Increased Oral Bioavailability of Itraconazole and Its Active Metabolite, 7-Hydroxyitraconazole, When Coadministered With a Vitamin C Beverage in Healthy Participants

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Keywords: *vitamin C beverage; itraconazole; 7-hydroxyitraconazole; absorption; cola*

Journal of Clinical Pharmacology, 2011;51:444-451

Itraconazole is a triazole antifungal agent with a broad spectrum of activity, including activity against a wide variety of *Aspergillus* and *Candida albicans* and non-*Albicans* species, and is generally well tolerated.[1-3] As an extremely lipophilic compound, itraconazole is frequently poorly absorbed, with water solubility being the rate-limiting step in itraconazole absorption from the gastrointestinal tract.

Itraconazole is a weak base (pK_a = 3.7) with high lipophilicity (log D greater than 5).[4] Its aqueous solubility is estimated at approximately 1 ng/mL at neutral pH and approximately 4 µg/mL at pH 1,[4] and thus it is ionized and water soluble only at low pHs, as in gastric juice.

Itraconazole is available as capsules or an oral solution, and doses of 200 mg daily or 200 mg twice a day are used therapeutically.[5] Because it has relatively low bioavailability after oral administration, especially when given in capsule form,[6,7] gastric acidity is required for drug dissolution and adequate absorption with capsule formulations. Decreased absorption has been observed in the fasting state and in patients with low gastric acidity.[5] Furthermore, in persons with AIDS, the absorption of itraconazole from capsules was reduced by 50% compared with absorption in healthy persons.[8] Hypochlorhydria and thus a relatively high gastric pH, a frequent complication of human immunodeficiency virus (HIV) infection, may be responsible for this phenomenon.[9] In addition, histamine H2-receptor antagonists such as ranitidine or proton pump inhibitors such as omeprazole[10] reduce gastric acidity and cause significant impairment of itraconazole absorption.

The coadministration of an acidic beverage (eg, a cola soft drink) effectively improves the bioavailability of itraconazole capsules.[11,12] However, there are some disadvantages to using a cola soft drink to achieve maximum absorption. Over the past several decades, increased consumption of sugar-sweetened soft drinks has paralleled an increase in obesity.[13,14] Patients with diabetes mellitus or obesity may not be candidates for the use of cola soft drinks. Caffeine is also present in some soft drinks, including colas. It is the most widely used psychoactive substance[15,16] and has been considered by some investigators to be a drug of abuse. Caffeine is classified as a stimulant and is typically used for its ability to arouse the

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Submitted for publication September 2, 2009; revised version accepted February 8, 2010.
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DOI:10.1177/0091270010365557

central nervous system. Although recognized as safe by the US Food and Drug Administration (FDA), caffeine use in excess can result in serious health hazards and, in rare cases, even death.[17,18] Moreover, even with smaller amounts, some caffeine-sensitive individuals may experience mild, temporary effects, including headache, restlessness, and irritability, when their daily intake is quickly and substantially altered.

Vitamin C is an essential micronutrient involved in many biological and biochemical functions. Commonly referred to as an antioxidant, vitamin C is one of the body's best defenses against free radicals. Vitamin C is commonly used to prevent the common cold in winter, and regular vitamin C consumption may decrease the duration of cold symptoms in both adults and children.[19] Vitamin C is not produced or stored by the body and thus must be replenished daily.

A vitamin C beverage drink as a supplement is a healthy and convenient way to consume the recommended daily allowance of essential vitamins, especially vitamin C, and minerals. In Korea, vitamin C beverages marketed by various manufacturers provide a wide dose range. The Vita500 drink, one of the most common beverages in Korea, includes 500 mg of ascorbate and has a pH of 2.7. It was chosen as the acidic, vitamin C–containing beverage for this study. The use of Vita500 offers the advantage of convenience, as it is easy to use and widely available.

