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SHORT COMMUNICATION

Influence of Fluconazole on the Pharmacokinetics of Omeprazole in Healthy Volunteers

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ABSTRACT: Influence of fluconazole on the pharmacokinetics of omeprazole was evaluated by single oral administration of omeprazole capsule 20 mg (control group), or single oral administration of fluconazole capsule, 100 mg, and omeprazole, 20 mg, after 4 days of daily oral administration of fluconazole, 100 mg (treated group), to 18 healthy male volunteers. Omeprazole is extensively metabolized in the liver through 5-hydroxylation and sulfoxidation reactions catalyzed predominantly by CYP2C19 and CYP3A4, respectively. Fluconazole is a potent competitive inhibitor of CYP2C19 and a weak inhibitor of CYP3A4. In treated group, the area under the plasma concentration–time curve of omeprazole from time zero to time infinity (AUC) was significantly greater (3090 vs 491 ng h/ml), terminal half-life of omeprazole was significantly longer (2.59 vs 0.85 h), and peak plasma concentration of omeprazole (C_{max}) was significantly higher (746 vs 311 ng/ml) than that in control group. The greater AUC and higher C_{max} in treated group could be due to inhibition of omeprazole metabolism by fluconazole. Copyright © 2002 John Wiley & Sons, Ltd.

Key words: drug interaction; omeprazole; fluconazole; pharmacokinetics; healthy volunteers

Introduction

Fluconazole is a broad-spectrum bis-triazole antifungal drug widely used in the treatment of systemic fungal infections, particularly in the immunosuppressed patients with cancer and AIDS [1]. Many cancer patients have been treated with proton pump inhibitors for the gastrointestinal adverse drug reactions induced by chemotherapy or fluconazole in hospitals. In *in vitro* human liver microsome studies, fluconazole was found to be a potent competitive inhibitor of the hepatic microsomal cytochrome P450 (CYP)2C19-catalyzed 4-hydroxyation of (S)-mephenytoin and 8-hydroxylation of (R)-wafarin [2,3], and is a fairly weak inhibitor of the CYP3A4-mediated reactions compared with ketoconazole and itraconazole; fluconazole inhibited cyclosporine oxidation [3–6], midazolam α-hydroxylation [7–9], N-dealkylation and hydroxylation of terfenadine [10], and 10-hydroxylation of (R)-warfarin [11]. In *in vivo* human studies, fluconazole inhibited CYP3A4 and CYP2C19; fluconazole decreased the urinary 6-β-hydroxycortisol to cortisol ratio by 50% [12], increased the area under the plasma concentration–time curve (AUC) of terfenadine by 52% and prolonged the QTC internal of terfenadine [13], reduced the total body clearance of intravenous midazolam by 51%, and increased AUC of oral midazolam by 3.5 folds [14]. The mean area under the triazolam concentration–time curve (AUC) was

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increased 1.6-, 2.1- and 4.4-fold by fluconazole 50, 100 and 200 mg, respectively [15]. The effects of fluconazole on the pharmacokinetics and/or pharmacodynamics of other drugs were extensively reviewed [3,16–18].

Omeprazole is rapidly absorbed, the extent of absolute oral bioavailability ranges from 40 to 58% [19], and is extensively metabolized in the liver through 5-hydroxylation and sulfoxidation reactions catalyzed predominantly by CYP2C19 and CYP3A4, respectively [20,21]. Although the effects of omeprazole on the pharmacokinetics and/or pharmacodynamics of drugs were extensively studied [22], the effects of fluconazole on the pharmacokinetics of omeprazole seemed not to have been studied. The purpose of this study is to report pharmacokinetic changes of oral omeprazole by oral fluconazole in healthy male volunteers.

Materials and Methods

Subjects

Eighteen healthy male volunteers participated in this study after each gave a written informed consent. Their mean age was 25 years (ranging from 22 to 28 years) and mean weight was 67 kg (ranging from 56 to 78 kg). The health of the volunteers was ascertained by routine laboratory tests including hematology, blood chemistry, and urinalysis. None of the volunteers were receiving any medications continuously.

Study design

The present study was performed according to add on study design. All volunteers received single oral omeprazole (Losec® capsules, lot no. 8010, Astra, Seoul, Republic of Korea), 20 mg, with a glass of tap water at 9 a.m. on day 1 (control group). After a wash-out period of ten days, they received oral fluconazole (Diflucan® capsules, lot no. 3910-9304, Pfizer, Seoul, Republic of Korea), 100 mg, at 9 a.m. from day 12 to day 15. On day 16 (treated group), omeprazole, 20 mg, with fluconazole, 100 mg, was administered orally with a glass of tap water at 9 a.m. All volunteers fasted for 10 h before administration of omeprazole and had a standard meal 4 h later on days 1 and 16. Alcohol- or caffein-containing beverages were forbidden during the test period.

Blood sampling time schedules

Blood samples (5 ml) were collected in heparinized tubes via an indwelling catheter in the forearm vein before (to serve as a control), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 h after omeprazole dose. After centrifugation, a 1.2-ml aliquot of plasma sample was collected and transferred to a test tube containing 180 μl of 0.1 M carbonate buffer (pH 9.8) and stored frozen at −70°C until high performance liquid chromatographic (HPLC) analysis of omeprazole [23].

