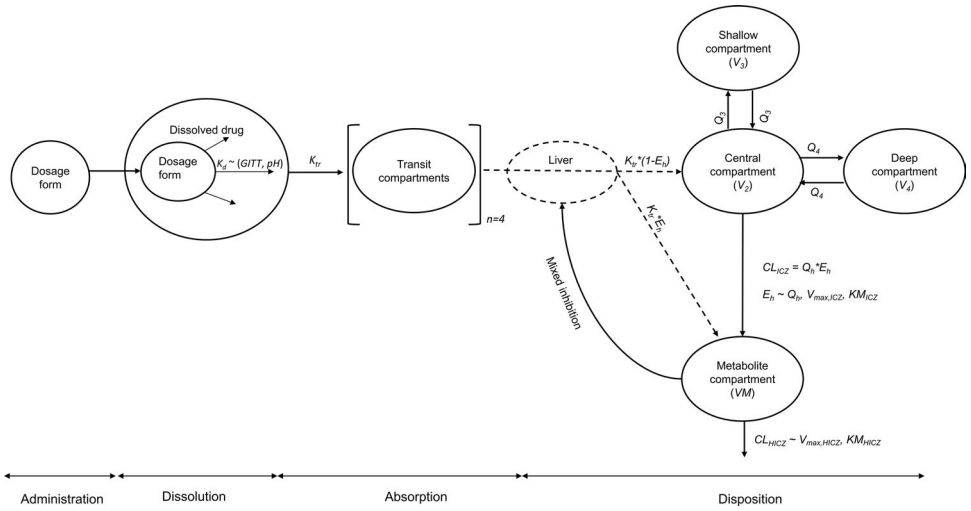

Fig. 1 Structural diagram of the population in vitro–in vivo pharmacokinetic model. K_{tr} transit compartment rate constant, *CL/F* apparent central clearance, *V2/F*, *V3/F* apparent central and peripheral volume of distribution, respectively, Q_2/V_2, Q_3/V_3 apparent compartmental clearances, *GITT* gastrointestinal transit time, k_d dissolution rate constant, E_h hepatic extraction ratio, Q_h liver plasma flow, V_{max} maximum rate of metabolism; *KM* concentration at half V_{max}. The figure was reprinted by permission from Springer Customer Service Centre GmbH: Springer Nature, Journal of Pharmacokinetics and Pharmacodynamics, Population in vitro–in vivo pharmacokinetic model of first-pass metabolism: itraconazole and hydroxy-itraconazole, Abuhelwa AY, Mudge S, Upton RN, Foster DJR, 2018

also integrated into the model to capture omeprazole gastric pH changes on itraconazole dissolution and absorption. Gastric pH for subjects receiving omeprazole was extracted from a study by Gan et al. [22]. In this study, omeprazole 40 mg was administered daily to eight healthy subjects for 8 days. The reported 24-h median gastric pH of day 7 was 4.93 (inter-quartile range (IQR) 3.84–5.59) compared to placebo (1.68, IQR 1.49–1.96). The mean and standard deviation of gastric pH were therefore estimated from the reported median and IQR using the method described by Wan et al. [23]. The estimated distribution of gastric pH in healthy subjects receiving omeprazole implemented in the model was 4.79 ± 1.56 (mean ± SD).

2.3.3 Model Evaluation

Visual predictive checks (VPCs) of the final updated model [24] were performed to evaluate the predictive performance and adequacy of the model for describing itraconazole and hydroxyitraconazole concentrations. The final model was used to simulate 200 versions of the original dataset based on the final estimated parameter values. The observed concentrations and the median and 90% confidence interval of the observed and simulated concentrations were plotted.

2.3.4 Simulations

Simulations, using the final updated model and final parameter values, were used to investigate the effects of concomitant omeprazole administration on the predicted itraconazole and hydroxyitraconazole exposure from SUBA-itraconazole and Sporanox. Simulations for 1000 subjects receiving single-dose SUBA-itraconazole 2×65 mg or Sporanox 2×100 mg with or without omeprazole in the fasted state were performed. Simulations assumed a typical individual weight of 70 kg. Pharmacokinetic evaluations were performed at 0.2-h intervals for up to 24 h. Itraconazole and hydroxyitraconazole exposures were assessed by area under the concentration–time curve (AUC_{0-24}), maximum concentration (C_{max}) and the time at C_{max} (T_{max}). The AUC_{0-24} was calculated using linear trapezoidal integration of model-predicted concentrations. C_{max} and T_{max} were collated directly from the simulated data. Calculations were performed in R.

3 Results

3.1 IVIV Pharmacokinetic Model

The previously published IVIV pharmacokinetic model had the following covariate effects in its final model—a scale factor on the central volume of distribution for the oral data, allometric scaling of plasma blood flow ($Q_{h,plasma}$), a covariate effect parameter of multi-dose studies on the logit-transform fraction absorbed parameter ($LGTF_{abs}$), an effect of fed status on $LGTF_{abs}$ and absorption rate constant (K_{tr}), and an effect of formulation on $LGTF_{abs}$. These covariates remained significant in the final updated model including all the available datasets. The NONMEM run record of screened covariates in the updated model is provided in Table 3.

Table 3 Run records of the updated pharmacokinetic model of the combined intravenous and oral pharmacokinetic data

Run number	Model description	OFV	Delta OFV	Minimization
1	Base model[a]	− 32492.3	0	Yes
2	Base model-removing fed status covariate parameter on $LGTF_{abs}$	− 32407.1	85.2	Yes
3	Base model-removing fed status covariate parameter on absorption rate	− 31767.5	724.8	No
5	Base model-removing formulation covariate parameter on $LGTF_{abs}$	− 32182.2	310.1	Yes
4	Base model-removing multi-dose covariate parameter on $LGTF_{abs}$	− 30607.5	1884.9	No
6	Base model-removing scale factor on central volume of distribution of itraconazole	− 32378	114.4	Yes
7	Base model-adding omeprazole effect on V_{max} of itraconazole and hydroxyitraconazole	− 32501.4	−9	Yes
8	Base model-adding omeprazole effect on V_{max} of itraconazole and hydroxyitraconazole and $LGTF_{abs}$	− 32528.5	−36.2	Yes

The (+) or (−) sign in the delta OFV column indicate an increase or a drop in the objective function value (OFV), respectively, compared to the base model

$LGTF_{abs}$ is the logit-transformed parameter of fraction absorbed, $V_{max,itraconazole,hydroxyitraconazole}$ is the maximum rate of itraconazole and hydroxyitraconazole metabolism

[a]Base model is the first pass metabolism model including covariate effects as per the published model analysis [5]

Additional covariates were also screened. In particular, the covariate effect of co-administrating omeprazole with the SUBA-itraconazole on the in vivo exposure of itraconazole and hydroxyitraconazole. Despite including the omeprazole gastric pH effects on itraconazole dissolution in the IVIV model, boxplots of ETA versus omeprazole co-administration suggested that omeprazole potentially decreased the metabolism of itraconazole and hydroxyitraconazole and increased the fraction absorbed of itraconazole (Figure S1 in the supplementary material). The covariate effect of omeprazole on the metabolism of itraconazole and hydroxyitraconazole and the fraction of itraconazole absorbed were significant and therefore retained in the final model.