It has been reported that antacids and colas reduced and increased, respectively, the oral bioavailability of itraconazole; however, there is insufficient information on the effect of altered itraconazole absorption on pharmacokinetic changes of its active metabolite, 7-hydroxyitraconazole. In the liver, itraconazole is extensively processed into many metabolites, via CYP3A4/5; one of these metabolites, 7-hydroxyitraconazole, occurs at plasma levels 2-fold those of itraconazole.[6,20] Hydroxyitraconazole was shown to have in vitro antifungal activity comparable to that of itraconazole itself.[20] In addition, itraconazole has also been found to be a substrate of P-glycoprotein (P-gp).[21] P-gp activity is one important mechanism that decreases the oral bioavailability of drugs by limiting intestinal absorption.[22-24] After oral administration of an itraconazole capsule, because of this, its pharmacokinetic properties would be affected by several factors, including its dissolution, the amount and activity of CYP3A4/5, and the P-gp activity in the gastrointestinal tract and/or liver. Thus, to fully understand the mechanism of action and to assess the total antifungal activity in plasma, the simultaneous determination of itraconazole and 7-hydroxyitraconazole levels is necessary.

The present study was conducted to investigate the pharmacokinetics of itraconazole and its active metabolite, 7-hydroxyitraconazole, after a single dose of itraconazole 200 mg capsule alone or coadministered with a cola drink or a vitamin C beverage (Vita500).

METHODS

Participants

Twelve healthy participants (6 men and 6 women) were enrolled after providing written informed consent. The study was approved by the Ethics Committee of Busan Paik Hospital, Inje University College of Medicine, South Korea. The median age of the participants was 24 years (range, 23-29), and the mean weight was 64.2 ± 14.9 kg (range, 52.5-86.4). The participants were examined by physicians and appeared to be healthy on the basis of a detailed physical examination and laboratory tests. Pregnant or lactating women were excluded, and all women were required to have a negative urine pregnancy test prior to study participation. Participants with a history or evidence of hepatic, renal, gastrointestinal, or hematological abnormalities; any other acute or chronic disease; or a known allergy to any drug were excluded. Participants were also excluded if they tested positive for hepatitis B and C, as well as HIV, or had alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin levels above the upper limit of the reference range. None of the participants smoked tobacco or used any continuous medication. No medications, herbal medicine, alcohol, citrus juices, or beverages containing caffeine were permitted for 10 days prior to the study and for the duration of the study.

Study Design

Purified bottled water (Evian; Danone, Paris, France), vitamin C beverage (Vita500; Kwang-Dong Pharmaceutical Co, Seoul, Korea), and cola (Coca-Cola; Coca-Cola Co, Atlanta, Georgia) were purchased from a local grocery. The study was conducted in an open-label, randomized, 3-phase crossover design with a washout period of 2 weeks between phases to compare the pharmacokinetics of itraconazole and

7-hydroxyitraconazole. The participants were hospitalized the night before the study started. After an overnight fast, each participant received a single oral dose of 200 mg of itraconazole (Sporanox 100 mg, 2 capsules; Janssen, Korea) with 240 mL of water (control), 240 mL of an acidic beverage containing vitamin C (Vita500), or 240 mL of cola. For 2 hours after dosing, the participants were not allowed to have anything by mouth, including water, and were required to stay in a supine position. At 4 and 10 hours after dosing, they received a standardized meal. Blood samples were collected before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, and 48 hours after dosing, through an indwelling venous catheter. The participants were forbidden to use any other medication for 10 days before the study and during the study. Caffeine, citrus juices, and alcohol-containing beverages were not allowed during the study. Each sample was collected into a heparin Vacutainer tube and centrifuged immediately (3000 *g*, 10 minutes, 4°C). The plasma samples were stored at –80°C until liquid chromatography/tandem mass spectrometry (LC/MS/MS) analysis.

Chemicals

Itraconazole, 7-hydroxyitraconazole, and miconazole were purchased from SynFine Research, Inc (Richmond Hill, Canada). Other chemicals were of reagent grade or high-performance liquid chromatography (HPLC) grade and were used without further purification.

