Pharmacokinetic Interaction of Finasteride With Tamsulosin Hydrochloride: An Open-Label, Randomized, 3-Period Crossover Study in Healthy Chinese Male Volunteers

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ABSTRACT

Purpose: The primary aim of this study was to evaluate whether there was clinically significant pharmacokinetic (PK) interaction between finasteride and tamsulosin in healthy Chinese male subjects.

Methods: This was an open-label, randomized, 3-period, crossover study. Subjects received single and multiple doses of 5 mg finasteride alone, single and multiple doses of 0.2 mg tamsulosin hydrochloride sustained-release capsule alone, and single and multiple doses of 5 mg finasteride with 0.2 mg tamsulosin hydrochloride, in an order determined by a computerized randomization schedule. Blood samples were collected up to 48 hours after dosing on study day 1 and up to 24 hours after dosing on study day 9 for determination of plasma concentrations with a validated LC-MS/MS method. Pharmacokinetic parameters were estimated via noncompartmental methods. Tolerability was evaluated by monitoring adverse events, laboratory assays, vital signs, and 12-lead ECG.

Findings: Fifteen subjects were enrolled, and 14 completed the study. The geometric mean ratios (GMRs) (90% CIs) of $AUC_{\tau,ss}$ and $C_{max,ss}$ values of finasteride at steady state between coadministration of finasteride and tamsulosin hydrochloride and finasteride alone were 1.14 (1.05–1.23) and 1.06 (0.99–1.14), respectively. The GMRs (90% CIs) for AUC_{0-t} and C_{max} values of finasteride for a single dose of coadministration of finasteride and tamsulosin hydrochloride and finasteride alone were 1.02 (0.94–1.11) and 1.06 (1.01–1.11), respectively. The GMRs (90% CIs) for $AUC_{\tau,ss}$ and $C_{max,ss}$ values of tamsulosin at steady-state for coadministration of finasteride and tamsulosin hydrochloride and tamsulosin hydrochloride alone were 1.18 (1.05–1.33) and 1.23 (1.06–1.43), respectively. The GMRs (90% CIs) for AUC_{0-t} and C_{max} values of tamsulosin for a single dose of coadministration of finasteride and tamsulosin hydrochloride and tamsulosin hydrochloride alone were 1.04 (0.97–1.10) and 1.04 (0.98–1.11), respectively. Statistical analyses confirmed that the 90% CIs for these PK parameters were within the predefined not clinically significant PK drug-drug interaction effect boundaries (0.5–2.0) in this study. If comparing the findings with narrower boundaries (0.8–1.25), the conclusion may not be supportive for tamsulosin hydrochloride. During the study, a total of 4 adverse events were reported in 3 subjects including allergic reaction, abnormal findings on an ECG, a slight increase in alanine aminotransferase, and a positive result on glucose urine test.

Implications: Both finasteride and tamsulosin hydrochloride were well tolerated. Coadministration of finasteride and tamulosin hydrochloride seems unlikely to lead to a clinically significant PK drug-drug interaction, after a single dose and at steady state. (*Clin Ther*. 2014;▮:▮▮▮–▮▮▮) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: drug-drug interaction, finasteride, healthy subjects, pharmacokinetics, tamsulosin hydrochloride.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic disease that affects as many as 50% of men by the age of

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50 years, and the incidence of BPH becomes higher with increasing age. If no timely treatment is given, it will lead to some serious complications such as kidney stones, urinary tract infection, and renal insufficiency. Medical therapy for BPH consists primarily of 5α-reductase inhibitors (5αRIs) such as finasteride and dutasteride and α_1 receptor antagonists (α_1 blockers) such as tamsulosin hydrochloride, terazosin, and doxazosin. Because 5αRIs and α_1 blockers have complementary mechanisms of action, it is plausible that 5αRIs combined with α_1 blockers could have an increased or even synergistic effect in the treatment of BPH. Recently, some clinical studies[1,2] and clinical practice showed that combination therapy with 5αRIs and α_1 blockers can provide significantly greater benefit than 5αRIs or α_1 blockers alone. In China, the instructions for tamsulosin hydrochloride administration specifically mentions that for the patient with BPH, a 5α-reductase inhibitor (such as finasteride* manufactured by Hangzhou MSD Pharmaceutical CO., LTD) should be added to the tamsulosin hydrochloride treatment regimen.

Finasteride is a 5α-reductase inhibitor that prevents the conversion of testosterone to dihydrotestosterone. The pharmacokinetic (PK) properties of finasteride in healthy adult subjects have been reported.[3,4] After oral administration, finasteride is rapidly absorbed, and C_{max} is generally reached within 1 to 2 hours. Finasteride is extensively metabolized in the liver, primarily via the cytochrome P-450 3A4 enzyme subfamily. Two metabolites, the t-butyl side-chain monohydroxylated and monocarboxylic acid metabolites, were identified that have no more than 20% of the 5α-reductase inhibitory activity of finasteride. After an oral dose of ^{14}C-labeled finasteride in a man, a mean of 39% of the dose is excreted in the urine in the form of metabolites and 57% is excreted in the feces. The $t_{½}$ in plasma was reported to be 6 hours in healthy young Western subjects. A longer $t_{½}$ and greater AUC were observed in subjects 70 years of age and older than in subjects 45 to 60 years of age.

Tamsulosin hydrochloride is a selective α_1-adrenoceptor antagonist that causes smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. The PK properties of tamsulosin in healthy adult subjects have also been reported.[5] Tamsulosin exhibits linear kinetics with doses ranging from 0.1 to 1.0 mg after single and multiple dosing, achieving steady-state concentrations by the fifth day of once-daily dosing. Food has effect on the oral bioavailability of tamsulosin. When tamsulosin hydrochloride is administered with food, the time to C_{max} (T_{max}) is prolonged, and AUC and C_{max} are decreased. Tamsulosin is extensively metabolized by cytochrome P-450 enzymes including CYP3A4 and CYP2D6 in the liver, and $<10\%$ of the dose is excreted in urine unchanged. The $t_{½}$ in plasma of a sustained-release capsule formulation is longer (9–13 hours in healthy subjects, 14–15 hours in BPH patients) than that of an intravenous or oral immediate-release formulation.

CYP enzyme induction or inhibition of the drug is one of the main reasons for a drug-drug interaction. Limited available information showed that strong inhibition of CYP2D6 (paroxetine) and CYP3A4 (ketoconazole) can lead to increased exposure of tamsulosin.[6] However, the available data regarding the PK interaction between finasteride and tamsulosin in healthy subjects or BPH patients is very rare. Only 1 available article suggested that coadministration of 5 mg finasteride once daily and 0.2 mg tamsulosin once daily did not affect the steady-state pharmacokinetics of the 2 agents.[7] According to the requirements of US Food and Drug Administration in China, before an international multiple-center Phase III study examining the safety and efficacy of coadministration of finasteride and tamsulosin hydrochloride in patients with BPH could be conducted, it is necessary to confirm the lack of a clinically significant PK drug-drug interaction between the 2 agents and to support the dose used of the 2 agents in the international multicenter Phase III study. Therefore, the aims of the current study were to evaluate the effect of coadministration of finasteride and tamsulosin hydrochloride on the PK parameters of finasteride and tamsulosin after single and multiple dose administration, to determine whether there is any clinically significant PK drug-drug interaction between finasteride and tamsulosin, and to assess the tolerability of the finasteride and tamsulosin hydrochloride in Chinese subjects.

METHODS

This open-label, randomized, 3-period, cross-over study was conducted at Clinical Pharmacology Center of Zhongshan Hospital in Shanghai, China. The

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