Effect of Ketoconazole on the Pharmacokinetics of the 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor ABT-384 and Its Two Active Metabolites in Healthy Volunteers: Population Analysis of Data from a Drug-Drug Interaction Study

Guohua An, Wei Liu, David A. Katz, Gerard Marek, Walid Awni, and Sandeep Dutta

Department of Pharmaceutics, University of Florida, Orlando, Florida (G.A.); and Department of Clinical Pharmacology and Pharmacometrics (W.L., W.A., S.D.) and Neuroscience Clinical Development (D.A.K., G.M.), Global Pharmaceutical R&D, AbbVie, North Chicago, Illinois

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ABSTRACT

ABT-384 [1-piperazineacetamide, N-[5-(aminocarbonyl) tricyclo[3.3.1.13,7]dec-2-yl]-α,α-dimethyl-4-[5-(trifluoromethyl)-2-pyridinyl]-, stereoisomer] is a potent and selective inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (HSD-1). ABT-384 has been shown to be safe and well tolerated in humans at doses up to 100 mg daily, and to fully inhibit both peripheral and brain HSD-1 at a dose of 2 mg daily. The effect of ketoconazole on the pharmacokinetics of ABT-384 and its two active metabolites, A-1331480 and A-847082, was investigated in healthy volunteers. When 10 mg of ABT-384 was coadministered with ketoconazole, ABT-384 exposures increased 18-fold for area under the plasma concentration-time curve from time 0 to infinity and 3.5-fold for $C_{\text{max}}$. The results suggest that ABT-384 is a sensitive substrate of CYP3A. After ketoconazole coadministration, exposures of A-1331480 and A-847082 were also greatly increased. A population pharmacokinetic model was constructed for ABT-384 and its metabolites using NonMEM. A two-compartment model with three transit absorption compartments best described ABT-384 data. The model predicted a 69.3% decrease in ABT-384 clearance and 91.1% increase in the volume of distribution of ABT-384 in the presence of ketoconazole. A-1331480 was shown to be formation rate–limited and A-847082 was elimination rate–limited. Both metabolites were characterized by a one-compartment model with first-order rate constants of formation and elimination. Overall the model adequately captured the concentration-time profiles of ABT-384, A-1331480, and A-847082 in both ABT-384-alone and ketoconazole-coadministration conditions. Although ABT-384 exposures were greatly increased in the presence of ketoconazole, coadministration of ABT-384 with ketoconazole or other strong/moderate CYP3A inhibitors is not expected to contribute to any major clinical safety issues considering the favorable safety profile of ABT-384.

ABBRVIATIONS: ABT-384, 1-piperazineacetamide, N-[5-(aminocarbonyl) tricyclo[3.3.1.13,7]dec-2-yl]-α,α-dimethyl-4-[5-(trifluoromethyl)-2-pyridinyl]-, stereoisomer; AUC, area under the plasma concentration-time curve from time 0 to infinity; $C_{\text{max}}$, maximum observed plasma concentration; CL, clearance; HSD, 11β-hydroxysteroid dehydrogenase; IV, interindividual variability; IOV, inter-occasion variability; P-gp, P-glycoprotein; RV, residual variability; $T_{\text{max}}$, time to $C_{\text{max}}$.

Introduction

The intracellular level of glucocorticoids is controlled by two isoforms of 11β-hydroxysteroid dehydrogenase (HSD) (Stewart and Krozowski, 1999). HSD-1 catalyzes the interconversion of the inactive forms of glucocorticoids (cortisone, 11-dehydrocorticosterone) to their active forms (cortisol, corticosterone) in several tissues, including liver, adipose, brain, and several other tissues (Tomlinson et al., 2004). Opposing the action of HSD-1, HSD-2 serves a protective function to form glucocorticoids (cortisone, 11-dehydrocorticosterone) to their inactive forms (cortisone, 11-dehydrocorticosterone) in several tissues, including liver, adipose, brain, and several other tissues (Tomlinson et al., 2004).