Bioanalysis

The plasma concentrations of itraconazole and 7-hydroxyitraconazole were analyzed using LC/MS/MS, according to the procedure outlined by Bharathi et al[25] with a minor modification. The system consisted of an Agilent 1100 HPLC system coupled with an API4000 Q TRAP (MS/MS) mass spectrometer (Applied Biosystems, Foster City, California). Briefly, itraconazole and 7-hydroxyitraconazole were extracted from 150-µL aliquots of human plasma by liquid-liquid extraction, using 1 mL of t-butylmethylether. Chromatographic separation was performed on a Zorbax C_{18} column (50 × 2.1 mm, 5 µm) at 40°C with an isocratic mobile phase consisting of acetonitrile and distilled water (75:25, v/v) containing 0.1% formic acid (flow rate, 0.3 mL/min; total runtime, 2.0 minutes). Detection and quantification were performed using a mass spectrometer in the selected reaction monitoring mode with positive electrospray ionization at *m/z* 705→392 for itraconazole, *m/z* 721→408 for 7-hydroxyitraconazole, and *m/z* 417→161 for miconazole. The optimized ion spray voltage and temperature were set at 5500 V and 400°C, respectively. The typical ion source parameters, declustering potential, entrance potential, and collision cell exit potential were 120, 10, and 12 V, respectively. The collision energy was set at 48, 49, or 25 V for itraconazole, 7-hydroxyitraconazole, or miconazole, respectively. Nitrogen gas was used as the nebulizer gas, curtain gas, and collision-activated dissociation gas. This assay was linear over a concentration range of 2 to 1000 ng/mL and had a lower limit of quantification of 2 ng/mL for both itraconazole and 7-hydroxyitraconazole. The coefficient of variation for assay precision was <13.6%, and the accuracy was >93.1%. No relevant cross-talk or absolute or relative matrix effects were observed.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated by a noncompartmental analysis, using WinNonlin Professional software (Version 5.2, Pharsight Corp, Mountain View, California). The AUC_t was computed using the log-linear trapezoidal rule. The peak plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were read directly from the experimental data.

Safety Assessments

Throughout the clinical study, safety was evaluated based on adverse event (AE) monitoring, clinical laboratory values, vital sign measurements, and physical examination findings.

Statistical Analysis

For each statistical comparison, the AUC_t and C_{max} for itraconazole and 7-hydroxyitraconazole were analyzed as log-transformed data, using a mixed effects model that allowed for the fixed effect of sequence, period, and treatment and for the random effect of subject. The geometric mean ratios (GMRs) and 90% confidence interval (CI) for these ratios (itraconazole with cola vs itraconazole alone or itraconazole with vitamin C beverage vs itraconazole alone) were estimated. When the 90% CI fell within 0.8 to 1.25, the effect of cola or vitamin C beverage on itraconazole pharmacokinetics was regarded as