The final pharmacokinetic model parameters for all fixed and random effects are presented in Table 4. Standard goodness-of-fit plots of oral itraconazole and hydroxyitraconazole concentrations across single and multi-dose studies are presented in Figures S2 and S3 of the supplementary material. As shown in Table 4, all fixed and random effects parameters were estimated precisely with acceptable standard errors. The diagnostic plots for itraconazole and hydroxyitraconazole were in general compatible with an unbiased model (Figures S2 and S3) and the data were symmetrically distributed and tightly clustered around the identity lines for both itraconazole and hydroxyitraconazole, indicating that data were adequately described by the population model.

The NONMEM code of the final updated IVIV pharmacokinetic model is provided in the supplementary material.

3.2 Model Evaluation

The VPC plots for the final model showed the model to have acceptable predictive performance for single- and multi-dose studies (Figure S4 in the supplementary material). Additionally, the model showed an adequate predictive performance for SUBA-itraconazole administered with or without omeprazole as presented in Fig. 2. Overall, there was an acceptable agreement between the time course of the median and 5th and 95th percentiles of model predictions and observed data for itraconazole and hydroxyitraconazole.

3.3 Captured Omeprazole Effects in the Final Model

Omeprazole increased the typical fraction of drug absorbed for SUBA-itraconazole by ~ 20% and had a significant effect in reducing the V_{max} of itraconazole and hydroxyitraconazole by 12%. A summary of the typical fraction of drug absorbed for Sporanox and SUBA-itraconazole is presented in Table 5. A tabulated summary of estimated absolute bioavailability for Sporanox and SUBA-itraconazole as a function of total daily dose, fed status and omeprazole use is presented in Table 6. Boxplots of the estimated post hoc hepatic extraction ratio (E_h) and absolute bioavailability as a function of the total daily dose of Sporanox and SUBA-itraconazole are presented in Figs. 3 and 4, respectively.

The typical fraction of drug absorbed (median, 95% confidence interval) for SUBA-itraconazole 130 mg with and without co-administration of omeprazole was (0.89, 0.67–0.97) versus (0.74, 0.41–0.92), respectively. The corresponding estimated absolute bioavailability of SUBA-itraconazole with and without co-administration of omeprazole was (0.56, 0.39–0.72) and (0.48, 0.23–0.69), respectively.

As shown in Fig. 3 and Fig. 4, the absolute bioavailability of itraconazole is dependent on the total daily dose where the E_h decreases with increased daily dose (i.e., concentration) because of the non-linear mixed inhibition metabolism of itraconazole. However, it

Table 4 Parameter values for the final in vitro-in vivo pharmacokinetic model

Code	Unit	Pop value[a]	% RSE	BSV (SD)	% RSE	ETA P value	Shrinkage (%)
$V_{max,itraconazole}$	ng/h	342,000	4.1	0.278	3.7	0.848	12
$K_{m,itraconazole}$	ng/ml	6050	4.8	–	–	–	–
V_2	L	34.1	4.9	0.354	9.5	0.046	26.3
Q_3	L/h	5.43	9.6	–	–	–	–
V_3	L	196.1	15.4	–	–	–	–
Q_4	L/h	36.9	3.5	–	–	–	–
V_4	L	196.1	–	–	–	–	–
$V_{max,hydroxyitraconazole}$	ng/h	7570	1.8	0.291	3.7	0.649	12.3
$K_{m,hydroxyitraconazole}$	ng/ml	252	3.1	–	–	–	–
VM	L	127	2.9	–	–	–	–
KI	ng/ml	320	2.6	–	–	–	–
K_{tr}	1/h	2.84	0.3	0.499	2.4	0.989	2.3
SCLV2	Ratio	4.16	7.3	–	–	–	–
$LGTF_{abs}$	–	−0.164	46.6	0.863	3.5	0.176	17.2
$FORMF_{abs}$	Ratio	1.22	5.8	–	–	–	–
$FEDK_{tr}$	Ratio	−0.559	2.7	–	–	–	–
$FEDF_{abs}$	Ratio	−0.598	11.4	–	–	–	–
$MULTIF_{abs}$–*SPO*	Ratio	1.50	0.20	–	–	–	–
$MULTIF_{abs}$–*SUBA*	Ratio	16	9.4	–	–	–	–
$PPICOVV_{max}$	Ratio	−0.117	27.2	–	–	–	–
$PPICOVF_{abs}$	Ratio	1.06	17.50	–	–	–	–
$STUDY705COVV_{max}$	Ratio	−0.235	12.6	–	–	–	–
K_{d2}-*Sporanox*	1/h	1.24	3.3	–	–	–	–
K_{d2}-*SUBA-itraconazole*	1/h	0.0104	11.6	–	–	–	–
RUVCVIVP	Ratio	0.37	5.7	–	–	–	–
RUVCVIVM	Ratio	0.134	9.4	–	–	–	–
RUVCVSORALP	Ratio	0.463	2.4	–	–	–	–
RUVCVSORALM	Ratio	0.451	2.1	–	–	–	–
RUVCVMORALP	Ratio	0.129	4.7	–	–	–	–
RUVCVMORALM	Ratio	0.0712	5.8	–	–	–	–
RUVADDMORALP	ng/ml	14.7	38	–	–	–	–
RUVADDMORALM	ng/ml	27	12.2	–	–	–	–

BSV between subject variability, *SD* standard deviation, *%RSE* percent of relative standard error, $V_{max,itraconazole}$ maximum rate of itraconazole metabolism, $K_{m,itraconazole}$ concentration at half $V_{max,itraconazole}$, V_2 central volume of distribution-itraconazole, Q_3 inter-compartmental clearance (1)- itraconazole, V_3 peripheral volume of distribution (1)- itraconazole, Q_4 inter-compartmental clearance (2)- itraconazole, V_4 peripheral volume of distribution (2)- itraconazole, $V_{max,hydroxyitraconazole}$ maximum rate of hydroxyitraconazole metabolism, $K_{m,hydroxyitraconazole}$ concentration at half $V_{max,hydroxyitraconazole}$, V_M apparent central volume of distribution-hydroxyitraconazole, *KI* inhibition constant, K_{tr} transit absorption rate constant, $SCLV_2$ scale factor on central volume of distribution of itraconazole, $LGTF_{abs}$ logit-transformed parameter of fraction absorbed, $FORMF_{abs}$ effect of formulation on fraction absorbed, $FEDK_{tr}$ effect of fed status on K_{tr}, $FEDF_{abs}$ effect of fed status on $LGTF_{abs}$, $MULTIF_{abs}$-*SPO* effect of multi-dose Sporanox administration on fraction absorbed, $MULTIF_{abs}$-*SUBA* effect of multi-dose SUBA-itraconazole administration on fraction absorbed, $PPICOVV_{max}$ effect of omeprazole on $V_{max,itraconazole}$ and $V_{max,hydroxyitraconazole}$, $PPICOVF_{abs}$ effect of omeprazole on F_{abs}, $STUDY705COVV_{max}$ study 10850705 effect on $V_{max,itraconazole}$ and $V_{max,hydroxyitraconazole}$, K_{d2}-*Sporanox* pH-independent pathway dissolution parameter for Sporanox, K_{d2}-*SUBA-itraconazole* pH-independent pathway dissolution parameter for SUBA-itraconazole, *RUVCVIVP* proportional residual error-intravenous itraconazole, *RUVCVIVM* proportional residual error-intravenous hydroxyitraconazole, *RUVCVSORALP* proportional residual error-oral single-dose studies-itraconazole, *RUVCVSORALM* proportional residual error of oral single studies-hydroxyitraconazole, *RUVCVMORALP* proportional residual error of oral multi-dose studies-itraconazole, *RUVCVMORALM* proportional residual error of oral multi-dose studies-hydroxyitraconazole, *RUVADDMORALP* additive residual error of oral multi-dose studies-itraconazole, *RUVADDMORALM* additive residual error of oral multi-dose studies-hydroxyitraconazole

