Effect of Ketoconazole on the Pharmacokinetics of the Dipeptidyl Peptidase-4 Inhibitor Teneligliptin: An Open-Label Study in Healthy White Subjects in Germany

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ABSTRACT

Objective: The aim of this study was to examine the effect of ketoconazole, a potent cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp) inhibitor, on teneligliptin pharmacokinetics and to evaluate the safety of combined administration of teneligliptin with ketoconazole.

Methods: This open-label, fixed-sequence study was conducted in 16 healthy adult volunteers in Germany. On day 1, under fasting conditions, 20 mg of teneligliptin was administered to evaluate the pharmacokinetics of teneligliptin alone. For 3 days (days 8–10), 400 mg of ketoconazole was administered once daily. On day 11, teneligliptin 20 mg and ketoconazole 400 mg were concurrently administered, and for 2 days (days 12 and 13), ketoconazole was administered once daily. The pharmacokinetic parameters (C_{max}, T_{max}, AUC, terminal $t_{½}$, apparent total plasma clearance, and V_d during the terminal phase) of teneligliptin on days 1 and 11 were calculated. The safety profile was evaluated based on adverse events and clinical findings. To investigate the role of human P-gp in membrane permeation of teneligliptin, an in vitro study was performed to measure the transcellular transport of teneligliptin across monolayers of human P-gp-expressing cells and control cells.

Results: For C_{max} and AUC, the geometric least squares mean ratios (90% CIs) of teneligliptin with ketoconazole to teneligliptin alone were 1.37 (1.25–1.50) and 1.49 (1.39–1.60), respectively. There was no change in $t_{½}$ of the terminal elimination phase. In addition, the tolerability of teneligliptin coadministered with ketoconazole was acceptable. The in vitro study revealed corrected efflux ratios for teneligliptin of 6.81 and 5.27 at teneligliptin concentrations of 1 and 10 μM, respectively.

Conclusions: Because the exposure to teneligliptin in combined administration with ketoconazole, a potent CYP3A4 and P-gp inhibitor, was less than twice that of administration of teneligliptin alone, it is suggested that combined administration of teneligliptin with drugs and foods that inhibit CYP3A4 should not cause a marked increase in exposure. The results of our in vitro study suggest that teneligliptin is a substrate of P-gp. Clinical Trial Registration: EudraCT No. 2009-016652-51. (*Clin Ther.* 2014;36:760–769)

Key words: dipeptidyl peptidase-4 inhibitor, drug–drug interactions, ketoconazole, pharmacokinetics, teneligliptin.

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the small intestine in response to

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meal ingestion.[1] GLP-1 has an important role in regulating postprandial blood glucose levels because it stimulates insulin secretion in a glucose-dependent manner and inhibits glucagon secretion.[2] Despite its unique nature and desirable effects, such as the enhancement of pancreatic β-cell mass, inhibition of gastric emptying, and reduction of food intake,[3–6] the clinical use of GLP-1 is restricted because of its short half-life that is caused by rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4).[7,8] Therefore, DPP-4 inhibition has been viewed as a rational target for enhancing GLP-1 activity and thereby lowering blood glucose levels in a glucose-dependent manner.

Teneligliptin is a novel DPP-4 inhibitor that improves blood glucose levels over 24 hours with a 20-mg once-daily regimen in patients with type 2 diabetes mellitus, without causing hypoglycemic symptoms or serious adverse events (AEs).[9] In humans, teneligliptin is absorbed rapidly, and its plasma concentration profile exhibits biphasic elimination. AUC values for single doses of teneligliptin increase with doses from 2.5 to 320 mg in a dose-dependent manner (unpublished data). Approximately 66% of teneligliptin is eliminated by metabolism in the liver, and ~34% is excreted via the kidneys.[10] Major metabolizing enzymes involved in the metabolism of teneligliptin are cytochrome P450 (CYP) 3A4 and flavin-containing monooxygenase 3 (FMO3). However, because the metabolites produced by CYP3A4 and FMO3 are common to thiazolidine-1-oxide derivatives, the contribution of metabolic clearance by CYP3A4 to systemic clearance of teneligliptin in in vivo studies is unclear. Consequently, it is difficult to estimate the extent of increased exposure to teneligliptin during coadministration with CYP3A4 inhibitors. In addition, there are patients with diabetes mellitus who have concurrent hypertension who may be administered CYP3A4 inhibitors such as diltiazem; therefore, there is a need to investigate the extent of increase in exposure to teneligliptin when coadministered with CYP3A4 inhibitors. According to a 2010 review of the available data on drug–drug interactions for a range of other gliptins (sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin),[11] almost no drug–drug interactions or only minor drug–drug interactions have been reported between these DPP-4 inhibitors and a variety of other drugs (including glucose-lowering agents, statins and antihypertensive agents, CYP3A4/P-glycoprotein [P-gp] inhibitors such as ketoconazole and cyclosporine, and agents with a narrow therapeutic safety window such as warfarin). However, it is important for clinicians to be aware that the teneligliptin-metabolizing capacity of CYP3A4 is influenced by various medications, foods, and *CYP3A4* polymorphisms; therefore, the effects of CYP3A4 inhibitors should be quantified. The known potent CYP3A4 inhibitor ketoconazole is recommended in guidance on drug–drug interactions provided by the European Medicines Agency and the US Food and Drug Administration. The goal of the present study was to evaluate the pharmacokinetic effects and safety profile of the administration of teneligliptin at a dose of 20 mg once daily (which is an approved dosage regimen in Japan) combined with the CYP3A4 inhibitor ketoconazole. In light of previous findings,[10] the absorbed fraction of teneligliptin has been presumed to be favorable (43%–74%), and it has been inferred that teneligliptin is not readily influenced by P-gp inhibition in the small intestine. In addition, because teneligliptin has multiple elimination pathways, such as oxidative metabolism by CYP3A4 and FMO3 and renal excretion, the effect of single-enzyme inhibition is considered to be minor. It has thus been postulated that such drug–drug interactions are less likely to markedly increase exposure.

Given this background, the aim of our study was to quantify the extent of the increase in exposure caused by inhibiting CYP3A4 and P-gp after combined administration of teneligliptin with CYP3A4 or P-gp inhibitors. Because ketoconazole has an inhibitory action against the transport activity of P-gp,[12] we also performed an in vitro study to verify whether teneligliptin is a substrate of P-gp and investigate the role of human P-gp in membrane permeation of teneligliptin. We then discussed whether the influence of ketoconazole on P-gp might affect teneligliptin pharmacokinetics.

SUBJECTS AND METHODS

Clinical Study

Study Population

Healthy male and female white subjects aged between 18 and 64 years, weighing between 50 and 110 kg, and with a body mass index between 18 and 30 kg/m^2, including nonsmokers or social smokers (up to 5 cigarettes/d), who were willing and able to participate in the study were eligible for inclusion. Subjects were required to be free from clinically significant illness or disease as determined by a medical history, physical examination, and results of laboratory and other tests. No prescription or nonprescription