Chronically elevated glucocorticoid levels have been reported to be associated with type 2 diabetes, obesity, metabolic disease, osteoporosis, glaucoma, major depressive disorder, and Alzheimer disease (Dallman et al., 2004; Tomlinson et al., 2004; Swaab et al., 2005; Green et al., 2006). The potential important role of HSD-1 in these disorders has been increasingly recognized recently (Tomlinson et al., 2004; Wamil and Seckl, 2007). For example, transgenic mice with HSD-1 overexpression selectively in adipose have increased intra-adipose glucocorticoid concentrations and a dramatic phenotype of central obesity, insulin resistance, and hyperglycemia (Masuzaki et al., 2001). Transgenic mice with HSD-1 overexpression selectively in liver demonstrated insulin resistance and hyperlipidemia (Andres et al., 2003). Aged HSD-1 knockout mice resist the usual cognitive impairments seen in aged wild-type mice (Yau et al., 2001). In addition, cognitive improvements with HSD-1 inhibition have been reported in both rodents and humans (Yau et al., 2001; Sandeep et al., 2004).

Considering the important role of HSD-1 in tissue-specific metabolism of glucocorticoids, inhibition of HSD-1 to decrease the intracellular level of cortisol represents an attractive therapeutic target for those disorders that may be caused by glucocorticoid elevation (Tomlinson et al., 2004). Several compounds, including chenodeoxycholic acid, glycyrrhetinic acid, and carbenoxolone, have been found to have inhibitory effect on...
HSD-1. However the clinical applications of these compounds are limited as they are either not potent or nonspecific HSD inhibitors. For example, carbonoxolone exhibits potent HSD-1 inhibition and has been found to increase hepatic insulin sensitivity in humans. However, its nonspecific inhibition on HSD-2 results in cortisol-dependent mineralocorticoid excess with hypertension and hypokalemic alkalosis, thus precluding its further use in the clinic (Andrews et al., 2003). In addition to those compounds that have been available on the market, clinical trials of several HSD-1 inhibitors have been completed and these compounds showed promising therapeutic potential for type 2 diabetes and metabolic syndrome (Rosenstock et al., 2010; Feig et al., 2011).

ABT-384 (1-Piperazineacetamide, N-[5-(aminocarbonyl) tricyclo[3.3.1.1^{3,7}]dec-2-yl]-α,α-dimethyl-4-[5-(trifluoromethyl)-2-pyridinyl]-, stereoisomer) is a potent and selective HSD-1 inhibitor which exhibits time profiles of ABT-384 and its two metabolites.

Ketoconazole modulation was developed to capture the concentration-ABT-384 and its two active metabolites A-1331480 and A-847082 in was to evaluate the effect of ketoconazole on the pharmacokinetics of by co-medications that are CYP3A inhibitors. The aim of this study metabolism accounts for a substantial portion of ABT-384 elimina-

"[3.3.1.13,7]dec-2-yl\]–dimethyl-4-[5-(trifluoromethyl)-2-pyridinyl]-, a peripheral metabolic syndrome (Rosenstock et al., 2010; Feig et al., 2011). showed promising therapeutic potential for type 2 diabetes and compounds that have been available on the market, clinical trials of HSD-1 inhibitors or inducers within 30 days prior to study drug administration were excluded. The study protocol was approved by the ethics committee, and all subjects provided written informed consent to participate. The study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

**Single-Dose Pharmacokinetics of ABT-384 with and without Ketoconazole**

The effect of ketoconazole on the pharmacokinetics of a single dose of ABT-384 was assessed in an open-label, two-period study. ABT-384 was administered orally under fasting condition. Twelve subjects participated in this study.

In period 1, subjects received a single 10-mg dose of ABT-384 on study day 1. Serial blood samples were collected for assay of ABT-384 and its two active metabolites A-847082 and A-1331480 prior to dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 60, 72, and 96 hours after oral dosing on study day 1.

