Effect of Ketoconazole on Lobeglitazone Pharmacokinetics in Korean Volunteers

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ABSTRACT

Purpose: Lobeglitazone, a peroxisome proliferator–activated receptor-γ agonist, is metabolized primarily by the cytochrome P450 (CYP) 3A4 isoenzyme. Individuals concomitantly taking lobeglitazone and a CYP3A4 inhibitor may experience some adverse effects secondary to increased systemic exposure to lobeglitazone. To address such potential concern, we evaluated the effects of ketoconazole, a prototypic CYP3A4 inhibitor, on the pharmacokinetic (PK) properties and associated adverse effects of lobeglitazone.

Methods: A PK drug-drug interaction study was conducted in healthy individuals between 20 and 45 years old in a randomized, open-label, 2-way crossover design. Even though the PK study was performed on a single dose of lobeglitazone, multiple ketoconazole doses were given to ensure that the full extent of inhibition of CYP3A4 was maintained during the PK sampling. All study participants received a single oral dose of lobeglitazone 0.5 mg with or without 9 oral 200-mg doses of ketoconazole pretreatment twice daily. The primary PK parameter end points (AUC and C_{max}) were estimated using noncompartmental analysis, and the 90% CIs for the geometric mean ratios (ratio of lobeglitazone and ketoconazole to lobeglitazone alone) were investigated. Tolerability (adverse events, vital signs, ECG, and laboratory tests) was also assessed.

Findings: A total of 24 Korean men (mean age, 26 years; age range, 20-32 years; mean weight, 68 kg; weight range, 59-81 kg) completed the study and were evaluable for lobeglitazone PK properties and tolerability. The mean (SD) C_{max} values of lobeglitazone with and without ketoconazole were 49 (7) ng/mL and 48 (6) ng/mL at 1.5 and 1.0 hours after dosing, respectively. The mean (SD) AUC_{∞} values were 532 (117) ng · h/mL and 405 (110) ng · h/mL, respectively. Although the C_{max} was not significantly affected, the geometric mean ratio for AUC_{∞} was increased by a point estimate of 1.33 (90% CI, 1.23-1.44). A single oral administration of lobeglitazone 0.5 mg with or without ketoconazole pretreatment did not produce any clinically significant adverse effects on vital signs, 12-lead ECG profiles, or laboratory tests.

Implications: The administration of lobeglitazone, 0.5 mg alone or in combination with multiple doses of ketoconazole, was generally well tolerated. The systemic exposure of lobeglitazone was increased to a modest extent by pretreatment with 9 twice-daily doses of ketoconazole. Clinicaltrials.gov identifier: NCT01330563 (*Clin Ther*. 2014;36:1064–1071)

Key words: CYP3A4, drug interaction ketoconazole, lobeglitazone, pharmacokinetics.

INTRODUCTION

Diabetes mellitus is a multifaceted disorder characterized by chronic hyperglycemia resulting from the defects in insulin secretion, insulin action, or both.[1]

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Deficient insulin action involves various metabolic disturbances, including high triglyceride levels, low HDL-C levels, and particle changes in LDL-C, which are more atherogenic.[2] Insulin resistance was reported as a frequency >85% in the diabetic population without regional or environmental influence.[3]

Thiazolidinediones (TZDs), also known as glitazones, are synthetic ligands for peroxisome proliferator–activated receptor (PPAR)-γ that are expressed primarily on adipocytes and in muscle to a lesser extent.[4,5] PPAR-γ activation stimulates fatty acid storage in adipocytes, which leads to decreased availability of free fatty acid and adipocyte-derived signaling molecules and improves insulin sensitivity in skeletal muscle.[5–7] Rosiglitazone* and pioglitazone† are prototypic TZDs.[8–10]

Lobeglitazone (CKD-501), developed by Chong Kun Dang Pharmaceutical Corp (Seoul, Korea) and approved for marketing by the Ministry of Food and Drug Safety (Chungcheongbuk-do, Korea) in July 2013, contains a TZD motif and is a PPAR-γ agonist.[11,12] The half-maximal effective concentration for PPAR-γ of lobeglitazone was 0.14 μM, whereas those for the PPAR-γ agonists rosiglitazone and pioglitazone were 0.11 and 0.55 μM, respectively.[11–14] After a single oral dose of 0.5 mg/kg ^{14}C-lobeglitazone in bile duct ligated monkeys, the mean biliary, fecal, and urinary recoveries of the radioactive dose were 58%, 10%, and 6%, respectively (data was not shown). In healthy individuals, the unchanged drug excreted in urine was <0.01%.[15] Therefore, it is presumed that most oral lobeglitazone is eliminated as unchanged or as metabolites by bile excretion and fecal elimination. Lobeglitazone is highly bound to plasma proteins in vitro by >99%, mostly albumin. The major metabolic cytochrome P450 (CYP) isozyme was 3A4 based on the results of in vitro recombinant human P450s (rhCYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, 3A5, 2E1, and control) studies. Only 17% remained for CYP3A4 at the end of the assay at 1 μM lobeglitazone. At 10 μM, 37% of the substrate was depleted with CYP3A4, but it was stable at >80% with other isozymes (data was not shown). Pioglitazone is also excreted as metabolites or their conjugates with negligible renal elimination, and exposure increased to 3-fold when used with a strong CYP inhibitor for main metabolic enzyme, CYP2C8.[16]

*Trademark: Avandia® (GlaxoSmithKline, Brentford, England).
†Trademark: Actos® (Takeda Pharmaceuticals, Deerfield, Illinois).

Because CYP3A4 inhibitors are likely to inhibit lobeglitazone metabolism, the individuals concomitantly taking lobeglitazone and a CYP3A4 inhibitor may experience some adverse effects secondary to increased systemic exposure to lobeglitazone. Ketoconazole is a potent CYP3A4 inhibitor that will likely provide sensitive assessment.[17,18]

To determine the effect of a CYP3A4 inhibitor on the pharmacokinetic (PK) properties and adverse effects of lobeglitazone, the authors conducted a drug-drug interaction study. More specifically, the study was conducted in Korean volunteers to evaluate the effect of multiple ketoconazole doses on the single-dose PK properties of lobeglitazone in a randomized, open-label, 2-way crossover manner. The results of the study are reported in this article.

MATERIALS AND METHODS

Study Participants

The study was performed at the Clinical Trials Center of Severance Hospital (Seoul, Korea). Volunteers were recruited and allowed to participate in the study after signing written informed consent forms. The study protocol was approved by the institutional review board at Severance Hospital before the initiation of the study.

The volunteers 20 to 45 years old with a body mass index between 18.5 and 25 kg/m^2 were eligible to participate in this study. Volunteers with any clinically significant abnormalities on physical examination, medical history, 12-lead ECG, or clinical laboratory tests were not allowed in the study. The volunteers had to have negative urine drug screening results with no history of alcohol or drug abuse. The volunteers allergic or hypersensitive to the TZD class of drugs, such as rosiglitazone and pioglitazone, or those taking any TZD class of drugs were excluded. The volunteers were excluded if they were drinking excessive amount of caffeine (>5 cups of coffee per day) or smoking heavily (>10 cigarettes per day). Volunteers were excluded if they participated in a different clinical study or plasma apheresis within 30 days or donated blood within 60 days of the study start. Within 1 month before the start of the study, consumption of foods, herbal products, or medications known to inhibit or induce CYP3A4, CYP2D6, or CYP2C19 were also excluded. Ingestion of other prescription or herbal medications within 14 days or over-the-counter medications within 7 days of start of the study was not permitted.