HPLC Analysis of omeprazole

Plasma concentrations of omeprazole were analyzed by the reported HPLC method [23]. A 50-ml aliquot of methanol containing 25 μg/ml of lansoprazole, the internal standard of HPLC assay, was added to the plasma sample. The plasma sample was extracted with 2 ml of dichloromethane and 4 ml of ethylether. After centrifugation, the organic layer was collected. After evaporation, the residue was reconstituted with a 250-μl aliquot of mobile phase (distilled water: acetonitrile: *n*-octylamine = 650:350:1, v/v/v) and a 50-μl aliquot was injected directly onto a reversed-phase HPLC column (C_{18}; particle size 5 m; 250 mml, × 4.6 mm, i.d.; Kromasil, Bohus, Sweden). The flow rate of mobile phase was 1.2 ml/min and the column effluent was monitored using a UV detector set at 302 nm. The detection limit of omeprazole was 2 ng/ml. The standard curve with omeprazole concentrations ranging from 2 to 1000 ng/ml was linear and the mean intra-day ($n = 4$) and inter-day (consecutive 4 days) coefficients of variation in the concentration ranges were 4.0 and 5.4%, respectively.

Pharmacokinetic analysis

The area under the plasma concentration–time curve from time zero to time infinity (AUC) was calculated by the trapezoidal rule-extrapolation method; this method utilized the logarithmic trapezoidal rule [24] for the calculation of the

area during the declining plasma level phase and the linear trapezoidal rule for the rising plasma level phase. The area from the last data point to time infinity was estimated by dividing the last measured plasma concentration by the terminal rate constant. The harmonic mean method was used to calculate the mean value of terminal half-life [25].

Statistical analysis

A p-value of less than 0.01 was considered to be statistically significant using a paired t-test.

Results and Discussion

The mean plasma concentration–time profiles of omeprazole for two groups are shown in Figure 1, and the relevant pharmacokinetic parameters are listed in Table 1. The absorption of omeprazole was fast; omeprazole was detected in plasma from the first blood sampling time (30 min) and the peak plasma concentration (C_{max}) reached 1.5 ~ 3 h after oral administration for both groups (Figure 1). In fluconazole-treated group, the plasma concentrations of omeprazole were higher than those in control group (Figure 1), and this resulted in a significantly greater AUC, 6.3 times, in fluconazole-treated group (Table 1). This could be due to increased absorption and/or decreased metabolism of omeprazole by fluconazole. The contribution of increased absorption to 6.3 times increase in AUC is unlikely since omeprazole is rapidly absorbed and the absolute oral bioavailability of omeprazole is 40–58% in humans [20]. In contrast, the contribution of decreased metabolism to 6.3 times increase in AUC could be considerable, since omeprazole is metabolized in liver by CYP2C19 and CYP3A4 and fluconazole is a potent inhibitor of CYP2C19 and a weak inhibitor of CYP3A4 in humans as mentioned earlier. CYP3A isoforms are present in both liver and gastrointestinal tract mucosa in humans [26]. Therefore, 6.3 times increase in AUC of omeprazole by fluconazole could be mainly due to the inhibition of CYP2C19 and CYP3A4 by fluconazole. The inhibited metabolism of omeprazole by fluconazole resulted in a significantly higher C_{max}, 2.4 times, and a significant longer terminal half-life, 3 times, than that in control group (Table 1).

It was reported [27] that the degree of suppression of gastric acid secretion by omeprazole is correlated with the AUC of omeprazole

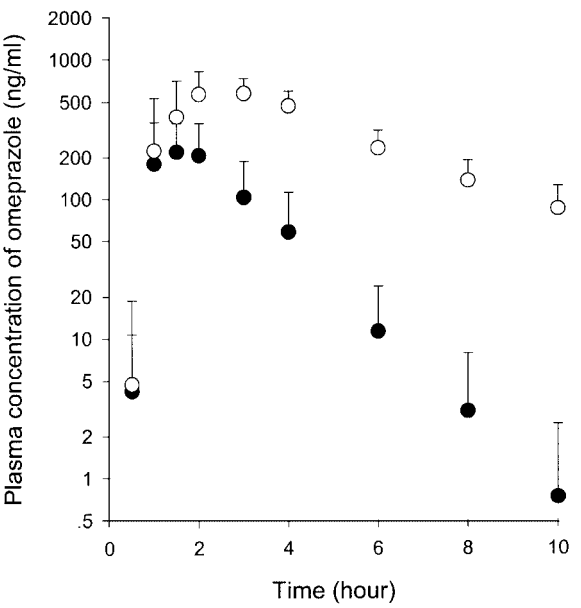

Figure 1. Mean plasma concentration–time profiles of omeprazole in control (●) and fluconazole-treated (○) groups. Bars represent standard deviation

Table 1. Mean (± standard deviation) pharmacokinetic parameters of omeprazole after oral administration of omeprazole alone (control group) and with fluconazole after 4-day premedication of fluconazole (treated group)

	Control group	Treated group	p-value
AUC (ng h/ml)	491 ± 347	3090 ± 725	< 0.005
Terminal half-life (h)	0.953 ± 0.349	2.70 ± 0.523	< 0.005
C_{max} (ng/ml)	311 ± 153	746 ± 174	< 0.005
T_{max} (h)	1.50 ± 0.542	2.00 ± 0.642	< 0.005

and is not directly related to the plasma concentrations of the drug at any given time. In fluconazole-treated group, the AUC was 6.3 times greater than that in control group (Table 1); therefore, omeprazole effect could be increased by fluconazole. In the present study, no side effects were observed for both groups of volunteers. More studies are required to ascertain whether the omeprazole dosage regimen is needed to be modified during multiple administration of omeprazole and fluconazole.

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