In period 2, subjects received 400 mg ketoconazole once daily for 10 days, from study day –3 through study day 7. On study day 1, subjects also received a single 10-mg dose of ABT-384 at the same time as ketoconazole. Serial blood samples were collected for assay of ABT-384 and its two active metabolites A-847082 and A-1331480 prior to dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hours after oral dosing on study day 1. The doses of ABT-384 between the two periods were separated by 14 days. Subjects were confined for approximately 6 days in period 1 and 12 days in period 2.

Safety of the study was evaluated by clinical monitoring based on assessments of adverse events, physical examinations, laboratory tests, vital signs, and electrocardiograms.

**Analytical Methods**

Plasma concentrations of ABT-384 and its two active metabolites A-1331480 and A-847082 were determined using a validated liquid chromatography method with tandem mass spectrometric detection, as previously described (Liu et al., 2013). The lower limit of quantitation value was approximately 0.2 ng/ml for ABT-384, A-1331480, and A-847082. The analytical method was validated over the concentration range of 0.201–209 ng/ml for ABT-384, and 0.198–201 ng/ml for A-1331480 and A-847082. All calibration curves had r² values > 0.996. The coefficient of variation values were ≤ 8.3% for ABT-384, ≤ 4.4% for A-1331480, and ≤ 11.1% for A-847082; the mean bias values ranged from 3.0 to 10.9% for ABT-384, –4.7 to 0.4% for A-1331480, and 0.0 to 9.7% for A-847082. Samples with concentrations above the upper limit of quantitation for any given run were diluted with blank plasma and re-assyayed. Values that were less than the lower limit of quantitation for a given run were reported as zero. The plasma samples were stored at −20°C or lower. The storage stability was 274 days. All samples were analyzed within the validated storage stability.

**Pharmacokinetic Analysis**

The plasma pharmacokinetic parameters of ABT-384 and its two active metabolites A-1331480 and A-847082 were initially estimated using a standard noncompartmental analysis with WinNonlin Professional software (version 5.2; Pharsight Corporation, Mountain View, CA). The following pharmacokinetic parameters were determined for all three compounds: the maximum observed plasma concentration (Cmax), and time to Cmax (Tmax), the apparent terminal phase elimination rate constant (λ), terminal phase elimination half-life (t1/2), the area under the plasma concentration-time curve (AUC) from time 0 to infinity (AUC0-∞), or last time point (AUCt), and ratio of the investigated drug AUC in the presence of ketoconazole to that in the absence of ketoconazole. For ABT-384, additional parameters including the apparent oral clearance (CL/F) and the apparent volume of distribution (Vd/F) were also estimated.

**Population Pharmacokinetic Modeling**

**Population Model-Building Criteria.** The population pharmacokinetic analysis was conducted using the nonlinear mixed-effects modeling software

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**Materials and Methods**

**Subjects**

Male and female subjects between the ages of 18 and 55 years were eligible for inclusion into the study. All subjects were in good health, as determined by medical history, physical examination, vital signs, electrocardiography, and clinical laboratory measurements. Subjects receiving any known CYP3A inhibitors or inducers within 30 days prior to study drug administration were excluded. The study protocol was approved by the ethics committee, and all subjects provided written informed consent to participate. The study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

![ABT-384](image-url)
The pharmacokinetic data of ABT-384 and its two metabolites A-1331480 and A-847082 were analyzed in a stepwise manner: The population pharmacokinetic model of ABT-384 was defined first; the corresponding final Bayes estimations of ABT-384 pharmacokinetic parameters were then fixed during the development of pharmacokinetic models of A-1331480 and A-847082. The actual sampling times were used in the analysis. The first-order conditional estimation method with the interaction (FOCEI) and a user-defined subroutine (ADVAN6) were used to estimate the typical population parameters, random interindividual variability (IVI), interoccasion variability (IOV), and residual variability between observed and individually predicted plasma ABT-384 concentrations. All IVI and IOV were assumed to be normally distributed (mean 0, variance $\sigma^2$) and described by an exponential model. The residual error model was described by combined additive and exponential random effect model. Model development was guided by the objective function value, graphical goodness-of-fit analysis, the precision of parameter estimation, and the plausibility of the estimated parameters. The likelihood ratio test was used for comparing nested models and a drop of 3.84 or more in the objective function was considered as significant.

