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# Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects

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**Aims**
Fungal infection is a significant comorbidity in patients with diabetes mellitus, and ketoconazole, an antifungal agent, causes a number of drug interactions with coadministered drugs. Rosiglitazone is a novel thiazolidinedione antidiabetic drug, mainly metabolized by CYP2C8 and to a lesser extent CYP2C9. We investigated the possible effect of ketoconazole on the pharmacokinetics of rosiglitazone in humans.

**Methods**
Ten healthy Korean male volunteers were treated twice daily for 5 days with 200 mg ketoconazole or with placebo, using a randomized, open-label, two-way crossover study. On day 5, a single dose of 8 mg rosiglitazone was administered orally, and plasma rosiglitazone concentrations were measured.

**Results**
Ketoconazole increased the mean area under the plasma concentration–time curve for rosiglitazone by 47% [$P = 0.0003$; 95% confidence interval (CI) 23, 70] and the mean elimination half-life from 3.55 to 5.50 h ($P = 0.0003$; 95% CI in difference 1.1, 2.4). The peak plasma concentration of rosiglitazone was increased by ketoconazole treatment by 17% ($P = 0.03$; 95% CI 5, 29). The apparent oral clearance of rosiglitazone decreased by 28% after ketoconazole treatment ($P = 0.0005$; 95% CI 18, 38).

**Conclusions**
This study revealed that ketoconazole affected the disposition of rosiglitazone in humans, probably by the inhibition of CYP2C8 and CYP2C9, leading to increasing rosiglitazone concentrations that could increase the efficacy of rosiglitazone or its adverse events.

## Introduction

Rosiglitazone is a novel insulin-sensitizing, oral antidiabetic agent of the thiazolidinedione class, used in the treatment of patients with Type 2 diabetes mellitus, and is an effective and well-tolerated agent for lowering blood glucose [1, 2]. It improves insulin sensitivity through the activation of the nuclear receptors, peroxisome proliferator-activating receptor gamma (PPARγ) [3]. It is rapidly and completely absorbed, with absolute bioavailability estimated to be over 99% following oral administration [4]. It is metabolized through *N*-demethylation and *p*-hydroxylation, mainly by CYP2C8 and to a lesser extent CYP2C9 [5], and does not undergo enterohepatic recirculation [5, 6].

Ketoconazole, an imidazole antifungal agent, is an effective drug for treating fungal infections [7]. It is a potent inhibitor of cytochrome P450 isoforms *in vitro* and *in vivo*, which results in many clinically signifi-

cant drug interactions with coadministered drugs [8, 9].

Type 2 diabetes mellitus is a common progressive disease affecting 1–4% of the population that leads to significantly increased comorbidity [10]. In addition to antidiabetic drugs, many other drugs may be prescribed to treat comorbidities in diabetic patients, which may result in drug interactions. It has been reported that systemic antifungal agents have been used in 3.0% of patients with Type 2 diabetes mellitus [10].

As ketoconazole could be prescribed to treat fungal infection in patients also receiving rosiglitazone, there might be potential for a deleterious drug interaction. In addition, it has been reported that ketoconazole had a comparable inhibitory effect on CYP2C8-catalysed paclitaxel 6α-hydroxylation to that of quercetin, a selective potent inhibitor of CYP2C8 [11]. Furthermore, ketoconazole showed a potent inhibitory effect on CYP2C8-catalysed torsemide metabolism *in vitro* [12]. These results suggest that ketoconazole may act as an inhibitor of CYP2C8 in addition to CYP3A4. By contrast, another *in-vitro* study showed little inhibition of rosiglitazone metabolism by ketoconazole, but concentrations of ketoconazole were far lower than therapeutic concentrations. There have been no data in humans investigating a drug interaction between ketoconazole and rosiglitazone.

The aim of the present study was to evaluate possible effects of ketoconazole on the pharmacokinetics of rosiglitazone in healthy volunteers.

## Methods

### *Subjects*

Ten healthy Korean men (age 22–34 years; weight 63–75 kg) participated in the study after they had given written informed consent. The volunteers were confirmed as healthy by medical history, physical examination, and routine laboratory tests before they were enrolled in the study.

### *Study design*

The study protocol was approved by the Institutional Review Board of Gil Medical Centre, Gachon Medical School, Incheon, Korea. A randomized, open-label, two-way crossover study was performed. The study phases were separated by a 4-week washout period, and the general study design was identical in both phases. The volunteers were given either 200 mg ketoconazole (Kun Wha Pharmaceutical Co., Seoul, Korea) or matched placebo orally twice daily for 5 days at 08.00 h and 20.00 h and the order of administration of two drugs was determined by the randomization schedule generated prior to the start of the study. On the morning of day 5, a single oral dose of 8 mg rosiglitazone (Avandia®; GlaxoSmith-Kline Korea, Seoul, Korea) was administered with water at 09.00 h. An interval of 1 h between the ingestion of ketoconazole and rosiglitazone was chosen to allow disintegration and dissolution of the ketoconazole tablet before the administration of rosiglitazone. The drugs used in this study were given in a sitting position, and the subjects remained seated for the next 3 h after administration of rosiglitazone. A standard light meal was given after 4 h. The subjects were under direct medical supervision throughout the day of rosiglitazone treatment.

