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Pharmacokinetic and Pharmacodynamic Evaluation of the Drug-Drug Interaction Between Isavuconazole and Warfarin in Healthy Subjects

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Abstract

This phase 1 trial evaluated pharmacokinetic and pharmacodynamic interactions between the novel triazole antifungal agent isavuconazole and warfarin in healthy adults. Multiple doses of isavuconazole were administered as the oral prodrug, isavuconazonium sulfate (372 mg 3 times a day for 2 days loading dose, then 372 mg once daily thereafter; equivalent to isavuconazole 200 mg), in the presence and absence of single doses of oral warfarin sodium 20 mg. Coadministration with isavuconazole increased the mean area under the plasma concentration-time curves from time 0 to infinity of S- and R-warfarin by 11% and 20%, respectively, but decreased the mean maximum plasma concentrations of S- and R-warfarin by 12% and 7%, respectively, relative to warfarin alone. Mean area under the international normalized ratio curve and maximum international normalized ratio were 4% lower in the presence vs absence of isavuconazole. Mean warfarin area under the prothrombin time curve and maximum prothrombin time were 3% lower in the presence vs absence of isavuconazole. There were no serious treatment-emergent adverse events (TEAEs), and no subjects discontinued the study due to TEAEs. All TEAEs were mild in intensity. These findings indicate that coadministration with isavuconazole has no clinically relevant effects on warfarin pharmacokinetics or pharmacodynamics.

Keywords

CYP2C9, CYP3A4, isavuconazole, isavuconazonium, warfarin

Invasive fungal diseases are a common complication in immunosuppressed patients, including those with malignancy or undergoing transplantation, and are associated with significant morbidity and mortality.[1,2] Owing to an evolving fungal epidemiology and the emergence of drug-resistant strains,[1,3,4] a versatile antifungal armamentarium is required to meet this challenge.

Isavuconazonium sulfate is a novel broad-spectrum water-soluble triazole antifungal prodrug that was approved in 2015 by the US Food and Drug Administration for the primary treatment of adults with invasive aspergillosis and mucormycosis and by the European Medicines Agency for the primary treatment of adults with invasive aspergillosis and for treatment of mucormycosis in patients for whom treatment with amphotericin B is inappropriate, based on the results of phase 3 clinical trials.[5,6] Its active moiety, isavuconazole, has been confirmed as a sensitive substrate and moderate inhibitor of cytochrome P450 (CYP) 3A4 in humans.[7] In phase 1 trials, isavuconazole has also been shown to be a weak inducer of CYP2B6, a weak inhibitor of uridine diphosphate glucuronosyltransferase, and a weak inhibitor of the transporters P-glycoprotein, organic cation transporters 1 and 2,

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as well as multidrug and toxin extrusion 1 in healthy human subjects.[8–10] Studies conducted in vitro suggest that isavuconazole also has inhibitory potential for CYP1A2 and CYP2C9. In human liver microsomes, the inhibition constant (IC_{50}) for phenacetin-*O*-dealkylase activity of CYP1A2 was 38.5 μmol/L, and the K_i for diclofenac 4′-hydroxylase activity of CYP2C9 was 8.6 μmol/L (data on file). At the recommended clinical dose of isavuconazole (200 mg 3 times daily for 2 days, then 200 mg daily), plasma concentrations are generally <7 μg/mL (data on file), and so IC_{50} or K_i values ≤ 16 μmol/L in vitro might suggest the greatest potential for interactions in vivo (isavuconazole molecular weight, 437.47 g/mol). In studies performed in vitro to assess potential induction of CYPs by isavuconazole in cultured human hepatocytes, the enzymatic activity of CYP1A2 (but not that of CYP2C9) was increased 2.8-fold, whereas mRNA levels were increased 5.4-fold (CYP1A2) and 3.1-fold (CYP2C9). However, the potential effects of isavuconazole on these CYPs in vivo have not been reported.

