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PHARMACOLOGY

Effects of Food and Omeprazole on a Novel Formulation of Super Bioavailability Itraconazole in Healthy Subjects

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ABSTRACT To address the limited bioavailability and intolerance of the conventional itraconazole (ITZ) formulations, a new formulation labeled super bioavailability (SUBA) itraconazole has been developed; however, the specific effects of food and gastric pH are unknown. This study evaluated the pharmacokinetic profile of SUBA itraconazole under fasting and fed conditions, as well as with the concomitant administration of a proton pump inhibitor. First, the effect of food was assessed in an open-label, randomized, crossover bioavailability study of 65-mg SUBA itraconazole capsules (2 65-mg capsules twice a day) in healthy adults ($n = 20$) under fasting and fed conditions to steady-state levels. Second, an open-label, two-treatment, fixed-sequence comparative bioavailability study in healthy adults ($n = 28$) under fasted conditions compared the pharmacokinetics of a single oral dose of SUBA itraconazole capsules (2 65-mg capsules/day) with and without coadministration of daily omeprazole delayed-release capsules (1 40-mg capsule/day) under steady-state conditions. In the fed and fasted states, SUBA itraconazole demonstrated similar concentrations at the end of the dosing interval, with modestly lower total and peak ITZ exposure being shown when it was administered under fed conditions than when it was administered in the fasted state, with fed state/fasted state ratios of 78.09% (90% confidence interval [CI], 74.49 to 81.86%) for the area under the concentration-time curve over the dosing interval (14,183.2 versus 18,479.8 ng · h/ml), 73.05% (90% CI, 69.01 to 77.33%) for the maximum concentration at steady state (1,519.1 versus 2,085.2 ng/ml), and 91.53% (90% CI, 86.41 to 96.96%) for the trough concentration (1,071.5 versus 1,218.5 ng/ml) being found. When dosed concomitantly with omeprazole, there was a 22% increase in the total plasma exposure of ITZ, as measured by the area under the concentration-time curve from time zero to infinity ($P = 0.0069$), and a 31% increase in the peak plasma exposure of ITZ, as measured by the maximum concentration ($P = 0.0083$).

KEYWORDS itraconazole, antifungal agents, pharmacokinetics

Itraconazole (ITZ) is an orally administered broad-spectrum antifungal triazole used for both the prophylaxis and treatment of systemic fungal infections (1–4). Both itraconazole and its major active metabolite, hydroxyitraconazole (OH-ITZ), exert antifungal activity through the inhibition of fungal cytochrome P450 (CYP)-dependent 14-α-demethylase, which mediates the synthesis of ergosterol, a vital component of the fungal cell membrane (3). ITZ is well established as a mold-active antifungal agent, and a concentration effect has been demonstrated in numerous prior studies (5). However, wide interpatient variability in bioavailability and the poor gastrointestinal tolerability of conventional ITZ formulations have made use of the agent

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challenging, and the agent has largely fallen out of favor because of the newer triazoles on the market (2, 5).

Itraconazole is a weakly basic Biopharmaceutics Classification System (BCS) class II (low-solubility/high-permeability) drug with a pH-dependent dissolution (pK_a value, 3.7) requiring an acidic gastric environment for sufficient drug dissolution and adequate absorption (6). The coadministration of oral ITZ capsules with agents that inhibit gastric acidity, such as antacids and proton pump inhibitors, has been shown to reduce ITZ absorption (7). These studies using the ITZ oral capsule taken concurrently with omeprazole at 40 mg once daily showed a significant reduction in ITZ serum concentrations with a decline in the mean area under the concentration-time curve (AUC) from 0 to 24 h (AUC_{0-24}) and the maximum concentration (C_{max}) of ITZ by 64% and 66%, respectively (7). Similarly, H2 blockers and other antacids have been shown to reduce ITZ absorption (8, 9). Later studies using the ITZ oral solution did not demonstrate this same pH-dependent effect; however, gastrointestinal disturbance with the ITZ oral solution is seen in 15 to 57% of patients, potentially limiting patient tolerability (2).