### *Sample preparations*

Blood samples were drawn immediately before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 14 h after the administration of rosiglitazone. Blood samples, collected in heparinized glass tubes (Vacutainer®; Becton Dickinson, Franklin Lakes, NJ, USA), were centrifuged (209 g) for 15 min, and the separated plasma samples stored at −80 °C until assay.

Plasma rosiglitazone concentrations were quantified using high-performance liquid chromatography with a fluorescence detector described previously [13]. The limit of quantification for rosiglitazone was 5 ng ml$^{-1}$ using a 0.2-ml plasma sample volume. The precision and accuracy for the quality controls were high, with a coefficient of variation of <8% within runs (intraday) and between runs (interdays).

### *Pharmacokinetic calculations*

The pharmacokinetic parameters of rosiglitazone were estimated by noncompartmental methods, using WinNonlin® V2.0 (Scientific Consulting Inc, Apex, NC, USA). The elimination rate constant ($k_e$) was determined by linear regression analysis of the log-linear part of the plasma concentration–time curve. The total area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal rule. The AUC from 0 to infinity [AUC(0,∞)] was calculated as AUC(0,∞) = AUC + $C_t/k_e$ (where $C_t$ was the last plasma concentration measured). The half-life ($t_{1/2}$) of rosiglitazone was calculated using: $t_{1/2} = \ln 2/k_e$. The apparent oral clearance (CL/F) of rosiglitazone was calculated as CL/F = dose/AUC(0,∞). The maximum plasma concentration ($C_{max}$) and the time to reach $C_{max}$ ($t_{max}$) were estimated directly from the observed plasma concentration–time data.

### *Statistical analysis*

The results are expressed as means ± standard deviations. The pharmacokinetic parameters of rosiglitazone

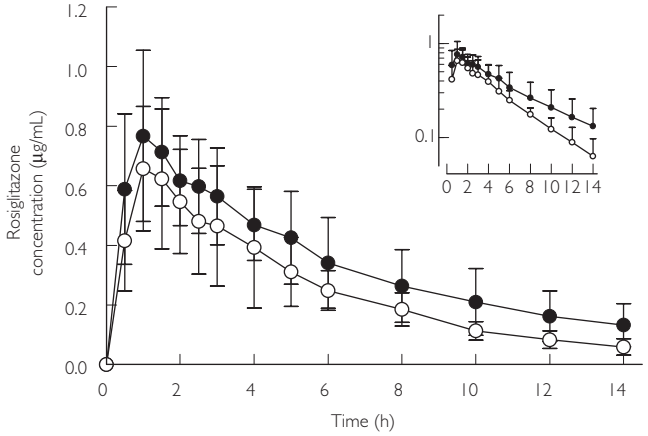


**Figure 1**

Mean plasma concentrations of rosiglitazone in 10 healthy subjects after a single oral dose of 8 mg rosiglitazone following a 5-day pretreatment with placebo or ketoconazole twice daily. Rosiglitazone in the placebo phase (○); rosiglitazone in the ketoconazole phase (●). Variability is shown as SD. Inset: semilogarithmic scale