Warfarin is a widely used anticoagulant medication that is administered as a racemic mixture of S- and R-enantiomers.[11] S-Warfarin, which is responsible for most of the pharmacological activity of warfarin, is metabolized primarily by CYP2C9; the R-enantiomer, which is 2.7 to 3.8 times less potent than S-warfarin, is metabolized by CYP1A2 and CYP3A4.[11] Because it is likely that patients receiving isavuconazole therapy may also require treatment with warfarin or with other substrates of CYP2C9 or CYP1A2, a phase 1 trial was conducted to evaluate the potential pharmacokinetic (PK) and pharmacodynamic (PD) interaction between therapeutic doses of isavuconazole and warfarin in healthy adults. There is increasing evidence that different CYP2C9 genotypes and polymorphism of the gene encoding the warfarin target, vitamin K epoxide reductase (*VKORC1*), may impact warfarin PK and PD, respectively.[12] Therefore, warfarin PK and PD were also assessed in healthy subjects who had different CYP2C9-predicted phenotypes and *VKORC1* genotypes.

Methods

Study Design

Before initiation of the study, the protocol was reviewed and approved by the Institutional Review Board (IRB) for the study center (Spaulding Clinical Research, LLC, West Bend, Wisconsin; Chesapeake IRB, Columbia, Maryland). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonisation Guidelines, and local applicable regulations. All participating subjects provided approved, written, informed consent prior to any study procedures.

This was a phase 1 open-label trial (ClinicalTrials.gov identifier: NCT01657825) conducted to evaluate the PK and PD effects of coadministration of multiple doses of isavuconazole (administered as isavuconazonium sulfate; CRESEMBA® oral capsules; Astellas Pharma US, Inc., Northbrook, Illinois) with a single dose of warfarin sodium (COUMADIN® oral tablets; Bristol-Myers Squibb, Princeton, New Jersey) in healthy male subjects. Healthy medication-free adult males aged 18 to 55 years, weighing ≥ 45 kg, with a body mass index (BMI) of 18 to 32 kg/m^2, prothrombin time (PT) within the normal range (expressed as an international normalized ratio [INR] of 0.8 to 1.2), and with no clinically significant coexisting disease history, were eligible to enroll in this study. Subjects were excluded if they had a history of bleeding disorders, vitamin K deficiency, peptic ulceration, gastrointestinal bleeding, hemorrhagic tendencies, blood dyscrasias, or coagulation-related abnormalities.

Dosing and Sampling Schedules

In this report, dosing information is expressed as the isavuconazole equivalent of the prodrug, eg, oral capsules each contained isavuconazonium sulfate 186 mg, equivalent to isavuconazole 100 mg. The clinically targeted dose of isavuconazole is 200 mg 3 times a day (TID) for 2 days loading dose (administered as isavuconazonium sulfate 372 mg), followed by 200 mg once daily (QD).

Subjects were screened between days –28 and –2, prior to check-in at the study center, where they remained intermittently from day –1 through day 29. A follow-up visit was conducted on day 35 (± 2 days). On day 1, subjects received a single dose of oral warfarin sodium 20 mg (Figure 1). After washout, subjects received an oral loading dose of isavuconazole 200 mg TID ($\sim$8 hours apart) on days 16 and 17, then 200 mg QD on days 18 to 28. A single dose of oral warfarin sodium 20 mg was also given on day 20, concomitant with isavuconazole. Subjects fasted for ≥ 10 hours prior to warfarin administration and continued to fast for 4 hours following administration. Isavuconazole was also administered under fasting conditions on day 19. On day 20, isavuconazole was administered immediately after warfarin.

Blood samples were collected for PK analyses of S- and R-warfarin at predose on days 1 and 20 and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, 120, 144, 168, and 216 hours postdose. Samples were drawn for PK analysis of isavuconazole at predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 16 hours postdose on day 19; and at predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours postdose on day 20.