Previous studies on the effect of food have also shown significant differences in the absorption of ITZ in the fed and fasting states. The absorption of the conventional ITZ capsule formulation was significantly reduced in the fasting state, with the mean C_{max} after fasting being ~60% of that after a standard meal (10, 11). Conversely, the ITZ oral solution has the opposite effect, with studies demonstrating that the mean bioavailability is 29% higher in the fasted state (12). These studies led to the recommendations for the capsule formulation to be administered with a high-fat-content meal and the oral solution to be taken on an empty stomach (13–15).

To address the bioavailability and intolerance concerns over conventional itraconazole formulations, a new formulation labeled super bioavailability (SUBA) itraconazole has been developed by Mayne Pharma International. SUBA itraconazole is a novel formulation containing a solid dispersion of ITZ in a polymeric matrix to enhance its dissolution and intestinal absorption, with SUBA itraconazole therefore exhibiting greater bioavailability than the conventional products (16). Previous studies have demonstrated that the relative bioavailability of SUBA itraconazole compared to that of itraconazole capsules was 173%, with 21% less variability (6). Likewise, a recent study in patients with hematological malignancy or undergoing allogeneic stem cell transplantation demonstrated that the serum ITZ concentrations achieved with SUBA itraconazole were superior to those achieved with the conventional ITZ oral solution (17). Despite these recent publications demonstrating the potential pharmacokinetic advantages of a new ITZ formulation, the specific effect of food and alterations of gastric pH with a proton pump inhibitor (PPI) on SUBA itraconazole has not been described. This study was conducted to evaluate the pharmacokinetic profile of SUBA itraconazole under fasting and fed conditions, as well as with the concomitant administration of the PPI omeprazole.

RESULTS

Effect of food. A summary of the results for SUBA itraconazole in the fed and fasted states is provided in Tables 1 and 2 and Fig. 1. Overall, SUBA itraconazole demonstrated similar concentrations at the end of the dosing interval, with modestly lower total and peak ITZ exposures being found when it was administered under fed conditions than when it was administered in the fasted state, with fed state/fasted state ratios of 78.09% (90% confidence interval [CI], 74.49 to 81.86%) for the area under the concentration-time curve over the dosing interval ($AUC_{tau;}$ 14,183.2 versus 18,479.8 ng · h/ml), 73.05% (90% CI, 69.01 to 77.33%) for the maximum concentration (C_{max}) at steady state ($C_{max,ss}$; 1,519.1 versus 2,085.2 ng/ml), and 91.53% (90% CI, 86.41 to 96.96%) for the tough concentration (C_{trough}; 1,071.5 versus 1,218.5 ng/ml) being found. Similarly, total and peak OH-ITZ exposures were modestly lower under fed conditions than under fasted conditions, with fed state/fasted state ratios of 84.98% (90% CI, 82.02 to 88.06%) for AUC_{tau} (27,719.0 versus 32,819.7 ng · h/ml), 82.63% (90% CI, 79.64 to 85.72%) for $C_{max,ss}$

TABLE 1 Summary of itraconazole pharmacokinetics for SUBA itraconazole in the fed and fasted states[a]

Parameter	Treatment	Arithmetic mean or median (% CV)	Geometric mean or range	Arithmetic mean for treatments A vs B		Intrasubject CV (%)
				Ratio (%)	90% CI	
$C_{max,ss}$ (ng/ml)	A	1,519.1 (43)	1,403.1	73.05	69.01–77.33	10
	B	2,085.2 (43)	1,920.7			
C_{trough} (ng · h/ml)	A	1,071.5 (36)	1,008.7	91.53	86.41–96.96	10
	B	1,218.5 (51)	1,102.1			
AUC_{tau} (ng · h/ml)	A	14,183.2 (35)	13,370.0	78.09	74.49–81.86	9
	B	18,479.8 (44)	17,122.2			
$T_{max,ss}$ (h)	A	4.00	0.00–10.00			
	B	3.50	1.00–5.00			

[a]Data are for 20 subjects in each treatment group, and the data represent the arithmetic mean and geometric mean for all parameters except $T_{max,ss}$, for which the median and range, respectively, are shown. Treatment A consisted of 65-mg SUBA itraconazole capsules (2 capsules on days 1 to 14 BID and once a day on day 15) in the fed state. Treatment B consisted of 65-mg SUBA itraconazole capsules (2 capsules on days 1 to 14 BID and once a day on day 15) in the fasted state.