**Population Pharmacokinetic Base Structural Model.** Considering the minimal difference in molecular weight between ABT-384 and its two metabolites (within 5% difference), ABT-384, A-1331480, and A-847082 concentration data were not converted to nanomolar unit in the analysis, and the final pharmacokinetic model was constructed using the data expressed in ng/ml. ABT-384 was described by a two-compartment model with first-order elimination from the central compartment. The absorption phase of ABT-384 was described by three transit compartments between dosing and the central compartment. The model of ABT-384 was parameterized in terms of bioavailability ($F_1$), first-order transition absorption rate constant ($K_{TR}$), volume distribution of the central compartment ($V_t$), distribution clearance ($Q$), and clearance (CL).

The active metabolites of ABT-384, both A-1331480 and A-847082, were each described by a one-compartment model with first-order formation and elimination. Initially, different metabolite generation routes were proposed for A-1331480 and A-847082. These two metabolites could be formed not only after ABT-384 enters the body, but also through first-pass metabolism from the central compartment. The absorption phase of ABT-384 was described by three transit compartments between dosing and the central compartment. The model of ABT-384 was parameterized in terms of bioavailability ($F_1$), first-order transition absorption rate constant ($K_{TR}$), volume distribution of the central compartment ($V_t$), distribution clearance ($Q$), and clearance (CL).

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The effect of ketoconazole on the pharmacokinetics of ABT-384, A-1331480, and A-847082 was estimated simultaneously using the following equation as previously reported (Kerbusch et al., 2001):

$$P_{pop} = \theta_{control} \times (1 + \theta_{ketoconazole})$$

where $P_{pop}$ is the population pharmacokinetic parameter, $\theta_{control}$ is the estimation of this parameter when ABT-384 was administered alone, $\theta_{ketoconazole}$ is the change in this parameter when ABT-384 was coadministered with ketoconazole. The observed difference was considered to be significant if the 95% confidence interval of $\theta_{ketoconazole}$ did not include zero.

**Model Evaluation.** To evaluate the final pharmacokinetic model, a visual predictive check was performed by simulating 1000 subjects following a 10-mg dose of ABT-384 using NONMEM. The final model parameters were used when the concentration-time profiles were simulated. The median, 5th, and 95th percentiles of the simulated concentrations were compared graphically to the observed data. The model was considered to be sufficient if most of the observed data fell within the 5th to 95th-percentile interval and was equally distributed around the median.

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**Fig. 2.** Pharmacokinetic model of ABT-384 and its two active metabolites. KTR, first-order transition absorption rate constant; Q, distribution clearance.
Results

Twelve subjects entered the study and received study medications. All subjects completed the study. A summary of subject demographics is presented in Table 1.

Noncompartmental Analysis

The mean ABT-384 plasma concentration-time profiles following a 10-mg single oral dose of ABT-384 with and without ketoconazole in healthy adults are shown in Fig. 3. The individual changes in ABT-384 exposures (AUC and C_{max}) caused by ketoconazole modulation are depicted in Fig. 4. The pharmacokinetic parameters of ABT-384 from a noncompartmental analysis are listed in Table 2. Compared with ABT-384-alone group, ABT-384 exposures increased 18-fold for AUC_{ss} and 3.5-fold for C_{max} after coadministration with ketoconazole. The harmonic mean half-life of ABT-384 in the ketoconazole-coadministration group (48 hours) was much longer than the half-life estimated after administration of ABT-384 alone (12 hours). ABT-384 T_{max} in the ketoconazole-coadministered group was slightly longer than that in the ABT-384-alone group.