[a]Population typical value

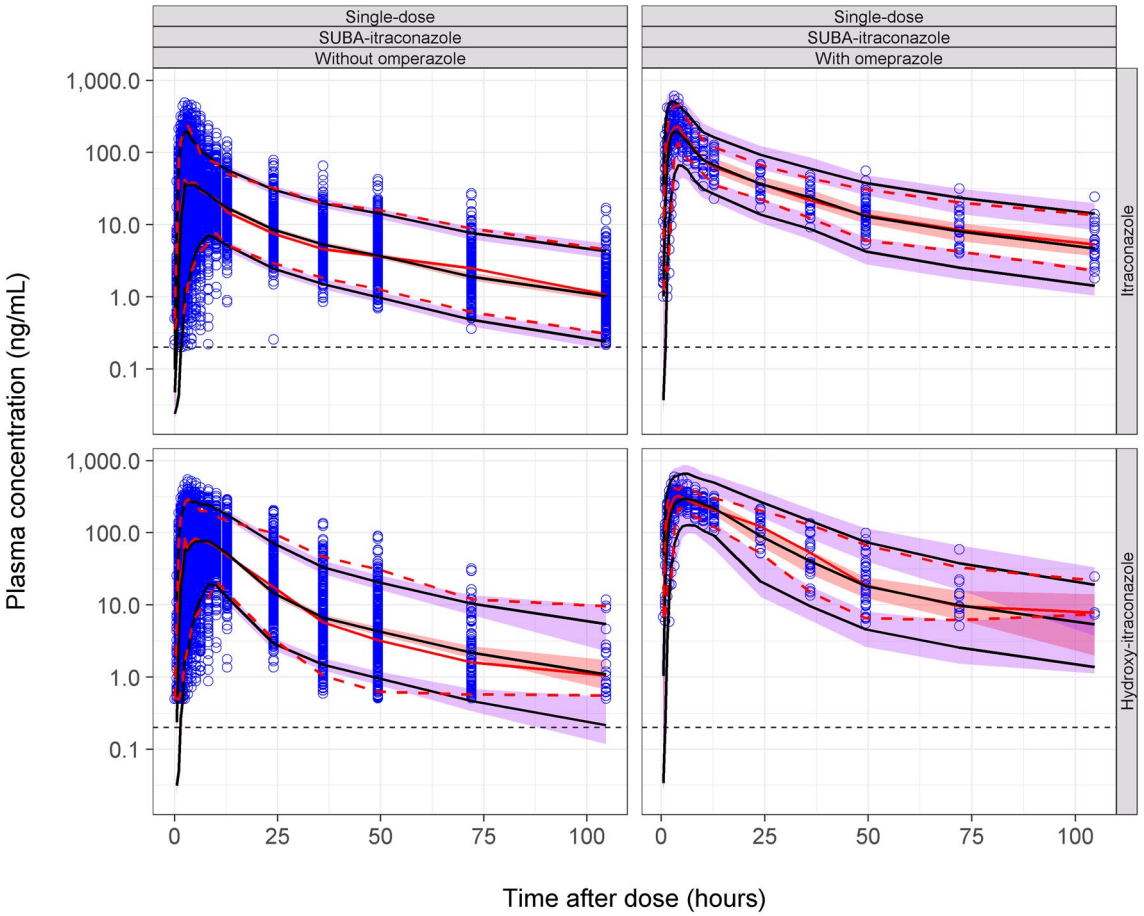

Fig. 2 Final in vitro–in vivo pharmacokinetic model-visual predictive checks of SUBA-itraconazole administered with or without omeprazole. Open circles represent observed itraconazole or hydroxyitraconazole concentrations. The solid black lines represent the 5th, 50th, and 95th percentiles of the simulated concentrations. The shaded areas represent the 90% confidence interval of the 5th, 50th, and 95th percentiles of the simulated concentrations. The solid red line represents the median of the observed concentrations

Table 5 Typical estimated fraction of itraconazole absorbed from Sporanox and SUBA-itraconazole

Formulation	Study	Status	Omeprazole	Typical fraction of drug absorbed
Sporanox	Single-dose	Fasted	No	0.46 (0.46, 0.17–0.78)
Sporanox	Single-dose	Fed	No	0.34 (0.32, 0.1–0.66)
SUBA-itraconazole	Single-dose	Fasted	No	0.71 (0.74, 0.41–0.92)
SUBA-itraconazole	Single-dose	Fasted	Yes	0.87 (0.89, 0.67–0.97)
SUBA-itraconazole	Single-dose	Fed	No	0.6 (0.61, 0.28–0.87)
Sporanox	Multi-dose	Fed	No	0.65 (0.68, 0.33–0.9)
SUBA-itraconazole	Multi-dose	Fasted	No	1 (1, 1–1)
SUBA-itraconazole	Multi-dose	Fed	No	1 (1, 1–1)

Values calculated as mean (median, 90% confidence interval)

is noticeable from Fig. 4 that the absolute bioavailability for the 600 mg daily dose of Sporanox and the 390 mg daily dose of SUBA-itraconazole (MPG013 study) are lower than the 400 mg daily dose of Sporanox (MPG015 and 10850706 studies) and the 260 mg daily dose of SUBA-itraconazole (MPG015 study). This is because the hepatic metabolism of itraconazole is concentration dependent; the MPG013 study was performed for 3 days only while subjects in MPG015 and 10850706 studies received itraconazole dosing for 15 days. Therefore, more of the drug accumulated in MPG015 and 10850706 subjects (i.e., higher