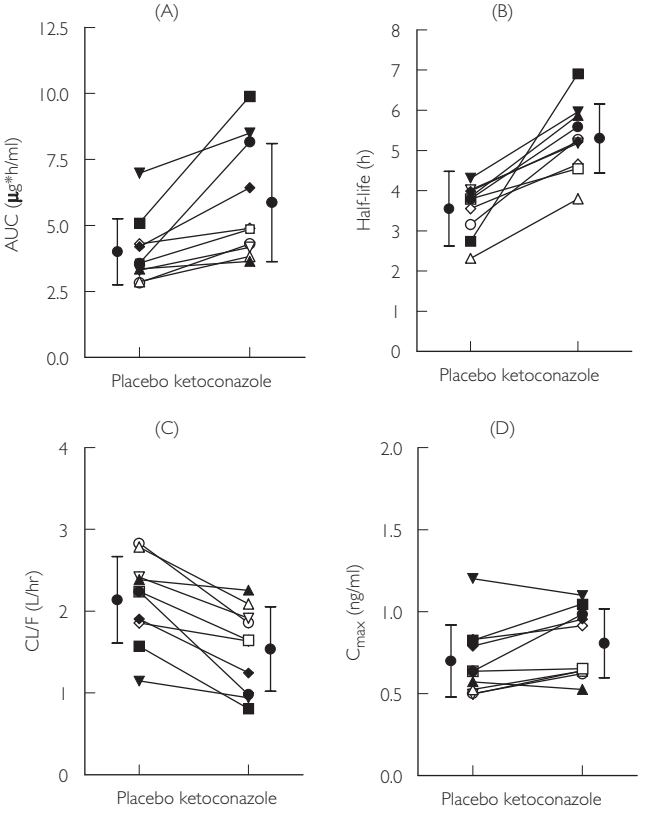


**Figure 2**

Individual total area under the concentration–time curve [AUC(0,∞)] (A), elimination half-life (B), oral clearance (CL/F) (C), peak plasma concentration ($C_{max}$) (D) values for rosiglitazone in 10 healthy subjects after a 5-day pretreatment with placebo or ketoconazole twice daily

were compared between the two phases with a paired *t*-test (two-tailed). The $t_{max}$ data were compared with the Wilcoxon signed-rank test. All the data were analysed with the statistical program Sigmastat® for Windows (version 2.0; SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant at $P < 0.05$.

## Results

Ketoconazole increased the plasma concentrations of rosiglitazone (Figure 1). After administration of ketoconazole, the mean AUC(0,∞) of rosiglitazone was increased by 47% ($P = 0.0003$). The elimination half-life of rosiglitazone was lengthened from 3.55 h to 5.50 h ($P = 0.0003$) and $C_{max}$ was also increased by 17% ($P = 0.03$; Table 1). The CL/F decreased about 30% after ketoconazole treatment compared with placebo treatment ($P = 0.0005$). The decrease in CL/F and the increases in $t_{1/2}$ and AUC after the ketoconazole treatment were observed in every subject (Figure 2).

## Discussion

Ketoconazole increased the AUC of rosiglitazone by 47% and decreased its oral clearance by 28% compared with placebo treatment. Theoretically, the potential for a drug interaction between two drugs may be low, because established data show that rosiglitazone is metabolized mainly by CYP2C8 and to a lesser extent CYP2C9 [4, 5] whereas ketoconazole is a potent inhibitor of CYP3A4 [8, 9]. In addition, it has been reported that the pharmacokinetics of rosiglitazone are unaffected by the various coadministered drugs [14–16]. By contrast, recently it has been reported that the pharmacokinetics of rosiglitazone are affected by the coadministered drugs [13, 17].

Considering the significant effect of ketoconazole on the pharmacokinetics of rosiglitazone in the present study, it is reasonable to postulate that ketoconazole may inhibit cytochrome P450 isoforms other than CYP3A4. Although ketoconazole is a potent inhibitor of CYP3A4 [9], some reports have shown that drugs that are not metabolized by CYP3A4 may be subject to drug interactions with ketoconazole [8, 9, 18]. In recent *in-vitro* studies, ketoconazole potently inhibited CYP2C8-catalysed paclitaxel and torsemide metabolisms [inhibitory constant ($K_i$) 2.5 μmol $l^{-1}$ and 11.8 μmol $l^{-1}$, respectively] [11, 12]. However, Baldwin *et al.* [5] showed ketoconazole did not inhibit rosiglitazone metabolism *in vitro* but using a concentration of ketoconazole (1 μM) far lower than usual therapeutic concentrations (5–20 μM for 200–400 mg daily) [7].

**Table 1**
Pharmacokinetic parameters of rosiglitazone in 10 healthy male Korean subjects after a single oral administration of 8 mg rosiglitazone following pretreatment with placebo or 200 mg ketoconazole twice daily for 5 days

| Variable | Placebo phase (control) | Ketoconazole phase | Mean difference between placebo and ketoconazole (95%CI) | P-value |
|---|---|---|---|---|
| $C_{max}$ (μg ml$^{-1}$) | 0.70 ± 0.22 | 0.81 ± 0.21* | 0.11 (0.01, 0.20) | 0.03 |
| Percentage of control (range) | 100% | 117% (91–155%) | 117% (105, 129) | |
| $t_{max}$ (h) | 1.0 (0.5–2.0) | 1.0 (0.5–2.5) | | 0.47 |
| $K_e$ (h$^{-1}$) | 0.20 ± 0.04 | 0.13 ± 0.02 | –0.07 (–0.09, –0.04) | 0.0004 |
| Half-life (h) | 3.55 ± 0.63 | 5.50 ± 1.35‡ | 1.75 (1.1, 2.4) | 0.0003 |
| Percentage of control (range) | 100% | 153% (120–252%) | 153% (130, 177) | |
| CL/F (l h$^{-1}$) | 2.14 ± 0.53 | 1.53 ± 0.53‡ | –0.6 (–0.35, –0.86) | 0.0005 |
| Percentage of control (range) | 100% | 72% (44–95%) | 72% (62, 82) | |
| AUC(0,14) (μg hm l$^{-1}$) | 3.69 ± 1.11 | 4.87 ± 1.60† | 1.18 (0.42, 1.94) | 0.007 |
| Percentage of control (range) | 100% | 133% (105–206%) | 133% (114, 151) | |
| AUC(0,∞) (μg hm l$^{-1}$) | 4.01 ± 1.25 | 5.87 ± 2.24† | 1.86 (0.72, 3.00) | 0.0003 |
| Percentage of control (range) | 100% | 147% (109–229%) | 147% (123, 170) | |