The mean A-1331480 and A-847082 plasma concentration-time profiles following a 10-mg single oral dose of ABT-384 with and without ketoconazole in healthy adults are shown in Fig. 3. The individual changes in exposures (AUC and C_{max}) of A-1331480 and A-847082 caused by modulation are depicted in Fig. 4. The pharmacokinetic parameters of A-1331480 and A-847082 from a noncompartmental analysis are presented in Table 3. When ABT-384 was coadministered with ketoconazole, A-1331480 AUC_{ss} increased 4.9-fold and A-1331480 C_{max} decreased 32% compared with ABT-384-alone group. Similarly to the ABT-384 half-life data, the harmonic mean half-life of A-1331480 was also increased (4.3-fold) in ketoconazole-coadministration group. Additionally, A-1331480 T_{max} in the ketoconazole-coadministered group was delayed (46 hours) compared with that in the ABT-384 only group (3.17 hours).

After coadministration with ketoconazole, exposures of A-847082 were also increased: A-847082 C_{max} increased 8.4-fold and AUC_{ss} increased more than 19-fold. Similarly to A-1331480, a delay in T_{max} was also observed in A-847082. The T_{max} of A-847082 was 7.9 hours when ABT-384 was administered alone and increased to 90 hours after ketoconazole coadministration. The effect of ketoconazole on A-847082 half-life cannot be estimated as the terminal phase of A-847082 pharmacokinetics could not be characterized during the investigated time period (i.e., 168 hours) in the ketoconazole-coadministered group.

Population Pharmacokinetic Modeling

Pharmacokinetic Modeling for ABT-384. As the direct connection between depot compartment and central compartment did not adequately capture the absorption phase, we incorporated transit compartments in the absorption phase. Among different number of transit compartments evaluated, a model with three transit compartments provided the best fitting. Our final model for ABT-384 is a two-compartment model with three transit absorption compartments and first-order elimination. The parameter estimates for the final model of ABT-384 are presented in Table 4. Among the estimated pharmacokinetic parameters of ABT-384, IIV was assigned on K_{TR}, CL, V_{p}, and F_{1}. As this study was conducted in a crossover manner, the IOVs for the K_{TR}, CL, and V_{p} were also determined in the final model. As shown in Table 4, the standard errors of the estimated parameters IIV, IOV, and residual variability were all within reasonable ranges. In addition, the model predicted a 69.3% decrease in clearance and 91.1% increase in central compartment volume of distribution of ABT-384 in the presence of ketoconazole. In vitro data indicated that CYP3A plays a predominant role in ABT-384 oxidative metabolism (AbbVie, unpublished data). Therefore, in the final model, CYP3A was assumed to be the only factor contributing to the first pass metabolism of ABT-384, and the bioavailability of ABT-384 (F_{1}) was fixed to 1 when ABT-384 was coadministered with ketoconazole. The model-estimated F_{1} was 0.181 when ABT-384 was administered alone. The model-estimated population ratio of ABT-384 AUC_{ss} with ketoconazole to ABT-384 AUC_{ss} without ketoconazole was 18; this estimated value is consistent with the one calculated from the observed data.

Table 2 presents the estimated parameters for the final model of A-1331480 and A-847082. Both A-1331480 and A-847082 pharmacokinetic data were described by a one-compartment model with first-order elimination. The estimated parameters for the final model of A-1331480 and A-847082 are summarized in Table 4. When ABT-384 was administered alone, the estimated apparent fractions of ABT-384