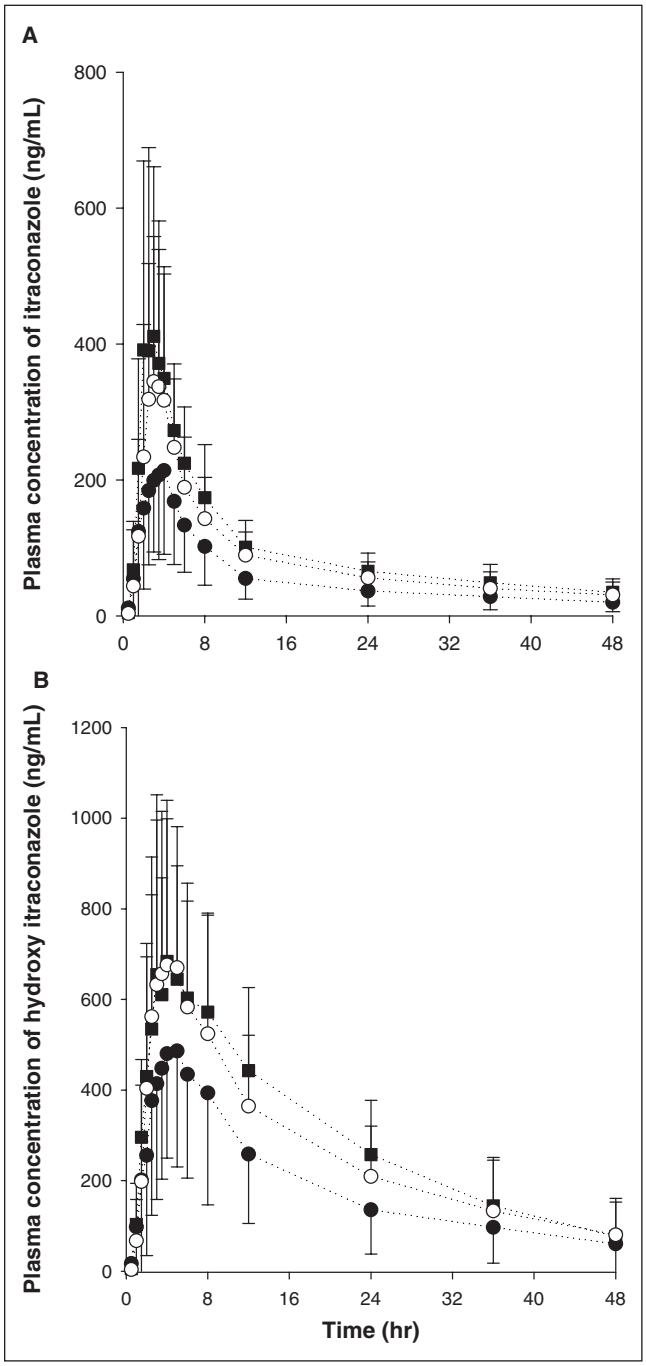

Figure 1. Plasma concentration-time profiles of itraconazole (A) and its active metabolite, 7-hydroxyitraconazole (B) after oral administration of itraconazole 200 mg capsule alone (●, n = 12), vitamin C beverage (○, n = 12), or coadministered with cola (■, n = 12).

not clinically relevant. Time to peak concentration (t_{max}) was analyzed using a nonparametric analysis with the Wilcoxon signed rank test. Differences were deemed to be statistically significant at $P < .05$. All statistical analyses were performed with the SAS software package (Version 9.1.3; SAS Institute, Cary, North Carolina). All data are expressed as means ± standard deviation (SD), except medians (ranges) for t_{max}.

RESULTS

All 12 participants (6 men and 6 women) enrolled successfully completely the study. No participant discontinued the study because of AEs or laboratories abnormalities. The pHs of the cola and vitamin C beverage (Vita500) used in this study were 2.5 ± 0.1 and 2.7 ± 0.1 (triplicate measurements), respectively.

The mean plasma itraconazole and 7-hydroxyitraconazole concentration-time profiles after oral administration of itraconazole capsules alone, with Vita500, and with cola are shown in Figure 1. The relevant pharmacokinetic parameters and GMR and 90% CI are listed in Table I. The plasma concentrations of itraconazole and 7-hydroxyitraconazole following coadministration with Vita500 or cola were higher than those following the administration of itraconazole capsules alone. Coadministration with Vita500 significantly enhanced itraconazole bioavailability, resulting in significantly higher C_{max} and AUC_t values, in comparison with the administration of itraconazole capsules alone; with Vita500 coadministration, the mean itraconazole C_{max} and AUC_t were approximately 56% and 49% ($P < .05$) higher, respectively, than those with itraconazole capsules alone, and the GMR and 90% CI for itraconazole were 1.58 (1.39-1.80) for the AUC_t and 1.56 (1.29-1.89) for C_{max}, respectively. Similarly, when itraconazole was coadministered with Vita500, the mean 7-hydroxyitraconazole C_{max} and AUC_t were approximately 44% ($P < .05$) and 40% higher, respectively, than the values with itraconazole capsules alone, and the GMR (90% CI) for 7-hydroxyitraconazole was 1.49 (1.31-1.69) for the AUC_t and 1.49 (1.27-1.73) for C_{max}. Similar results were also observed with cola coadministration. The GMR (90% CI) for itraconazole coadministered with cola versus itraconazole capsules alone was 1.85 (1.60-2.13) for the AUC_t and 1.97 (1.56-2.48) for C_{max}, and the respective values for 7-hydroxyitraconazole were 1.71 (1.52-1.92) for the AUC_t and 1.50 (1.19-1.89) for C_{max} (Table I). The GMR and 90% CI values for these parameters were not within the bioequivalence range of 0.8 to 1.25, indicating that coadministration with Vita500 or cola (acidic beverages) significantly improved the absorption of itraconazole. However,