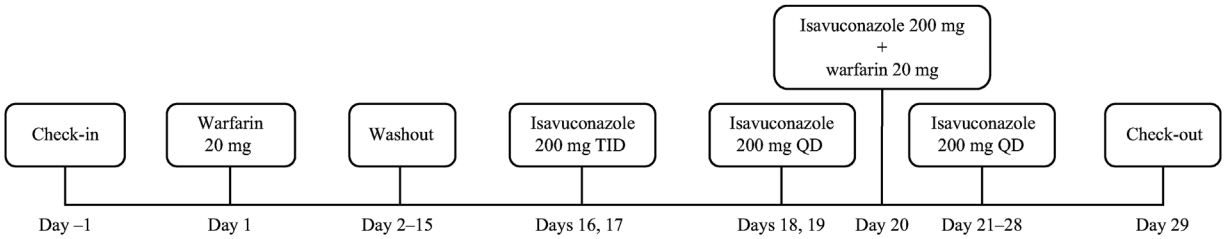

Figure 1. Dosing schedule. QD, once daily; TID, 3 times a day. Isavuconazole 200 mg was administered as isavuconazonium sulfate 372 mg.

Blood samples were also collected for PD analyses on day –1 as well as on days 1 and 20 at predose and at 6, 12, 24, 48, 72, 96, 168, and 216 hours postdose. An additional, single, whole-blood sample was collected prior to dosing on day 1 for CYP2C9 and *VKORC1* genotype testing.

Pharmacokinetic and Pharmacodynamic Assessments

The PK parameters of S- and R-warfarin and isavuconazole were assessed in plasma using validated liquid chromatography–mass spectrometry/mass spectrometry methods (Pharmaceutical Product Development, Middleton, Wisconsin). The method for bioanalysis of isavuconazole is described in Townsend et al.[7] Interassay precisions (percentage coefficient of variation, CV) of the 200, 400, 1000, 2500, and 8000 ng/mL isavuconazole quality control samples were 3.6%, 3.1%, 2.6%, 3.0%, and 2.7%, respectively, whereas, the interassay accuracies (percentage relative error, RE) were 1.5%, 3.5%, 5.0%, 3.1%, and 2.0%, respectively. For S- and R-warfarin, plasma samples (sodium heparin; 0.2 mL) were combined with internal standard (warfarin-d_6) and subjected to a liquid-liquid extraction using methyl-t-butyl ether and dichloromethane. The resulting supernatants were evaporated to dryness under a stream of nitrogen, followed by reconstitution of the residue with mobile phase (ammonium acetate, formic acid, acetonitrile, and methanol). Chromatographic separation was achieved using a Chiralcel column (250 × 4.6 mm, 10 μm; Daicel Chemical Industries Ltd, Osaka, Japan) with an isocratic mobile phase consisting of ammonium acetate, formic acid, acetonitrile, and methanol. An API3000 mass spectrometer (AB Sciex, Framingham, Massachusetts) in negative-ion mode was used to monitor the analytes. Multiple reaction-monitoring transitions were m/z 307.3→161.0 for S- and R-warfarin and 313.2→161.0 for the internal standard. The validated curve range was 5 to 1500 ng/mL, and any samples measuring above the upper limit were diluted 2-fold prior to analysis. Interassay precisions (percentage CV) of the S-warfarin 11.5, 27.6, 92, 276, and 1150 ng/mL quality control samples were 4.7%, 4.6%, 4.2%, 4.3%, and 4.1%, respectively, whereas the interassay accuracies (percentage RE) were 7.3%, 10.2%, 12.4%, 4.1%, and –6.0%, respectively. Interassay precisions (percentage CV) of the R-warfarin 11.5, 27.6, 92, 276, and 1150 ng/mL quality control samples were 5.1%, 2.9%, 4.0%, 3.7%, and 4.1%, respectively, whereas the interassay accuracies (percentage RE) were 7.0%, 10.0%, 11.1%, 3.7%, and –4.1%, respectively. All study samples were analyzed within the established long-term stability limit (511 days at –25 ± 5°C).