![Fig. 3. Mean concentration-time profiles of ABT-384 and its two active metabolites (A-1331480 and A-847082) following a 10-mg single oral dose of ABT-384 with and without ketoconazole (KTZ) coadministration in healthy adults.](image-url)
converted to A-1331480 (f_{m1}^*) and A-847082 (f_{m2}^*) were 0.231 and 0.0011, respectively. Both values were changed after ketoconazole coadministration (98% decrease for A-1331480 and 105% increase for A-847082). The estimated elimination rate constants of A-1331480 (k_{m1}) and A-847082 (k_{m2}) in ABT-384-alone condition were 0.843 and 0.0364, respectively, and 0.0248 and 0.0109, respectively, in ketoconazole-coadministration condition. The model-estimated ratio of AUC_{inf} with ketoconazole over AUC_{inf} without ketoconazole was 4.0 for A-1331480 and 38 for A-847082. The time course of observed versus population-predicted (PRED) plasma concentrations of A-1331480 and
A-847082 following a single 10-mg oral dose of ABT-384 with and without ketoconazole in healthy adults are presented in Fig. 5, B and C, respectively. Basic goodness-of-fit plots for A-1331480 and A-847082, including scatter plots of the observed versus population-predicted (PRED) concentrations and observed versus individual-predicted (IPRED) concentrations, are presented in the middle and low panels of Fig. 6. There appeared to be some overprediction of A-1331480 concentrations at the early phase. This less favorable fitting might be caused by the rapid formation of A-1331480 when ABT-384 was administered alone and the limited available data during the formation phase. The proposed model overall adequately captured A-1331480 and A-847082 data at both the population and individual levels.

Model Evaluation

The results of the visual predictive check of the final model are presented in Fig. 7 for ABT-384 (upper panel), A-1331480 (middle panel), and A-847082 (lower panel). As shown in Fig. 7, most of the observations were contained within the 90% prediction interval and equally distributed around the median, indicating that the final model is robust and sufficient.

Safety Summary

Five (5 of 12, 42%) subjects reported at least one treatment-emergent adverse event. The only adverse event reported by two or more subjects was headache (N = 4, 33%). All remaining adverse events were reported by a maximum of one subject in each treatment. No deaths, other serious adverse events, or discontinuations due to adverse events occurred during the study. Two treatment-emergent adverse events (feeling jittery and dizziness) were assessed by the investigator as possibly related to ABT-384. All of the treatment-emergent adverse events were assessed by the investigator as mild in severity. No potentially clinically meaningful changes in laboratory parameters, vital signs, or electrocardiogram values were observed.

Discussion

In the present study, ABT-384 exposures increased 18-fold for AUC<sub>0-12</sub> and 3.5-fold for C<sub>max</sub> when 10-mg single oral dose of ABT-384 was coadministered with ketoconazole 400 mg once daily. These results suggest that CYP3A represents a primary metabolic pathway of ABT-384 in human, and ABT-384 is a sensitive substrate of CYP3A.

The metabolite A-1331480 concentration declined with a half-life similar to ABT-384 under both ABT-384-alone and ketoconazole-coadministration conditions, indicating that the decline in A-1331480 concentration was governed by the elimination of ABT-384 but not its own elimination. This phenomenon suggests that the elimination rate constant of A-1331480 (k<sub>el</sub>) is greater than the elimination rate constant of ABT-384 (k) and the elimination of A-1331480 is formation rate-limited. In contrast, the other active metabolite A-847082 declined more slowly than ABT-384 and consequently has a much longer half-life, indicating that the elimination of A-847082 was elimination rate-limited as the decline of A-847082 was governed by its own elimination (k<sub>el</sub> < k).

The pathway that is responsible for the formation of A-1331480 was not assessed in vitro. However, based on the fact that CYP3A is a primary oxidative metabolic pathway of ABT-384 and A-1331480 is the most abundant oxidative metabolite of ABT-384 in human, we speculate that A-1331480 may be generated through CYP3A.

ABT-384 single-dose pharmacokinetics has been evaluated at doses ranging from 1 mg to 240 mg in healthy volunteers in the first-in-human study, and ABT-384 exposures were found to be dose-proportional across the 8 to 240-mg dose range (Liu et al., 2013). As the dose of ABT-384 administered in the current study was 10 mg, a linear pharmacokinetic model incorporating ketoconazole modulation was constructed to describe ABT-384 data. The model predicted a 69.3% decrease in ABT-384 clearance in the presence of ketoconazole. This is consistent with the known inhibitory effect of ketoconazole on CYP3A-mediated ABT-384 metabolism.