(2,520.5 versus 3092.0 ng/ml), and 87.81% (90% CI, 84.42 to 91.33%) for C_{trough} (2,240.5 versus 2,566.5 ng/ml) being found.

Effect of omeprazole. A summary of the results for SUBA itraconazole dosed concurrently with omeprazole is shown in Tables 3 and 4 and Fig. 2. When dosed concomitantly with omeprazole, there was a 22% increase in the total plasma exposure of ITZ, as measured by the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) ($P = 0.0069$) and a 31% increase in the peak plasma exposure of ITZ, as measured by the C_{max} ($P = 0.0083$). The median time to C_{max} (T_{max}) was marginally shorter in the presence of omeprazole (3.25 h) than in the presence of the drug alone (3.5 h), the mean half-life ($t_{1/2}$) for the two treatment groups was similar at approximately 28 h, and the shapes of the individual concentration-time profiles were nearly identical for the two treatments, as shown in Fig. 2.

Safety. The administration of 65-mg SUBA itraconazole capsules was well tolerated by all subjects participating in this study. When coadministered with omeprazole, there were 2 treatment-emergent adverse events (TEAEs) affecting 2 subjects (7.1%) deemed treatment related (a possible or probable relationship to the study drug); these included 2 events of grade 1 headache in 1 subject (3.5%) and flatulence in 1 subject (3.5%). When administered in the fed and fasted states, there were 8 TEAEs in 4 subjects (16.7%) deemed treatment related; these included 5 events (1 event in the fed state and 4 events in the fasted state) of constipation in 2 subjects (8.3%), 1 event (in the fasted state) of fatigue in 1 subject (5%), 1 event (in the fed state) of nausea in 1 subject (5%), and 1 event (in the fed state) of headache in 1 subject (5%). All TEAEs were mild in severity. No subject discontinued from the study due to a TEAE. No serious adverse

TABLE 2 Summary of hydroxyitraconazole pharmacokinetics for SUBA itraconazole in the fed and fasted states[a]

Parameter	Treatment	Arithmetic mean or median (% CV)	Geometric mean or range	Arithmetic mean for treatments A vs B		Intrasubject CV (%)
				Ratio (%)	90% CI	
$C_{max,ss}$ (ng/ml)	A	2,520.5 (28)	2,421.3	82.63	79.64–85.72	7
	B	3,092.0 (33)	2,930.4			
C_{trough} (ng/ml)	A	2,240.5 (29)	2,148.7	87.81	84.42–91.33	7
	B	2,566.5 (31)	2,447.1			
AUC_{tau} (ng · h/ml)	A	27,719.0 (27)	26,661.2	84.98	82.02–88.06	6
	B	32,819.7 (30)	31,372.2			
$T_{max,ss}$ (h)	A	4.00	0.00–10.02			
	B	3.25	0.50–4.00			

[a]Data are for 20 subjects in each treatment group, and the data represent the arithmetic mean and geometric mean for all parameters except $T_{max,ss}$, for which the median and range, respectively, are shown. Treatment A consisted of 65-mg SUBA itraconazole capsules (2 capsules on days 1 to 14 BID and once a day on day 15) in the fed state. Treatment B consisted of SUBA itraconazole 65-mg capsules (2 capsules BID on days 1 to 14 and once a day on day 15) in the fasted state.