Table 6 Estimated absolute bioavailability of Sporanox and SUBA-itraconazole

Formulation	Study	Status	Omeprazole	Daily dose	Estimated absolute bioavailability	Overall estimated absolute bioavailability[a]
Sporanox	Multi-dose	Fed	No	200 mg daily	0.45 (0.43, 0.31–0.58)	0.5 (0.51, 0.32–0.66)
	Multi-dose	Fed	No	400 mg daily	0.57 (0.57, 0.43–0.67)	
	Multi-dose	Fed	No	600 mg daily	0.52 (0.5, 0.38–0.67)	
	Single-dose	Fasted	No	100 mg daily	0.23 (0.22, 0.08–0.42)	0.22 (0.2, 0.08–0.41)
	Single-dose	Fasted	No	200 mg daily	0.25 (0.22, 0.07–0.5)	
	Single-dose	Fed	No	100 mg daily	0.2 (0.18, 0.08–0.39)	
SUBA-itraconazole	Multi-dose	Fasted	No	260 mg daily	0.91 (0.91, 0.86–0.97)	0.85 (0.87, 0.69–0.94)
	Multi-dose	Fed	No	100 mg daily	0.77 (0.78, 0.62–0.86)	
	Multi-dose	Fed	No	130 mg daily	0.79 (0.8, 0.65–0.87)	
	Multi-dose	Fed	No	200 mg daily	0.87 (0.87, 0.81–0.92)	
	Multi-dose	Fed	No	260 mg daily	0.9 (0.9, 0.82–0.95)	
	Multi-dose	Fed	No	390 mg daily	0.85 (0.87, 0.7–0.92)	
	Single-dose	Fasted	No	100 mg daily	0.43 (0.46, 0.22–0.6)	0.36 (0.35, 0.15–0.61)
	Single-dose	Fasted	No	130 mg daily	0.48 (0.48, 0.23–0.69)	
	Single-dose	Fasted	No	50 mg daily	0.38 (0.37, 0.18–0.58)	
	Single-dose	Fasted	No	65 mg daily	0.37 (0.36, 0.17–0.56)	
	Single-dose	Fasted	Yes	130 mg daily	0.56 (0.56, 0.39–0.72)	
	Single-dose	Fed	No	50 mg daily	0.33 (0.31, 0.15–0.56)	
	Single-dose	Fed	No	65 mg daily	0.26 (0.26, 0.13–0.43)	

Values calculated as mean (median, 90% confidence interval)

[a]Regardless of fed status and daily dose

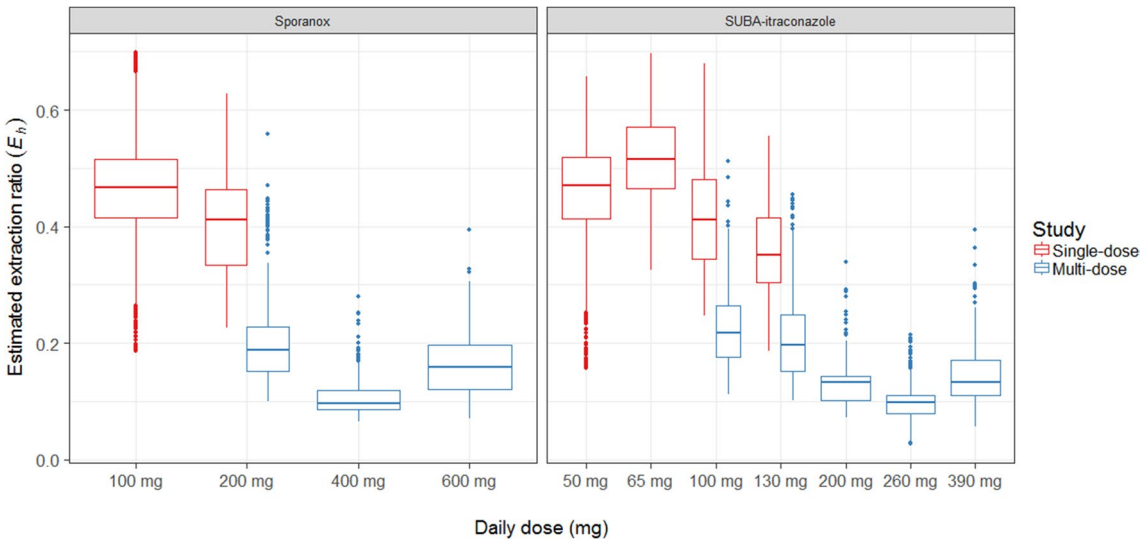

Fig. 3 Estimated post hoc hepatic extraction ratio (E_h) for Sporanox and SUBA-itraconazole as a function of total daily dose after single- and multi-dose administration. The bottom and top of each box represent the 25th and 75th percentiles and the line in the middle is the median. The whiskers represent ≤ 1.5 times the interquartile range. The dotted points represent outliers outside the whiskers

concentrations, lower E_h) compared to MPG013 subjects (i.e., lower concentrations, higher E_h), which resulted in lower absolute bioavailability as absolute bioavailability $= F_{\text{abs}} \times (1 - E_h)$.

3.4 Simulations: Omeprazole Effects

The population effect of omeprazole on the model-predicted itraconazole and hydroxyitraconazole

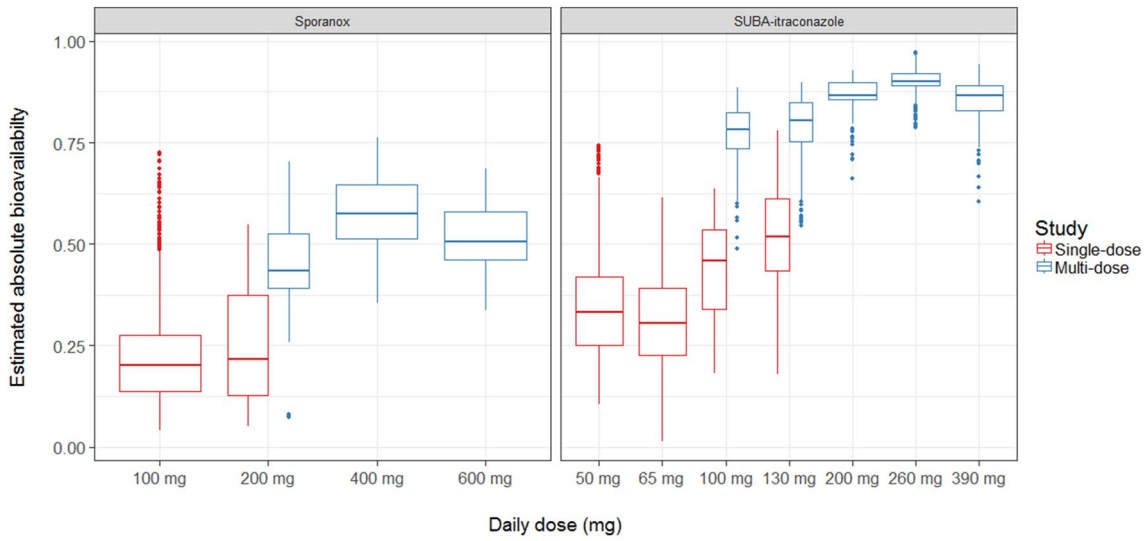

Fig. 4 Estimated post hoc absolute bioavailability of Sporanox and SUBA-itraconazole as a function of total daily dose after single- and multi-dose administration. The bottom and top of each box represent the 25th and 75th percentiles and the line in the middle is the median. The whiskers represent ≤ 1.5 times the interquartile range. The dotted points represent outliers outside the whiskers