Regarding the volume of distribution of ABT-384, initially it was assumed that it was not affected by the modulation and the same value was assigned in both with- and without-ketoconazole conditions. However, ABT-384 concentrations were always overestimated at the early phase in the ketoconazole-coadministration group, no matter how other parameters were adjusted. After allowing for ketoconazole modulation on ABT-384 volume of distribution, the model adequately captured ABT-384 data in both ABT-384 alone and ketoconazole-coadministered conditions. The model predicted a 91.1% increase in
volume of distribution of ABT-384 when ABT-384 was coadministered with ketoconazole. It has been reported that ketoconazole has inhibitory effect not only on CYP3A but also on efflux transporters such as P-glycoprotein (P-gp; Siegsmund et al., 1994; Zhang et al., 1998). It is well known that efflux transporters function as a protective efflux pumps and have the potential to limit bioavailability, limit tissue distribution, and increase the biliary and urinary excretion of xenobiotics that are substrates of efflux transporters (Sparreboom et al., 1997; Schinkel and Jonker, 2003; Leslie et al., 2005; Sharom, 2008). Based on the facts that efflux transporters can limit drug tissue distribution and ketoconazole has inhibitory effect on efflux transporter (such as P-gp), it is reasonable to speculate that ABT-384 may be a substrate of certain efflux transporter(s) and the increase in volume of distribution of ABT-384 in the presence of ketoconazole may be caused by the change in efflux transporter-mediated tissue distribution of ABT-384. Preliminary study using Caco-2 cell line has indicated that ABT-384 is unlikely a substrate of P-gp (AbbVie, unpublished data). As multiple transporters are expressed in Caco-2 cells and no specific P-gp inhibitor is available (Gutmann et al., 1999), the possibility of the involvement of P-gp in the transport of ABT-384 cannot be completely ruled out at this point. Whether ABT-384 is transported by other efflux transporters is unknown. Further investigation is warranted to evaluate the role of efflux transporters in the transport of ABT-384.

Based on the model prediction, ABT-384 has limited bioavailability ($F_e = 0.181$) when it is administered alone. Drug bioavailability is known to be a product of following three components: the fraction of the dose absorbed through the gut wall ($F_{abs}$), the fraction of the dose escaping gut wall ($F_{gut}$), and the fraction of the dose escaping liver ($F_{liver}$). Since ABT-384 is a low clearance drug (predicted CL is 4.25 l/h), the hepatic extraction ($E_{liver}$) of ABT-384 is expected to be low and consequently the hepatic availability of ABT-384 ($F_{liver}$) should be high. Based on the known solubility and permeability properties of ABT-384, $F_{abs}$ is likely to be high as well. Therefore, $F_{gut}$ may represent the major component contributing to the low bioavailability of ABT-384. It has been reported that the expression of CYP3A in human intestine is high (Watkins et al., 1987; Kolars et al., 1992). Since ABT-384 is known to be extensively metabolized through CYP3A, intestinal CYP3A may be the main reason leading to the low value of $F_{gut}$ and may have a relatively bigger contribution than hepatic CYP3A in the low bioavailability of ABT-384. In addition to CYP3A, efflux transporters, such as P-gp and breast cancer resistance protein, are also expressed abundantly in the intestine and are known to work as gatekeepers in limiting its substrates from entering systemic circulation (Sparreboom et al., 1997; Matheny et al., 2001). Based on the above information, although the role of efflux transporters in the transport of ABT-384 is unclear, their involvement in the low bioavailability of ABT-384 cannot be ruled out at this point.

It should be noted that, for metabolites that undergo formation-rate-limited disposition, it is not possible to estimate their elimination rate constants ($k_{elim}$) unambiguously. Therefore, for active metabolite A-1331480, a product of formation-rate-limited metabolism, the model-estimated $k_{elim}$ should be interpreted with caution. Regarding another active metabolite A-847082, although its decline is governed by its own elimination, the model-estimated $k_{elim}$ in ketoconazole-coadministration condition may not be accurate due to the insufficient investigated time period.