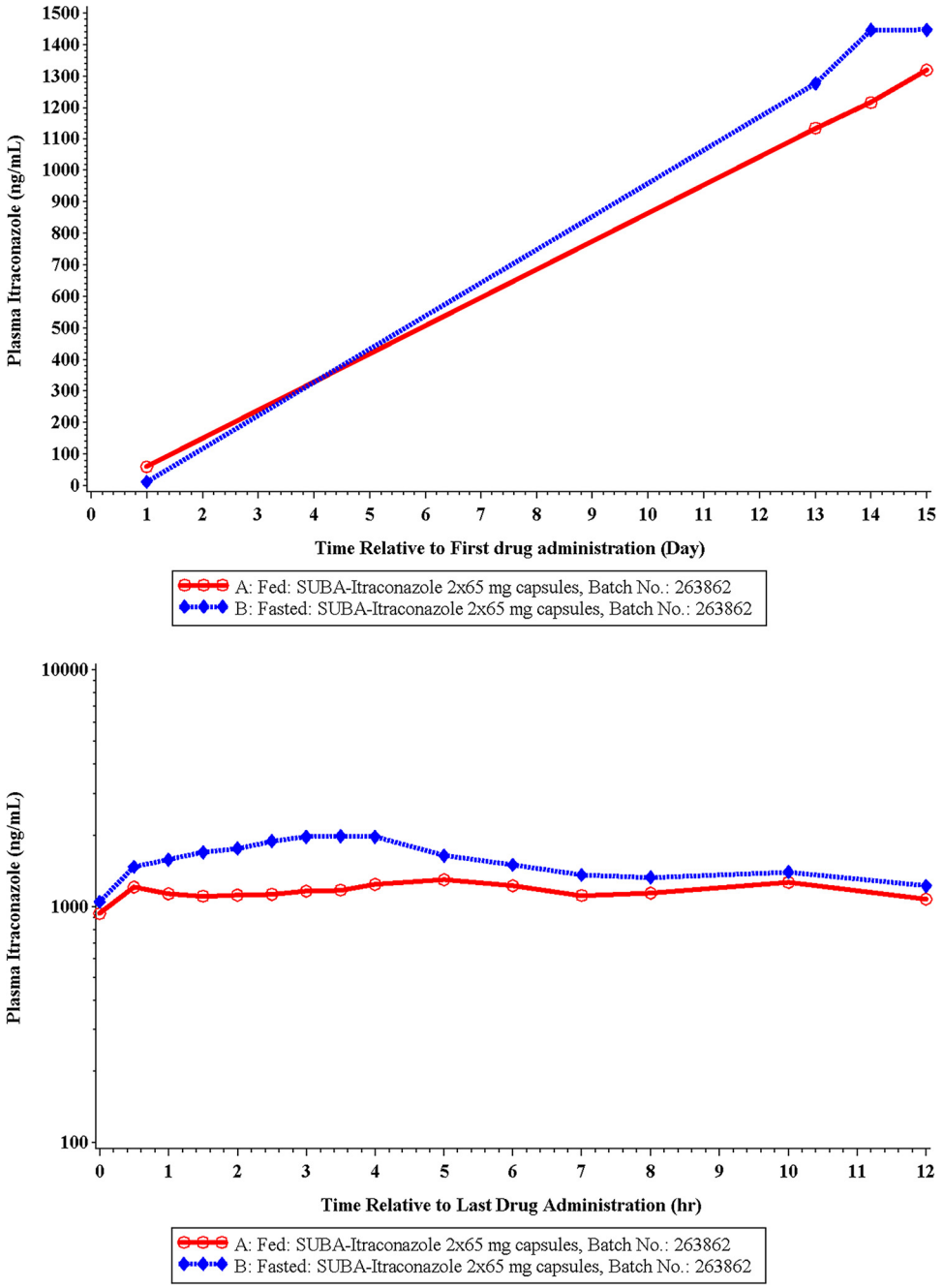

FIG 1 Mean plasma itraconazole concentrations for SUBA itraconazole in the fed and fasted states predose over the study period (top) and on day 15 given as log(concentration)-time profile (bottom).

events (SAEs) were reported during the conduct of this study, and none of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

DISCUSSION

The results of this study demonstrate that the absorption of SUBA itraconazole capsules differs from that of previous conventional itraconazole formulations, as both administration in the fasted state and coadministration of SUBA itraconazole and omeprazole moderately increased the absorption of ITZ.

As ITZ is very lipophilic, it is almost insoluble in water; hence, the presence of food was thought to increase the solubility of ITZ, thereby increasing its systemic absorption (10).

TABLE 3 Summary of itraconazole pharmacokinetics for SUBA itraconazole with omeprazole[a]

Parameter	Treatment A	Treatments A + B	Ratio	90% CI
AUC_{tau} (ng · h/ml)	2,640	3,212	121.66	107.82–137.28
$AUC_{0-\infty}$ (ng · h/ml)	2,846	3,478	122.19	108.72–137.32
C_{max} (ng/ml)	213.0	278.8	130.90	111.42–153.79

[a]Data are for 28 subjects in each treatment group. Treatment A consisted of SUBA itraconazole capsules only. Treatments A + B consisted of 65-mg SUBA itraconazole capsules and 40-mg omeprazole delayed-release capsules, USP.