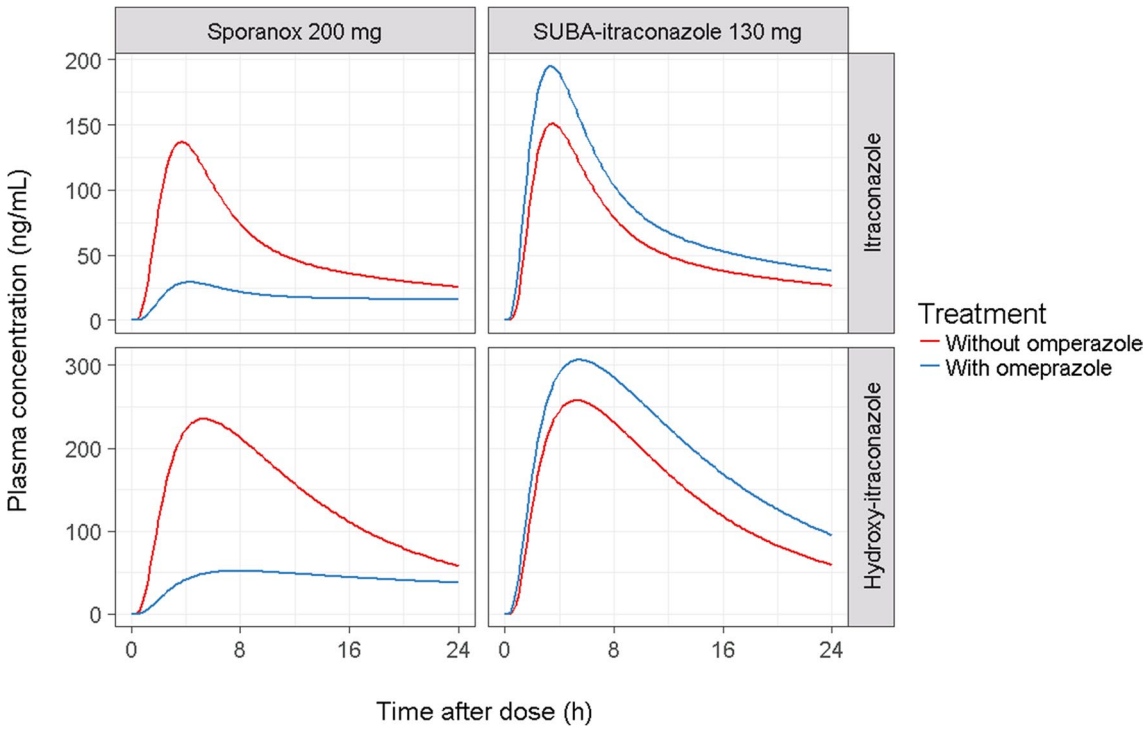

Fig. 5 Population effect of omeprazole on Sporanox and SUBA-itraconazole mean concentration pharmacokinetic profiles of itraconazole and hydroxyitraconazole. Model-predicted concentration profile after single-dose 130 mg SUBA-itraconazole and 200 mg Sporanox based on 1000 simulated subjects per dose

concentrations from Sporanox and SUBA-itraconazole formulations is shown in Fig. 5, while the effect on model-predicted NCA metrics is shown in Fig. 6 and tabulated in Table 7. The population effect of omeprazole co-administration with SUBA-itraconazole was to increase the itraconazole mean AUC_{0-24} to 135% and to increase C_{max} to 131% of that of SUBA-itraconazole without omeprazole co-administration.