Table I Pharmacokinetic Parameters of Itraconazole and Its Active Metabolite, 7-Hydroxyitraconazole, After Oral Administration of 200 mg Itraconazole Capsule Alone, Coadministered With Cola or Acid Beverage

Parameters	Itraconazole Alone Mean ± SD	With Vita500 Mean ± SD	With Vita500 GMR (90% CI)	With Coke Mean ± SD	With Coke GMR (90% CI)
Itraconazole					
AUC_t, ng h/mL	2290 ± 1430	3420 ± 1750*	1.58 (1.39-1.80)	4050 ± 2060*	1.85 (1.60-2.13)
C_{max}, ng/mL	248 ± 137	387 ± 212	1.56 (1.29-1.89)	478 ± 265*	1.97 (1.56-2.48)
Terminal half-life, h	20.1 ± 4.43	23.1 ± 8.18		22.4 ± 6.24	
t_{max}, h	3.25 (2-5)	3.25 (2-5)		3 (1.5-5)	
7-hydroxyitraconazole					
AUC_t, ng h/mL	7580 ± 5000	10600 ± 5900	1.49 (1.31-1.69)	11900 ± 5670*	1.71 (1.52-1.92)
C_{max}, ng/mL	519 ± 272	748 ± 371*	1.49 (1.27-1.73)	734 ± 354*	1.50 (1.19-1.89)
Terminal half-life, h	13.6 ± 5.55	14.1 ± 4.60		14.5 ± 5.02	
t_{max}, h	4.5 (3-6)	4 (2-5)		4 (2.5-8)	
Ratio of AUCs[a]	3.39 ± 1.53	3.03 ± 0.52		2.96 ± 0.35	

GMR, geometric mean ratio itraconazole with coke or Vita500 to itraconazole alone; CI, 90% confidence interval.
a They were calculated as the AUC_t ratios of 7-hydroxyitraconazole to itraconazole.
*$P < .05$.

the median t_{max} and terminal half-life values of itraconazole and 7-hydroxyitraconazole were comparable between itraconazole capsules administered alone and itraconazole capsules coadministered with Vita500 or cola (Table I). The metabolic ratios, calculated as the AUC_t ratio of 7-hydroxyitraconazole to itraconazole, were not different among the groups: 3.39 ± 1.53, 3.03 ± 0.52, and 2.96 ± 0.35 when itraconazole capsules were given alone, with Vita500, and with cola, respectively.