Previous studies have shown that the absorption of conventional formulations of ITZ capsules administered in the fasted state is reduced to 40 to 60% of that of capsules administered in the fed state (10, 11). However, the novel formulation SUBA itraconazole showed a moderate increase in the absorption of ITZ when it was administered in the fasted state, with the steady-state serum ITZ levels in the fasted state being 130% of those in the fed state and the steady-state serum OH-ITZ levels in the fasted state being 120% of those in the fed state. The serum trough levels at steady state were also moderately higher, with ITZ and OH-ITZ levels in the fasted state being approximately 115% of those in the fed state. This effect is thought to be due to the novel formulation containing a solid dispersion of itraconazole in a polymeric matrix to enhance its dissolution and intestinal absorption; therefore, it does not require the presence of food to increase ITZ solubility.

As ITZ is also weakly basic, it typically requires an acidic gastric environment for sufficient drug dissolution and adequate absorption. Jaruratanasirikul and Sriwiriyajan previously demonstrated that the coadministration of conventional ITZ with agents that inhibit gastric acidity, such as omeprazole at 40 mg, resulted in a significant reduction in the absorption of ITZ, with AUC_{0-24} and C_{max} being reduced by 64% and 66%, respectively (7). With the development of the conventional ITZ oral solution, Johnson et al. showed that the coadministration of omeprazole did not significantly affect the serum levels of ITZ or OH-ITZ (18). Unlike both previous formulations, however, the current study demonstrated a 22% increase in the total plasma exposure of ITZ (as measured by the $AUC_{0-\infty}$) when coadministered with omeprazole. This effect is postulated to be due to an altered intestinal environment pH, in which the dissolution of ITZ from the novel pH-dependent polymeric matrix dispersion is optimized as a result of the more basic stomach contents.

Several clinical trials suggest that therapeutic drug monitoring of azole antifungals is recommended to both reduce drug toxicity and optimize efficacy (5, 19). It has been established that serum trough ITZ concentrations lower than 1,000 ng/ml are predictive of therapeutic failure (20), with concentrations below 500 ng/ml being significantly more likely to result in the development of fungal infections in those receiving ITZ as prophylaxis (21). Multiple studies have reported that concentrations above 5,000 ng/ml (which was measured by bioassay and which is approximately equivalent to an ITZ concentration of 1,200 ng/ml measured by high-performance liquid chromatography) are associated with a stabilization or resolution of the fungal infection (22, 23). Additionally, although no study has conclusively linked toxicity to serum concentrations, it has been suggested that trough levels greater than 2,000 ng/ml may increase gastrointestinal toxicity (21), although further investigation with new formulations will

TABLE 4 Summary of hydroxyitraconazole pharmacokinetics for SUBA itraconazole with omeprazole[a]

Parameter	Treatment A	Treatments A + B	Ratio	90% CI
AUC_{tau} (ng · h/ml)	4,921	6,350	129.02	115.08–144.65
$AUC_{0-\infty}$ (ng · h/ml)	5,082	6,525	128.38	114.96–143.38
C_{max} (ng/ml)	276.9	342.1	123.54	111.88–136.42

[a]Data are for 28 subjects in each treatment group. Treatment A consisted of SUBA itraconazole capsules only. Treatments A + B consisted of 65-mg SUBA itraconazole capsuled and 40-mg omeprazole delayed-release capsules, USP.