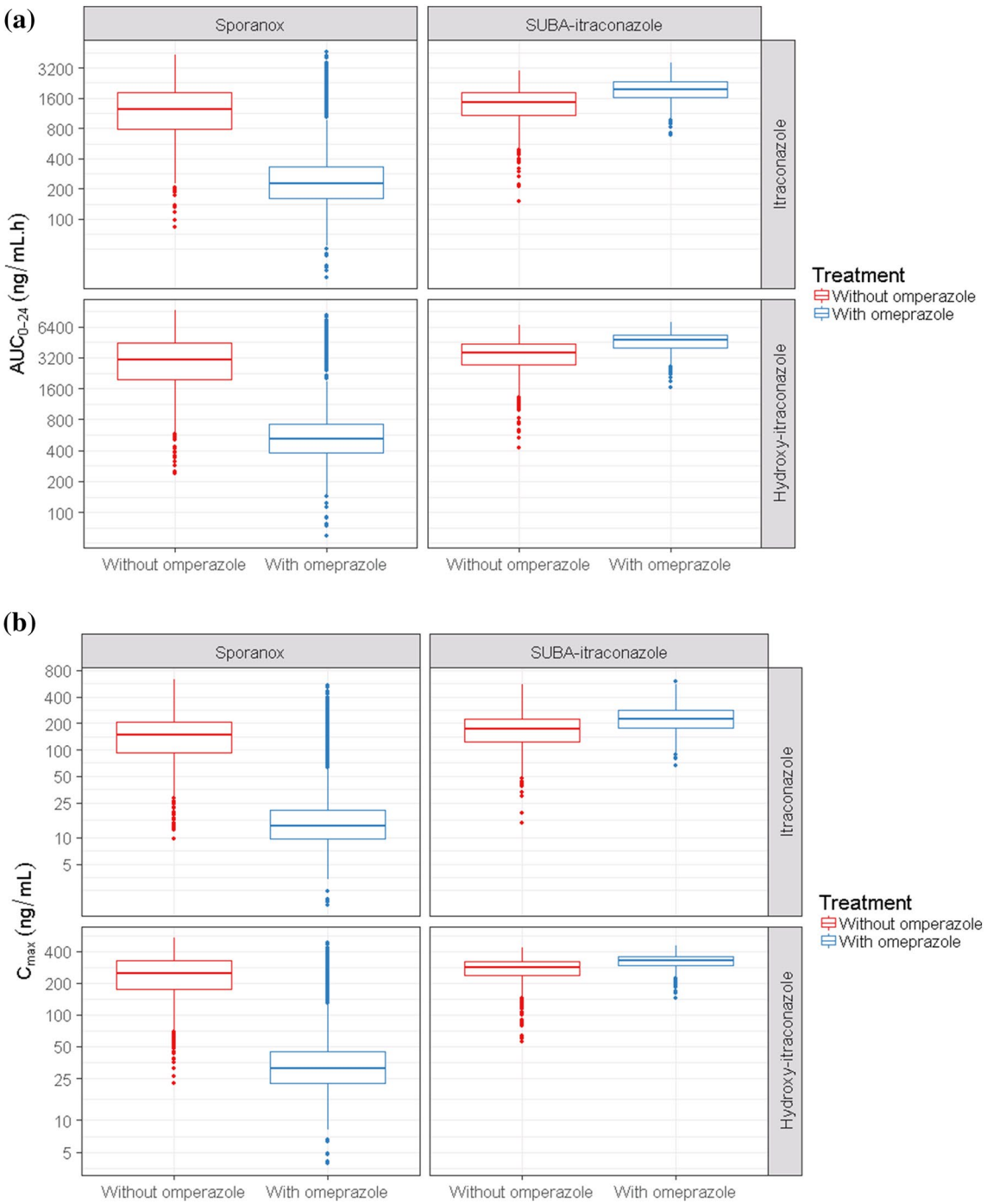

Fig. 6 Model-predicted omeprazole effect on itraconazole and hydroxyitraconazole NCA metrics. Model-predicted itraconazole and hydroxyitraconazole, AUC_{0-24} (upper) and C_{max} (lower) after single-dose 130 mg SUBA-itraconazole and 200 mg Sporanox based on 1000 simulated subjects per dose. The bottom and top of each box represent the 25th and 75th percentiles and the line in the middle is the median. The whiskers represent ≤ 1.5 times the interquartile range. The dotted points represent outliers outside the whiskers

The predicted itraconazole T_{max} (mean, 95% CI) upon omeprazole co-administration with SUBA-itraconazole was (3.6, 1.6–6.2 h) which was not significantly different to that of SUBA-itraconazole treatment only (3.7, 1.8–6.4 h). A similar pattern of corresponding effects was observed on the hydroxyitraconazole exposure metrics.

Opposite effects were observed for predicted Sporanox exposure metrics. The net effect of omeprazole was to decrease the mean AUC_{0-24} of itraconazole to 32.3% and to

Table 7 Predicted omeprazole effects on the exposure of itraconazole and hydroxyitraconazole for single-dose 130 mg SUBA-itraconazole and 200 mg Sporanox

Metric	Unit	Analyte	Study	Formulation	Dose	Omeprazole	median	gmean	mean	% CV	95% CI
AUC_{0-24}	ng/ml·h	Itraconazole	Single-dose	Sporanox	200 mg	No	1250	1142.5	1353	53.7	(347.9–2653.6)
				Sporanox	200 mg	Yes	226.5	268.2	436.5	146.6	(94.8–1957.2)
						% change (yes/no)	−81.9	−76.5	−67.7	–	
				SUBA-itraconazole	130 mg	No	1454.3	1355.6	1461.4	35.6	(622.5–2362)
				SUBA-itraconazole	130 mg	Yes	1967.4	1911.3	1976.1	25.1	(1182.2–2848.6)
						% change (yes/no)	35.3	41.0	35.2	–	
C_{max}	ng/ml			Sporanox	200 mg	No	146.4	132.2	157.3	55.4	(42.3–304.5)
				Sporanox	200 mg	Yes	13.7	17.7	38	189.5	(5.7–215.4)
						% change (yes/no)	−90.6	−86.6	−75.8	–	
				SUBA-itraconazole	130 mg	No	171.5	163.1	179.8	42.3	(70.4–318.8)
				SUBA-itraconazole	130 mg	Yes	221.9	222.6	235.8	34.3	(127.6–385.4)
						% change (yes/no)	29.4	36.5	31.1	–	
T_{max}	*h*			Sporanox	200 mg	No	3.6	3.7	3.9	34.1	(2.4–6.4)
				Sporanox	200 mg	Yes	24	15	18.6	46.9	(3.4–24)
						% change (yes/no)	566.7	305.4	376.9	–	
				SUBA-itraconazole	130 mg	No	3.4	3.5	3.7	37.7	(1.8–6.4)
				SUBA-itraconazole	130 mg	Yes	3.4	3.3	3.6	42.3	(1.6–6.2)
						% change (yes/No)	0.0	−5.7	-2.7	–	
AUC_{0-24}	ng/ml·h	Hydroxy-itraconazole		Sporanox	200 mg	No	3089.4	2774.2	3265.1	51.5	(796.8–6226)
				Sporanox	200 mg	Yes	514.4	613.8	985	143.2	(236.6–4543.4)
						% change (yes/no)	−83.3	−77.9	−69.8	–	
				SUBA-itraconazole	130 mg	No	3602.6	3302.4	3526.6	32.5	(1532.1–5368.6)
				SUBA-itraconazole	130 mg	Yes	4731.5	4538.5	4640.9	20.1	(2952.7–6065)
						% change (yes/no)	31.3	37.4	31.6	–	
C_{max}	ng/ml			Sporanox	200 mg	No	249.4	225.2	250.9	41.3	(82.6–427.8)
				Sporanox	200 mg	Yes	31.3	38	63.2	143.7	(14.2–300.1)
						% change (yes/no)	−87.4	−83.1	−74.8	–	
				SUBA-itraconazole	130 mg	No	281.9	263.7	274	24.8	(143.2–371.3)
				SUBA-itraconazole	130 mg	Yes	327	319.9	323.7	14.8	(239.4–395)
						% change (yes/no)	16.0	21.3	18.1	–	
T_{max}	*h*			Sporanox	200 mg	No	4.8	4.9	5.1	32	(3–8)
				Sporanox	200 mg	Yes	24	16.3	19	41.8	(4.4–24)
						% change (yes/no)	400.0	232.7	272.5	–	
				SUBA-itraconazole	130 mg	No	4.8	4.8	5.1	32.7	(2.8–8.2)
				SUBA-itraconazole	130 mg	Yes	5	4.9	5.2	35.1	(2.8–8.4)
						% change (yes/no)	4.2	2.1	2.0	–	

CV coefficient of variation, *CI* confidence interval, *gmean* geometric mean, AUC_{0-24} the area under the concentration–time curve from time zero to 24 h, C_{max} the maximum concentration, T_{max} the time at C_{max}

decrease C_{max} to 24% of that without omeprazole treatment. A similar pattern of corresponding effects was observed on the hydroxyitraconazole exposure metrics. The predicted itraconazole T_{max} (mean, 95% CI) upon omeprazole co-administration with Sporanox was longer and highly variable due to the high variability in the reported gastric pH value upon omeprazole co-administration (18.6, 3.4–24 h) compared to healthy subjects receiving Sporanox treatment only (3.9, 2.4–6.4 h). However, as detailed in the discussion section, Sporanox has minimal dissolution at pH > 4 [3] which makes dissolution rate, and hence the absorption rate, to be much slower than the elimination rate and, therefore, simulated subjects with gastric pH > 4 would show a flip-flop kinetic behavior of itraconazole where the terminal phase of pharmacokinetic profile represents the absorption rather than elimination. The latter behavior resulted in long simulated T_{max} values for subjects where the absorption is slower than the elimination (left-skewed T_{max} distribution). However, as appears in Fig. 5, the T_{max} of the mean simulated itraconazole and hydroxyitraconazole concentrations with and without omeprazole co-administration treatments, respectively, were ~ 4.6 h and 3.90 h for itraconazole and 6.74 h and 5.10 h for hydroxyitraconazole.