The primary PK parameters of S-warfarin were area under the concentration-time curve (AUC) from time 0 to infinity (AUC_∞), AUC from time of dosing to time of last measurable concentration (AUC_{last}), and maximum drug concentration (C_{max}). Secondary PK parameters included AUC_∞, AUC_{last}, and C_{max} for R-warfarin; time to C_{max} (t_{max}), half-life ($t_{½}$), clearance (CL/F), and volume of distribution (V_z/F) for S- and R-warfarin; and AUC for a dosing interval (AUC_τ), C_{max}, and t_{max} for isavuconazole. The PD parameters calculated were INR (a measure of anticoagulation intensity; including area under the INR-time curve [AUC_{INR}], maximum INR [MAX_{INR}]) and PT (including area under the PT-time curve [AUC_{PT}] and maximum PT [MAX_{PT}]).

Safety Assessments

Treatment-emergent adverse events (TEAEs) were monitored throughout the study. Safety was also assessed by vital-sign measurements, 12-lead electrocardiograms, clinical laboratory testing (hematology, chemistry, and urinalysis), and physical examinations.

Statistics

Demographics, baseline characteristics, and TEAEs were summarized using descriptive statistics in all enrolled subjects who received ≥1 dose of a study drug. The PK and PD parameters were evaluated in all subjects who received ≥1 dose of a study drug and whose PK and PD data were sufficient for the calculation of ≥1 of the PK or PD parameters, respectively. Levels of analyte below the level of quantification were

Table 1. Plasma Pharmacokinetic Parameters of S-Warfarin and R-Warfarin

	S-Warfarin		R-Warfarin	
Parameter[a]	Warfarin Alone (n = 20)	Warfarin + Isavuconazole (n = 20)	Warfarin Alone (n = 20)	Warfarin + Isavuconazole (n = 20)
AUC_{∞}, h·ng/mL	38 629 (9 698)	42 689 (10 299)	61 716 (11 730)	73 854 (12 085)
AUC_{last}, h·ng/mL	37 673 (9 289)	41 441 (9917)	57 839 (10 463)	67 767 (10 497)
C_{max}, ng/mL	1 127 (220)	991 (171)	1 135 (199)	1 049 (158)
t_{max}, hours	0.8 (0.5–4.0)	2.0 (0.8–4.0)	1.3 (0.5–4.0)	3.0 (0.8–4.0)
$t_{½}$, hours	42.0 (11.6)	42.8 (7.8)	52.8 (8.8)	59.2 (12.5)
CL/F, L/h	0.27 (0.07)	0.25 (0.06)	0.17 (0.03)	0.14 (0.03)

AUC, area under the concentration-time curve; C_{max}, maximum concentration; CL/F, clearance; $t_{½}$, half-life; t_{max}, time to C_{max}.
[a]Parameters are expressed as mean (standard deviation), except t_{max}, which is expressed as median (range).

entered as 0 for calculations. The PK parameters of S-warfarin were summarized by CYP2C9-predicted phenotype. To assess the effect of isavuconazole on the PK of S-warfarin, log-transformed AUC and C_{max} values of S-warfarin were analyzed using a linear mixed-effects model with treatment (warfarin alone and warfarin plus isavuconazole coadministration) as a fixed effect and subject as a random effect. The 90% confidence intervals (CI) were constructed around the geometric least-squares mean ratio of warfarin plus isavuconazole coadministration (day 20) to warfarin-alone administration (day 1) for the primary PK parameters.

In an exploratory analysis to assess the effect of warfarin on the PK of isavuconazole, log-transformed AUC_{τ} and C_{max} values of isavuconazole were analyzed using a mixed-effects model with treatment (isavuconazole alone and warfarin plus isavuconazole coadministration) as a fixed effect and subject as a random effect. The 90%CIs were constructed around the geometric least-squares mean ratio of warfarin plus isavuconazole coadministration (day 20) to isavuconazole alone administration (day 19) for the primary PK parameters.