DISCUSSION

We investigated the effects of a coadministered vitamin C beverage (Vita500) or cola on the pharmacokinetics of itraconazole and its active metabolite, 7-hydroxyitraconazole, after a single 200-mg dose of itraconazole in capsule form in healthy volunteers. As expected from previous data,[11,12] coadministration of itraconazole with an acidic cola beverage significantly increased its absorption; the mean itraconazole C_{max} and AUC_t were increased approximately 92% and 76%, respectively. However, our study is the first to demonstrate that coadministration of itraconazole with a vitamin C beverage, another type of acidic beverage, may also enhance itraconazole absorption, as indicated by a 56% increase in the itraconazole C_{max} and a 49% increase in the AUC_t, compared with the values for itraconazole capsules alone. In addition, we demonstrated increases in the C_{max} (44% increase) and AUC_t (40% increase) of 7-hydroxyitraconazole following itraconazole coadministration with Vita500, which were comparable to the effects of a cola beverage. The plasma concentration of 7-hydroxyitraconazole, an active metabolite of CYP3A4/5-mediated itraconazole metabolism, may be approximately double that of the parent drug, suggesting its major contribution to the overall mycological activity observed in itraconazole therapy.[20] The coadministration of itraconazole with Vita500 or cola improved oral bioavailability of both itraconazole and 7-hydroxyitraconazole; thus, the clinical efficacy of itraconazole should be enhanced.

The metabolic ratio, calculated as the AUC_t ratio of 7-hydroxyitraconazole to itraconazole, was unchanged (Table I) after coadministration with Vita500 or cola compared with the ratio after the administration of itraconazole capsules alone, indicating that these beverages did not influence the metabolism of itraconazole via intestinal and/or hepatic CYP3A enzymes. This suggests that cola and vitamin C–containing acidic beverages increase the C_{max} and AUC of itraconazole by increasing its absorption from the gastrointestinal tract and not by inhibiting its metabolism via CYP3A4/5. On the other hand, the median t_{max} was comparable among the 3 groups, suggesting that neither cola nor the vitamin C beverage affected the absorption rate of