4 Discussion

Here, we have presented an updated version of the previously published IVIV pharmacokinetic model [5] for SUBA-itraconazole and Sporanox capsules. The updated model included additional pharmacokinetic data from 5 clinical studies and, importantly, a drug–drug interaction study of steady-state omeprazole administration with SUBA-itraconazole. The present analysis focused particularly on mechanistic investigation and quantitative prediction of the effects of omeprazole on the in vivo pharmacokinetics of SUBA-itraconazole and Sporanox.

The same structural model of the previously published model was used here with all model parameters re-estimated after including the full available datasets from all studies. The final updated model described the first-pass metabolism, absolute bioavailability, GI pH, GI transit times and omeprazole effects, and the relative roles of first-pass metabolism and absorption and food effects on itraconazole and hydroxyitraconazole from SUBA-itraconazole and Sporanox. The estimated itraconazole and hydroxyitraconazole disposition parameters in the updated model were not significantly different to the published model except for $V_{amx,itraconazole}$ and $K_{m,itraconazole}$. However, the latter two parameters are highly correlated and the $K_{m,itraconazole}/V_{max,itraconazole}$ ratio was similar between the updated and previously published model. Food effects on itraconazole and hydroxyitraconazole pharmacokinetics, captured in the final updated model, were similar to those of the previously published model and will be discussed here.

The final model has identified mechanistic mechanisms of the drug–drug interactions of omeprazole with itraconazole and hydroxyitraconazole which were found to be significant in the final model. Generally, pharmacokinetic drug–drug interaction mechanisms of omeprazole may involve alternation of hepatic drug metabolism and/or alternation of drug absorption mediated via elevation of gastric pH and/or interaction of omeprazole with the ATP-dependent efflux transporters [12]. The final model indicated that omeprazole increased the exposure of itraconazole and hydroxyitraconazole from SUBA-itraconazole through two main mechanisms—(1) a drug–drug interaction at the level of hepatic metabolizing enzymes, and (2) increasing the fraction of itraconazole absorbed from the GI tract, while the impact of pH-mediated on dissolution and absorption was minimal.

Omeprazole is extensively metabolized by the liver, mainly via CYP2C19 and CYP3A4 [10], and itraconazole by CYP3A4 enzymes which can lead to competitive inhibition of itraconazole metabolism. The mixed inhibition clearance model of itraconazole assumes that hydroxyitraconazole undergoes further metabolism by the same metabolizing enzymes of itraconazole [5]; therefore, a similar effect on hydroxyitraconazole metabolism was also captured in the final model. The CYP3A4-mediated omeprazole competitive inhibition has been reported in various literature studies [25–27]. Multi-dose administration of omeprazole for 2 weeks (20 mg once daily) significantly increased the $AUC_{0–inf}$ of carbamazepine to 175% and decreased the clearance to 60% in patients with a duodenal ulcer [25]. The increase in carbamazepine exposure was thought to be attributed to the inhibition of CYP3A4-mediated carbamazepine oxidative metabolism by omeprazole. Similarly, clinically significant drug interactions have been associated with co-administration of omeprazole and tacrolimus which were mainly attributed to the shared CYP3A4 metabolism pathways for these drugs, especially in patients who are CYP2C19 poor metabolizers [27].

Alternation of the amount of drug absorbed upon concomitant administration of omeprazole might be related to omeprazole pH-mediated effects on drug release or alternation of active transport processes, particularly the P-gp transporters. Omeprazole increases mean gastric pH (mean ± SD) from 1.88 ± 0.46 in healthy subjects not receiving omeprazole [6] to 4.79 ± 1.56 [22] in healthy subjects receiving 40 mg omeprazole, and this impact was incorporated into the IVIV model. However, the SUBA-itraconazole formulation is designed to dissolve at high pH (pH ~ 6) and, therefore, is dependent on intestinal rather than gastric pH [3]. Thus, an increase in gastric pH to 4.79 was unlikely to influence the amount of itraconazole released from SUBA-itraconazole as the drug is released

at intestinal pH which rules out gastric pH effects on altering drug dissolution and absorption. Hence, the increased amount of drug absorbed was most likely attributed to altered active transport processes for itraconazole. Itraconazole is a substrate for P-gp transporters and omeprazole is a known inhibitor for P-gp function [10]. Therefore, the increased amount of itraconazole absorbed was most likely due to the interaction of omeprazole at the transport level inhibiting P-gp transporters and thus increasing the amount of dissolved drug that is absorbed. Evidence that proton pump inhibitors, including omeprazole, are substrates and inhibitors for P-gp has been reported in various literature reports [10, 28]. P-gp is a major determinant of digoxin absorption from the GI tract and omeprazole has been shown to increase the absorption permeability of digoxin to 2.6-fold across the colonic carcinoma cell line (Caco-2) [28]. Following multi-dose administration of 20 mg omeprazole, the digoxin exposure from a single dose of 1 mg digoxin was elevated by 10% for AUC and C_{max}, and two of 10 subjects included in the study had a 30% increase in exposure [29].

The model-predicted population effects of omeprazole on exposure from SUBA-itraconazole were shown to increase itraconazole AUC_{0-24} and C_{max} by 35 and 31%, respectively. The increased itraconazole exposure from SUBA-itraconazole was consistent with the observed data from the omeprazole interaction study (MPG016) and consistent with the fact that the formulation is designed to release the drug at intestinal pH and, therefore, alteration of gastric pH by omeprazole is unlikely to influence drug release. Thus, the net omeprazole effect would be an increase the exposure of itraconazole and hydroxyitraconazole as a result of the interaction with the p-gp and drug metabolism. On the contrary, the model-predicted population effects of omeprazole on exposure from Sporanox were shown to decrease itraconazole AUC_{0-24} and C_{max} by 68 and 76%, respectively. The Sporanox capsule is highly dependent on low gastric pH for adequate dissolution of the solid encapsulated drug. When co-administered with omeprazole, gastric pH increases to >4 at which itraconazole from Sporanox is nearly insoluble [3]. The significant pH-mediated reduction in dissolution and absorption due to increased gastric pH overrides any increased exposure due to drug–drug interaction at the CYP enzymes or interaction with P-gp transporters, resulting in an overall reduced itraconazole and hydroxyitraconazole exposure. Reduced itraconazole and hydroxyitraconazole exposure from Sporanox upon co-administration with omeprazole is consistent with several literature reports that studied the effect of omeprazole [30] or antacid suspension [31] on the pharmacokinetics of Sporanox capsules [30]. Jaruratanasirikul et al. [30] showed that with concomitant omeprazole treatment (40 mg once daily) for 2 weeks, the mean AUC_{0-24} and C_{max} from 200 mg single-dose Sporal (Janssen Pharmaceuticals, Inc.) were reduced by 64% and 66%, respectively. Along the same line, Lohitnavy et al. [31] showed that the exposure of itraconazole from 200 mg Sporal capsule was reduced by 66% and 70% for mean AUC_{0-24} and C_{max}, respectively. The results obtained from both latter studies are consistent with model predictions presented here (Table 7), indicating the validity of the IVIV model in predicting the effects of omeprazole and gastric pH changes on the in vivo exposure of itraconazole and hydroxyitraconazole.