The PD parameters of warfarin were summarized by *VKORC1* genotype. To assess the effect of coadministration of isavuconazole with warfarin on natural-log-transformed PD parameters AUC_{INR}, MAX_{INR}, AUC_{PT}, and MAX_{PT}, a mixed-effects model with treatment (warfarin alone and warfarin plus isavuconazole coadministration) and *VKORC1* genotype as fixed effects and subject as a random effect was used. The 90%CIs were constructed around the geometric least-squares mean ratio of warfarin plus isavuconazole coadministration (day 20) to warfarin-alone administration (day 1) for the PD parameters. The PK and PD parameters were calculated using noncompartmental analysis with Phoenix® WinNonlin® version 5.2.1 or higher (Certara USA, Inc., Princeton, New Jersey).

Table 2. Statistical Analysis of S-Warfarin and R-Warfarin Pharmacokinetic Parameters

	Geometric Least-Squares Mean Ratio, % (90% Confidence Interval)	
Parameter	S-Warfarin	R-Warfarin
AUC_{∞}	111 (106, 116)	120 (117, 124)
AUC_{last}	110 (106, 115)	118 (114, 121)
C_{max}	88 (83, 94)	93 (87, 99)

AUC, area under the concentration-time curve; C_{max}, maximum concentration.

All data processing, summarization, and analyses were conducted using SAS® Version 9.1 (Statistical Analysis Software, Cary, North Carolina).

Results

Subjects

A total of 21 subjects enrolled, and 20 completed this study between June and July 2012. One subject was enrolled but withdrew prior to receiving study drug. The mean (standard deviation) age, weight, and BMI of the subjects were 36.4 (8.1) years, 87.2 (13.9) kg, and 26.6 (2.6) kg/m^2, respectively. Thirteen (65.0%) subjects were white, 6 (30.0%) were black or African American, and 1 (5%) was from India.

Pharmacokinetics

Mean S-warfarin AUC_{∞} and AUC_{last} were 11% and 10% higher, and C_{max} was 12% lower, when coadministered with isavuconazole vs warfarin alone, respectively (Tables 1 and 2). Mean R-warfarin AUC_{∞} and AUC_{last} were 20% and 18% higher, and C_{max} was 7% lower, in the presence vs absence of isavuconazole, respectively (Tables 1 and 2). Mean concentration-time profiles of S- and R-warfarin under both dosing conditions are shown in Figure 2. Isavuconazole PK parameters

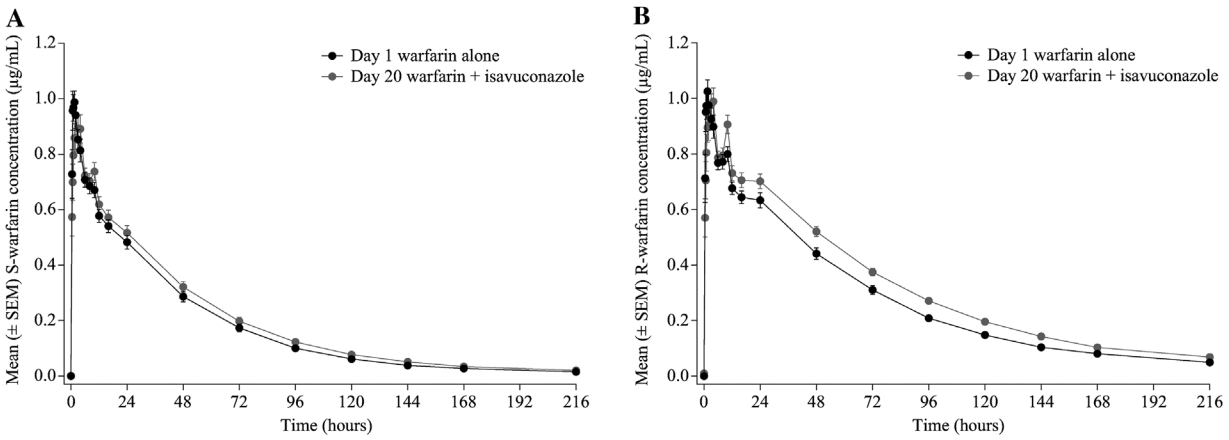

Figure 2. Mean concentration-time profiles for S-warfarin (A) and R-warfarin (B) in the presence and absence of isavuconazole. SEM, standard error of the mean.

were unchanged by coadministration with warfarin (Table 3). Geometric least-squares mean ratios (90%CI) for isavuconazole AUC_τ and C_{max} were 105% (103, 107) and 99% (95, 103), respectively.