*Data are mean values ±SD; $t_{max}$ data are given as median with range; $C_{max}$, peak plasma concentration; $t_{max}$, time to peak concentration; $K_e$, elimination rate constant; AUC, area under the plasma concentration–time curve. *P < 0.05 versus control; †P < 0.01 versus control; P < 0.001 versus control.*

Although we did not determine the concentrations of ketoconazole, our results indicate that currently used doses of ketoconazole cause a drug interaction with rosiglitazone, probably by the inhibition of CYP2C8. Because of linear pharmacokinetic characteristics of ketoconazole, lower clinical doses (200 mg daily) may have a lesser effect on the pharmacokinetics of rosiglitazone and larger doses of ketoconazole (800–1600 mg daily) may have a greater effect. Our data suggest that ketoconazole may also cause drug interactions with other important therapeutic drugs mainly catalysed by CYP2C8 [19–22].

It has also been reported that ketoconazole prolongs $t_{1/2}$ and increases the AUC of tolbutamide, which is metabolized by CYP2C9 [18]. According to *in-vitro* studies from our laboratory (K.-A. Kim *et al.*, unpublished data), ketoconazole showed an inhibitory effect on not only CYP2C8-catalysed paclitaxel 6α-hydroxylation but also CYP2C9-catalysed S-warfarin 7-hydroxylation in human liver microsomes. Therefore, theoretically the increase in AUC of rosiglitazone could be mediated via the inhibition of CYP2C8- and CYP2C9-catalysed rosiglitazone metabolism by ketoconazole. Unfortunately, we only determined the concentrations of rosiglitazone up to 14 h after dosing, so that the AUC(0,∞) during ketoconazole treatment may not be accurate. However, considering the increase of around twofold in the concentrations at 14 h after dosing and a significant decrease in the elimination rate constant, the AUC estimates are probably valid.

Even though genetic polymorphisms of CYP2C8 and CYP2C9 are very rare in Korean populations [23, 24], they may affect plasma concentrations of rosiglitazone and its pharmacokinetics. However, we could find no available data on this.

The oral bioavailability of rosiglitazone in humans is about 99%, so it is not significantly metabolized during the first pass [4]. Even though the change of $C_{max}$ was significant after ketoconazole treatment, the increase was modest at 17%, and supports negligible first-pass metabolism of rosiglitazone. A previous report showed that gemfibrozil, a potent inhibitor of CYP2C8, affected rosiglitazone pharmacokinetics, with a similar change of $C_{max}$ as in our results [17].

Clinically, the onset of antihyperglycaemic activity is noted as early as 2 weeks of rosiglitazone therapy, with maximal response at 6 and 12 weeks [25]. Because the blood glucose-lowering effect of rosiglitazone shows dose and concentration dependence at steady state [1, 2, 25], it is reasonable to assume that coadministration of rosiglitazone and ketoconazole could increase the efficacy. Rosiglitazone therapy does not appear to cause the hepatotoxicity observed with other thiazolidinediones [1, 2, 25–27]. However, symptomatic peripheral

and pulmonary oedema is quite common and occasionally profound, even presenting as anasarca [28–30]. This has emerged as the most serious adverse event clinically, and there may be higher risk of this and other adverse events during concurrent use of ketoconazole and rosiglitazone [31]. However, there are no available data concerning the relation between the concentration of rosiglitazone and occurrence of oedema clinically.

Pioglitazole is also commercially available from the thiazolidinedione class and is metabolized by CYP3A4 and CYP2C8/9 [32]. Ketoconazole might be expected to cause a significant interaction with pioglitazone. In addition, even though there are no data on the inhibitory effects of other azole antifungal agents on rosiglitazone metabolism, other interactions are possible [33, 34].

In conclusion, ketoconazole modestly decreased the oral clearance of rosiglitazone in humans. The mechanism that underlies the interaction between ketoconazole and rosiglitazone probably involves the inhibition of CYP2C8- and CYP2C9-catalysed rosiglitazone metabolism by ketoconazole. Concomitant administration of ketoconazole could thus result in increased plasma concentrations of rosiglitazone with increased efficacy and/or adverse events.

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