5 Conclusion

The IVIV pharmacokinetic model reported here is the most complete quantitative description of the clinical pharmacokinetics of itraconazole and hydroxyitraconazole currently available. It provides a good description of an extensive set of literature and clinical study datasets. It provides semi-mechanistic descriptions of the important role of non-linear kinetics for itraconazole and hydroxyitraconazole, and describes and quantitatively predicts the effect of omeprazole, gastric pH and food on the in vivo exposure of itraconazole and hydroxyitraconazole from SUBA-itraconazole and Sporanox formulations.

Acknowledgements AYA is supported at the School of Pharmacy and Medical Sciences at the University of South Australia by a Science and Industry Endowment Fund STEM + Business Fellowship of the Commonwealth Scientific and Industrial Research Organisation. The Australian Centre for Pharmacometrics is an initiative of the Australian Government as part of the National Collaborative Research Infrastructure Strategy.

Compliance with Ethical Standards

Funding All pharmacokinetic studies of Sporanox and SUBA-itraconazole used in the analysis were sponsored by Mayne Pharma International, Salisbury South, South Australia, Australia.

Conflict of Interest SM is an employee at Mayne Pharma. DJRF, RNU and AYA have acted as paid consultants for Mayne Pharma International, Salisbury South, South Australia, Australia.

Ethical Approval All oral pharmacokinetic studies were conducted by Mayne Pharma International, Salisbury South, South Australia, Australia, in accordance with the ICH Guidelines for Good Clinical Practice, the Declaration of Helsinki on the ethical conduct of medical research, and applicable regulatory requirements.

Informed Consent Each subject provided written informed consent before study participation.

References

1. Grant SM, Clissold SP. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in superfecial and systemic mycoses. Drugs. 1989;37(3):310–44.
2. Kim RB. Drugs as P-glycoprotein substrates, inhibitors, and inducers. Drug Metab Rev. 2002;34(1–2):47–54.
3. Abuhelwa AY, Mudge S, Hayes D, Upton RN, Foster DJ. Population in vitro–in vivo correlation model linking gastrointestinal transit time, pH, and pharmacokinetics: itraconazole as a model drug. Pharm Res. 2016;33(7):1782–94.
4. Abuhelwa AY, Foster DJ, Mudge S, Hayes D, Upton RN. Population pharmacokinetic modeling of itraconazole and hydroxyitraconazole for oral SUBA-itraconazole and sporanox capsule formulations in healthy subjects in fed and fasted states. Antimicrob Agents Chemother. 2015;59(9):5681–96.
5. Abuhelwa AY, Mudge S, Upton RN, Foster DJR. Population in vitro–in vivo pharmacokinetic model of first-pass metabolism: itraconazole and hydroxy-itraconazole. J Pharmacokinet Pharmacodyn. 2018;45(2):181–97.
6. Abuhelwa AY, Foster DJ, Upton RN. A quantitative review and meta-models of the variability and factors affecting oral drug absorption-part I: gastrointestinal pH. AAPS J. 2016;18(5):1309–21.
7. Abuhelwa AY, Foster DJ, Upton RN. A quantitative review and meta-models of the variability and factors affecting oral drug absorption-part II: gastrointestinal transit time. AAPS J. 2016;18(5):1322–33.
8. Wilde MI, McTavish D. Omeprazole: an update of its pharmacology and therapeutic use in acid-related disorders. Drugs. 1994;48(1):91–132.
9. Rang H, Dale M, Ritter J, Flower R, Henderson G. Rang and Dale's Pharmacology 6th. London: Elsevier Co; 2007.
10. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol. 2001;364(6):551–7.
11. Li W, Zeng S, Yu L-S, Zhou Q. Pharmacokinetic drug interaction profile of omeprazole with adverse consequences and clinical risk management. Ther Clin Risk Manag. 2013;9:259.
12. Ogawa R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. Clin Pharmacokinet. 2010;49(8):509–33.
13. European Medicines Agency (EMEA). Note for guidance on good clinical practice (CPMP/ICH/135/95). Step 5: consolidated guideline, including post step 4 errata. London: EMEA; 1996.
14. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA. 1997;277(11):925–6.
15. Beal S, Sheiner LB, Boeckmann A, Bauer RJ. NONMEM user's guides, Part V. (1989–2009). Ellicott City: Icon Development Solutions; 2009.
16. Holford, N.: Wings for NONMEM Version 7.30 for NONMEM 7.3. 2015. (2015)
17. Core Team R. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2014.
18. Wickham H. ggplot2: elegant graphics for data analysis. New York: Springer; 2009.
19. Wickham H. plyr—the split-apply-combine strategy for data analysis. J Stat Softw. 2011;40(1):1–29.
20. Wickham H. Scales: scale functions for graphics. 2014. http://CRAN.R-project.org/package=scales
21. Mandema JW, Verotta D, Sheiner LB. Building population pharmacokinetic-pharmacodynamic models. I. models for covariate effects. J Pharmacokinet Biopharm. 1992;20(5):511–28.
22. Gan K, Geus W, Lamers C, Heijerman H. Effect of omeprazole 40 mg once daily on intraduodenal and intragastric pH in H. pylori-negative healthy subjects. Dig Dis Sci. 1997;42(11):2304–9.
23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14(1):135.
24. Ette EI. Stability and performance of a population pharmacokinetic model. J Clin Pharmacol. 1997;37(6):486–95.
25. Naidu M, Shobha J, Dixit V, Kumar A, Kumar TR, Sekhar KR, et al. Effect of multiple dose omeprazole on the pharmacokinetics of carbamazepine. Drug Invest. 1994;7(1):8–12.
26. Christians U, Schmidt G, Bader A, Lampen A, Schottmann R, Linck A, et al. Identification of drugs inhibiting the in vitro metabolism of tacrolimus by human liver microsomes. Br J Clin Pharmacol. 1996;41(3):187–90.
27. Maguire M, Franz T, Hains DS. A clinically significant interaction between tacrolimus and multiple proton pump inhibitors in a kidney transplant recipient. Pediatr Transplant. 2012;16(6):E217–20.
28. Collett A, Tanianis-Hughes J, Carlson GL, Harwood MD, Warhurst G. Comparison of P-glycoprotein-mediated drug–digoxin interactions in Caco-2 with human and rodent intestine: relevance to in vivo prediction. Eur J Pharm Sci. 2005;26(5):386–93.
29. Oosterhuis B, Jonkman J, Andersson T, Zuiderwijk P, Jedema J. Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. Br J Clin Pharmacol. 1991;32(5):569–72.
30. Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. Eur J Clin Pharmacol. 1998;54(2):159–61.
31. Lohitnavy M, Lohitnavy O, Thangkeattiyanon O, Srichai W. Reduced oral itraconazole bioavailability by antacid suspension. J Clin Pharm Ther. 2005;30(3):201–6.