Although ABT-384 exposures were greatly increased in the presence of ketoconazole, ABT-384 was associated with few adverse events and no other safety signals in the current study. The safety of ABT-384 has been evaluated at much higher doses (single doses up to 240 mg and multiple doses up to 100 mg once daily for 21 days) in prior clinical studies (Liu et al., 2013). ABT-384 was generally well tolerated in those studies. The safety of ABT-384 has been evaluated at much higher doses (single doses up to 240 mg and multiple doses up to 100 mg once daily for 21 days) in prior clinical studies (Liu et al., 2013). ABT-384 was generally well tolerated in those studies. The effect of ABT-384 on peripheral and brain 11β-HSD1 activity was also evaluated. A regimen of ABT-384 2 mg daily for 5 days demonstrated full inhibition of both peripheral and brain HSD-1. Hence 2 mg daily is considered as a fully efficacious dose for all potential indications (Katz et al., submitted manuscript).
Because doses up to 50-fold higher have been generally well tolerated, coadministration of potentially efficacious ABT-384 doses with ketoconazole or another strong/moderate CYP3A inhibitor may be expected to be well tolerated. However, a somewhat increased dose may be necessary to maintain the efficacy of ABT-384 when coadministered with strong or moderate CYP3A inducers.

Based on the known potency of ABT-384 and its two active metabolites, the sum of drug exposures was estimated by adding up the weighted contributions of parent drug and metabolites. In the presence of ketoconazole, the overall increase of active drug exposure is estimated to be 2-fold for $C_{\text{max}}$ and 9-fold for AUC. For the 10-mg dose used in this study, these increases would not be expected to alter pharmacodynamic response or clinical efficacy, as daily doses of 2 mg or above are associated with full HSD-1 inhibition in both brain and liver (Katz et al., submitted manuscript). Inference is limited for predicted clinical doses that are severalfold lower. However lower dose or dosing frequency might maintain the same pharmacodynamic response and clinical efficacy when ABT-384 is administered together.
with strong or moderate CYP3A inhibitors. It should be noted that, as in vitro kinetics data indicated that the binding of ABT-384 to HSD-1 is fast and long lasting (fast $k_{on}$ and slow $k_{off}$; AbbVie, unpublished data), $C_{\text{max}}$ is considered a better indicator than AUC for the pharmacodynamic response.

In summary, ABT-384 exposures increased 18-fold for AUC and 3.5-fold for $C_{\text{max}}$ when 10 mg ABT-384 was coadministered with ketoconazole 400 mg once daily. The results suggest that CYP3A represents a primary metabolic pathway of ABT-384 in human and ABT-384 is a sensitive substrate of CYP3A. A population pharmacokinetic model was constructed for ABT-384 and its metabolites. The model adequately characterized the pharmacokinetics of ABT-384, A-1331480, and A-847082 in the absence and presence of ketoconazole. Although ABT-384 exposures were greatly increased in the presence of
ketoconazole, it is expected that ABT-384 can be safely coadministered with ketoconazole or another strong/moderate CYP3A inhibitors.

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Authorship Contributions

Participated in research design: Liu, Katz, Marek, Awni, Dutta.

Conducted experiments: An, Liu, Katz, Marek.

Performed data analysis: An.

Wrote or contributed to the writing of the manuscript: An, Katz, Dutta.

Fig. 7. Visual predictive check for ABT-384 (top), A-1331480 (middle), and A-847082 (bottom): observed concentration (open circles), 50th percentile (dashed line), and 90% prediction interval (solid lines). KTZ, ketoconazole.
References


Address correspondence to: Dr. Guohua An, Department of Pharmaceutics, University of Florida, 6550 Sanger Road, Orlando, FL 32827, E-mail: guohuaan@cop.ufl.edu