S-warfarin AUC appeared lower in subjects with the CYP2C9 extensive metabolizer predicted phenotype than in subjects with the intermediate metabolizer predicted phenotype (Supplementary Table S1). Otherwise, S-warfarin, R-warfarin, and isavuconazole PK did not appear to be different between subjects with different CYP2C9-predicted phenotypes (Supplementary Tables S1 and S2).

Pharmacodynamics

Compared with subjects having the wild-type *VKORC1* –1639 GG genotype or the –1639 GA variant, those with the –1639 AA genotype had increased INR and PT (Table 4). However, warfarin PD remained unaffected by coadministration with isavuconazole. The geometric least-squares mean ratios (90%CI) for AUC_{INR} and MAX_{INR} were 96% (93 100) and 96% (92 100), respectively. Ratios (90%CI) for AUC_{PT} and MAX_{PT} were 97% (94 100) and 97% (93 101), respectively.

Safety

There were no deaths or serious TEAEs, and no subjects discontinued the study due to a TEAE. No single type of TEAE was experienced by >1 subject, and all TEAEs were mild in intensity. Overall, 8 (40.0%) subjects experienced a TEAE: warfarin alone (n = 3), isavuconazole alone (n = 3), and warfarin plus isavuconazole (n = 5). Nervous system disorders (n = 4), including dizziness, headache, somnolence, and tremor, were the most commonly reported TEAEs (Supplementary Table S3). TEAEs were considered to be drug related in 6 (30.0%) subjects. There were no clinically relevant changes in vital-sign measurements or clinical laboratory evaluations.

Table 3. Plasma Pharmacokinetics of Isavuconazole

Parameter[a]	Isavuconazole Alone (n = 20)	Warfarin + Isavuconazole (n = 19)[b]
AUC_τ, h·µg/mL	93.2 (25.2)	97.2 (24.8)
C_{max}, µg/mL	6.2 (1.4)	6.1 (1.5)
t_{max}, h	3.0 (1.5-4.0)	3.0 (1.5-4.0)

AUC, area under the concentration-time curve; C_{max}, maximum concentration; t_{max}, time to C_{max}.
[a]Parameters are expressed as mean (standard deviation), except t_{max}, which is expressed as median (range).
[b]Parameters were not calculated for 1 subject due to incorrect sampling times.

Discussion

This phase 1 trial examined the PK interaction between isavuconazole and the CYP substrate warfarin, and the effects of isavuconazole on the PD of warfarin, in healthy human subjects. Coadministration with isavuconazole was associated with ~11% and 20% increases in the exposure of S-warfarin and R-warfarin, respectively. Warfarin PD remained unaffected by coadministration with isavuconazole.

The modest increase in R-warfarin exposure was likely caused by inhibition of CYP3A4, rather than CYP1A2, because isavuconazole is an established moderate inhibitor of the CYP3A4 enzyme,[7] but it did not affect the exposure of the CYP1A2 substrate caffeine.[9] The findings of the present study also demonstrate that clinically targeted doses of isavuconazole do not inhibit CYP2C9-mediated metabolism in vivo. By comparison, the antifungal agent fluconazole is an in vitro inhibitor of CYP2C9 and CYP3A4[13,14] but not of