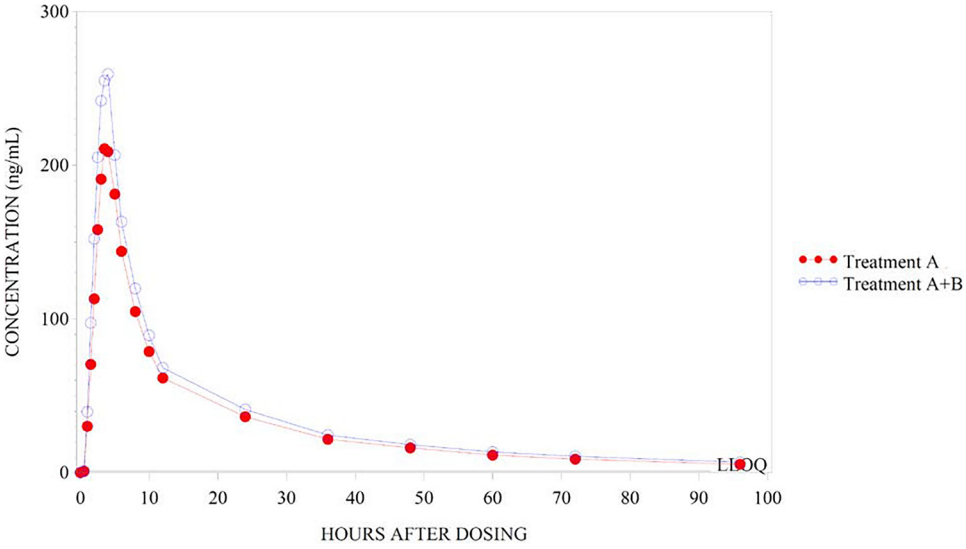

FIG 2 Mean plasma ITZ concentration-versus-time plot for SUBA itraconazole with omeprazole.

be required. In the current study, trough ITZ concentrations at steady state and under fasted conditions fell within the established recommended range of 1,000 to 2,000 ng/ml. As concomitant administration with omeprazole increased serum ITZ levels by approximately 20% after a single dose, it can be hypothesized that the trough ITZ concentration at steady state with coadministration of omeprazole would also be in this range.

A major challenge with ITZ use in clinical practice is the interpatient variability in achieving therapeutic serum concentrations. This factor, together with gastrointestinal side effects, has caused ITZ to somewhat fall out of favor compared to other currently available agents (5, 24). Pharmacokinetic studies of both healthy volunteers and the patient population have identified wide interpatient kinetic variation (25, 26). This variation in serum concentrations is largely due to differences in absorption of the oral formulations, with the most erratic absorption being observed with the capsule formulation (20), despite efforts to optimize absorption with meals or an acidic beverage (27, 28).

Complementing the results from a study in patients with hematological malignancy or undergoing allogeneic stem cell transplantation, which demonstrated that the mean trough serum concentrations at steady state of SUBA itraconazole were significantly higher than those achieved with the conventional ITZ oral solution, with less interpatient variability (1,577 ng/ml [coefficient of variation {CV}, 35%] versus 1,218 ng/ml [CV, 60%]; $P < 0.001$) (17), the results presented here demonstrate the potential of SUBA itraconazole for the treatment and prophylaxis of fungal infections. Unlike the conventional ITZ capsule formulation, which requires a high-fat meal for absorption, or the oral solution, which requires administration in a fasted state, SUBA itraconazole reached a more predictable therapeutic steady state in both the fasted and fed states.

In the United States, there is a boxed warning with conventional itraconazole capsules which states that the "use is contraindicated for treatment of onychomycosis in patients with ventricular dysfunction such as heart failure (HF) or a history of HF" due to cases of HF, peripheral edema, and pulmonary edema occurring in this patient population (13). In addition, negative inotropic effects have been observed following the intravenous administration of itraconazole. There are also both *in vitro* and clinical data suggesting that itraconazole and posaconazole may inhibit 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and 11β-hydroxylase (11βOH), resulting in the triad of hypertension, hypokalemia, and alkalosis due to cortisol inactivation (29–31). In some cases, this effect has been shown to be potentially dose related, at least for posaconazole (30). Therefore, with the increased absorption of the SUBA itraconazole formulation, caution should be taken and patients should be monitored for signs of HF. No study participants were observed to demonstrate any signs of electrolyte disbalance, hypertension, or HF.

The slightly higher bioavailability in a fasted state and with administration with omeprazole is potentially promising for the clinical use of SUBA itraconazole in patients unable to have a high-fat-content meal due to chemotherapy or after surgery. Likewise, the marginal increase in ITZ exposure with concomitant omeprazole administration may be advantageous, particularly for critically ill patients, who often require PPI prophylaxis.