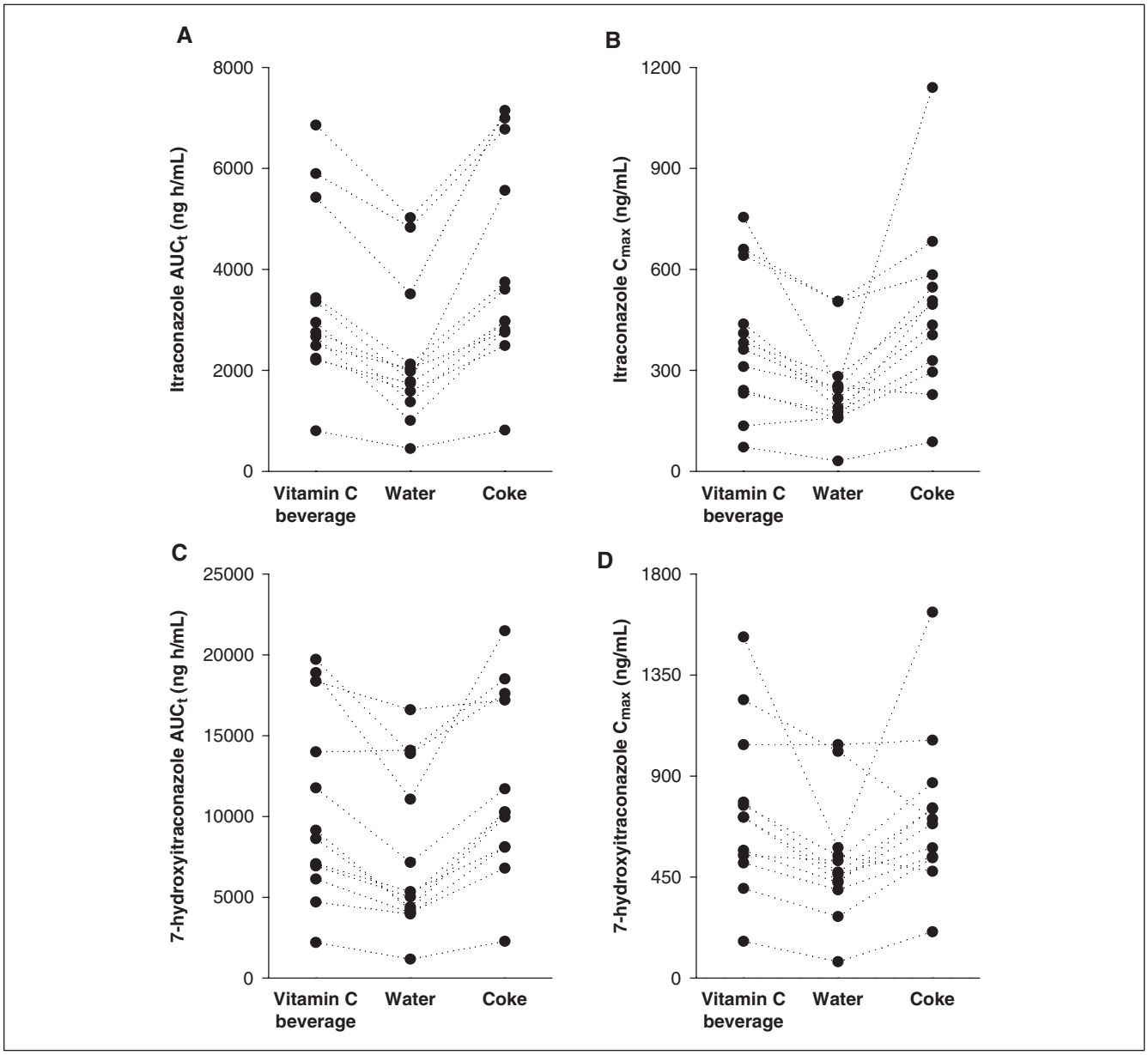

Figure 2. Individual subject AUC_t and C_{max} of itraconazole and its active metabolite, 7-hydroxyitraconazole, following 200 mg oral itraconazole capsule alone, coadministration with vitamin C beverage, or cola.

itraconazole. Our current results are consistent with result of previous studies.[11,12] However, it was reported that there was no response or only a slight response in the presence of neutral grastric pH (ie, achlorhydria).[26-28]

It is of note that the intake of the cola or acidic vitamin C–containing beverage did not change inter-individual differences (percent coefficient of variation [CV%]) in the pharmacokinetic parameters (ie, AUCs of itraconazole: 62% coadministered with water vs 51% with cola or 51% with the vitamin C beverage; AUCs of 7-hydroxyitraconazole: 62% coadministered with water vs 48% with cola or 56% with the vitamin C beverage; Table I and Figure 2).

Owing to the increased oral bioavailability of itraconazole and the predictability of an individual's plasma level, the concomitant intake of a cola or vitamin C beverage with itraconazole may be recommended.

The use of itraconazole in an oral solution form does not require the dissolution step, and thus any pH alterations of the gastric juices would not influence its systemic availability. When itraconazole oral solution was administered in healthy volunteers under the fasting state, the itraconazole AUC was higher (60% increase) than when itraconazole capsules were administered.[29] However, the cost of the oral solution is approximately 4 times the cost of 200-mg capsules of itraconazole in Korea ($8.10 for 20 mL itraconazole solution containing 200 mg itraconazole vs $2.06 for two 100-mg itraconazole capsules). Prolonged or chronic maintenance therapy, therefore, is more practical with the capsule formulation if factors that can decrease absorption are controlled.

As mentioned earlier, cola has some disadvantages as a coadministered acidic beverage. Specifically, higher consumption of sugar-sweetened beverages is associated with weight gain and increased risk for the development of type 2 diabetes mellitus, and caffeine is a psychoactive substance. On the basis of the pharmacokinetic data in the present study, we conclude that as with cola, the coadministration of a vitamin C beverage and itraconazole capsules may be useful for achieving maximum absorption of itraconazole in patients with drug- or disease-related gastric hypochlorhydria (pH > 4).

We thank Ju-Young Han and Soo-Jin Jung, clinical research coordinators, for their skilful assistance in organizing the study.

Financial disclosure: This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MOEST) (No. R13-2007-023-00000-0).

Financial disclosure: The authors do not have a commercial or any other association that might pose a conflict of interest.

Previous presentation of information: A portion of the information in this article has been presented previously at the 110th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, National Harbor, Maryland, March 2009.

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