Table 4. Summary of Warfarin Pharmacodynamic Parameters by *VKORC1* Genotype

	Warfarin Alone				Warfarin + Isavuconazole			
Parameter[a]	Overall (n = 20)	Genotype AA[b] (n = 2)	Genotype GA[b] (n = 8)	Genotype GG[b] (n = 10)	Overall (n = 20)	Genotype AA[b] (n = 2)	Genotype GA[b] (n = 8)	Genotype GG[b] (n = 10)
AUC_{INR}	258.9 (44.7)	348.8 (79.6)	256.1 (33.4)	243.3 (23.8)	249.3 (36.1)	312.8 (30.3)	246.6 (17.1)	238.7 (37.4)
MAX_{INR}	1.7 (0.6)	3.2 (1.1)	1.6 (0.4)	1.4 (0.2)	1.6 (0.6)	3.0 (0.3)	1.5 (0.3)	1.4 (0.3)
AUC_{PT}, h·s	2787 (422)	3663 (772)	2758 (299)	2634 (207)	2695 (344)	3323 (282)	2681 (148)	2579 (348)
MAX_{PT}, seconds	17.2 (6.2)	31.7 (11.3)	16.9 (3.4)	14.5 (1.7)	16.5 (5.2)	29.9 (2.7)	15.9 (2.9)	14.4 (2.3)

AUC, area under the curve; INR, international normalized ratio; PT, prothrombin time; *VKORC1*, vitamin K epoxide reductase complex subunit 1.
[a]All parameters are expressed as mean (standard deviation).
[b]Nucleotide position –1639.[18]

CYP1A2.[13] As a result of CYP2C9 and CYP3A4 inhibition, fluconazole has been shown to inhibit both S- and R-warfarin metabolism in human subjects.[15] The antifungal agents itraconazole and voriconazole are also in vitro inhibitors of CYP2C9[13]; however, PK interactions between these triazoles and warfarin have not been examined in a clinical setting.

In contrast to isavuconazole, which showed no significant effect on PT or INR, coadministration of fluconazole with warfarin significantly increases PT and INR values, which are associated with adverse bleeding events in patients.[14,16] Similarly, PT[16,17] and INR[16] are significantly increased when voriconazole and warfarin are administered together. Itraconazole does not appear to impact warfarin PD in vivo.[16] Coadministration of posaconazole and warfarin has not been examined in humans.[14]

Genetic factors affect patients' responses to warfarin and are important considerations when calculating appropriate dosages as certain genotypes are associated with increased bleeding complications.[11] Polymorphisms within the *CYP2C9* gene influence the activity of this isoenzyme, whereby individuals who are homozygous for the wild-type CYP2C9*1 allele have an extensive metabolizer predicted phenotype, whereas individuals who possess 1 or 2 copies of the CYP2C9*2 or CYP2C9*3 variant alleles are intermediate metabolizers and require lower doses of warfarin than extensive metabolizers.[11] As expected, S-warfarin exposure was somewhat lower in subjects with a CYP2C9 extensive metabolizer predicted phenotype compared with intermediate metabolizers, whereas R-warfarin exposure was comparable in subjects with both predicted phenotypes. Variations within the *VKORC1* gene also affect the activity of warfarin; ie, individuals possessing the AA polymorphism require significantly lower doses of warfarin than those with the GA or GG genotype.[18] Consistent with this association, warfarin INR and PT were found to be highest in subjects with the AA genotype, compared with the GA or GG genotypes, in the present study. Despite these genetic differences, the PK and PD of warfarin were unaffected by coadministration with isavuconazole in all subjects.

In summary, the results of the present study indicate that coadministration with isavuconazole should not complicate warfarin dosing. In addition, coadministration with warfarin does not affect the PK of isavuconazole.

Acknowledgments

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Declaration of Conflicting Interests

Isavuconazole was codeveloped by Astellas Pharma Global Development, Inc. and Basilea Pharmaceutica International Ltd. T.Y., A.D., D.K., C.L., H.P., S.A., and R.T. are employees of Astellas Pharma Global Development, Inc. A.J.D. is an employee of Spaulding Clinical Research who was contracted by Astellas Pharma Global Development, Inc. to perform work related to the study.

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Supporting Information

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