MATERIALS AND METHODS

Effect of food. First, the effect of food on steady-state levels was assessed in an open-label, randomized, crossover bioavailability study of 65-mg SUBA itraconazole capsules (2 65-mg capsules twice a day [BID]) in healthy adults under fasting and fed conditions. Subjects ($n = 20$) were administered two capsules of SUBA itraconazole twice daily on days 1 to 14 and once on the morning of day 15 at 30 min after the start of a high-fat, high-calorie breakfast or after an overnight fast of at least 10 h. The concentrations of ITZ and OH-ITZ in plasma were measured from predose samples collected prior to drug administration on days 1, 13, 14, and 15 and over a 12-h interval after dosing on day 15 in both periods. An assessment of safety was based on the frequency and severity of treatment-emergent adverse events (TEAEs), including monitoring of vital sign measurements, electrocardiogram measurements, clinical safety laboratory tests (liver and kidney function tests), and physical examination.

Effect of omeprazole. Second, an open-label, two-treatment, fixed-sequence comparative bioavailability study in healthy adults under fasted conditions compared the pharmacokinetics of a single oral dose of SUBA itraconazole capsules (2 65-mg capsules) with and without coadministration of multiple daily doses of omeprazole delayed-release capsules (1 40-mg capsule once a day; Sandoz, Inc.) under steady-state conditions. For the omeprazole coadministration dosing period, subjects ($n = 28$) received a single dose of an omeprazole delayed-release capsule on study days 1 to 6, and then on study day 7, the subjects received a single dose of SUBA itraconazole capsules coadministered with the last of seven daily omeprazole delayed-release capsules following an overnight fast of at least 10 h. The concentrations of ITZ and OH-ITZ in plasma were measured from predose samples collected within 60 min before dosing (0 h) and at intervals over 96 h after dosing in each study period: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0, 60.0, 72.0, and 96.0 h postdose.

Statistical methods. For the effect of food, the following steady-state pharmacokinetic parameters were estimated from samples taken on day 15 using a noncompartmental approach: AUC_{tau}, $C_{max,ss}$, T_{max} at steady state ($T_{max,ss}$) C_{trough}, predose concentration (C_{pd}), average concentration, percent fluctuation, and percent swing. Analysis of variance (ANOVA) was performed on log-transformed plasma ITZ and OH-ITZ $C_{max,ss}$, C_{trough}, and AUC_{tau} using the general linear model (GLM) procedure of the Statistical Analysis System (SAS; Version 9.4). Based on the log-transformed data, the ratios of the geometric mean ratios (GMRs) for treatments and the corresponding 90% confidence intervals (CIs) were calculated for $C_{max,ss}$, C_{trough}, and AUC_{tau}. For the effect of omeprazole, pharmacokinetic parameters were estimated from samples taken on day 7: AUC from 0 h to time t (AUC_{0-t}), $AUC_{0-\infty}$, the ratio of the $AUC_{0-\infty}$ for OH-ITZ to the $AUC_{0-\infty}$ for ITZ [$AUC_{0-\infty(OH\text{-}ITZ)}$/$AUC_{0-\infty(ITZ)}$], C_{max}, T_{max}, the elimination rate constant (k_{el}), and $t_{1/2}$ for ITZ and OH-ITZ. ANOVA was performed on the untransformed pharmacokinetic parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-\infty(OH\text{-}ITZ)}$/$AUC_{0-\infty(ITZ)}$, $t_{1/2}$, k_{el}, and T_{max} and the log-transformed plasma ITZ and OH-ITZ C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $AUC_{0-\infty(OH\text{-}ITZ)}/AUC_{0-\infty(ITZ)}$ using GLM with hypothesis testing for treatment effects at an α value of 0.05. Confidence intervals (90%) on the GMRs obtained from logarithmically transformed data for AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-\infty(OH\text{-}ITZ)}/AUC_{0-\infty(ITZ)}$, and C_{max} were constructed to test two one-sided hypotheses at an α value equal to a 0.05 level of significance.

This study was approved by the institutional review board (IRB) of the institution and was performed in compliance with Good Clinical Practice (GCP). All participants signed informed consent (IC) prior to study enrollment.

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S.M. is an employee at Mayne Pharma International. J.L. and G.R.T. have served as consultants for Mayne Pharma International.

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