Effect of Fluconazole on the Pharmacokinetic Properties of Imrecoxib, a Novel NSAID: A Single-center, Open-label, Self-controlled Study in Healthy Chinese Male Volunteers

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ABSTRACT

Purpose: Imrecoxib is one type of cyclooxygenase-2 inhibitor with the capability of reducing the potential cardiovascular risk caused by other NSAIDs. Co-administration with other medications can affect the cytochrome P450 (CYP) 2C9 enzyme function; thus, imrecoxib metabolism can be affected. The purpose of this research was to evaluate the effects of fluconazole, which is known to inhibit CYP2C9, on imrecoxib's pharmacokinetic (PK) parameters.

Methods: In this single-center, single-arm, open-label, self-controlled study, 12 healthy Chinese male volunteers (mean [SD] age, 22.6 [2.43] years) received the following 2 treatments separated by a washout period of 8 days under a fasting state: (1) a single oral dose of imrecoxib 100 mg; and (2) fluconazole 200 mg/d over 6 days followed by concurrent dosing of imrecoxib 100 mg and fluconazole 200 mg. Plasma concentrations of imrecoxib (M0) and its metabolites (4′-hydroxymethyl metabolite [M1] and 4′-carboxylic acid metabolite [M2]) for PK analysis were obtained at 0 (baseline) and 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, and 72 hours after imrecoxib dosing. Safety and tolerability assessments were performed throughout the study.

Findings: All subjects completed the study. There was 1 adverse event; drug-induced liver damage in 1 subject occurred after he received imrecoxib plus fluconazole, and the subject recovered without any sequelae. Coadministration with fluconazole resulted in much higher plasma imrecoxib concentrations, with an increase of 88% in C_{max} and 72% in AUC_{0-t} compared with only imrecoxib treatment, which showed that fluconazole may increase plasma exposure to imrecoxib. Fluconazole also caused a small, but not clinically relevant, decrease in M1 and M2 mean C_{max} (13% and 14%, respectively), but there was minimal change in M1 and M2 mean AUC_{0-t} (3% and 2%). However, there were no statistically significant differences in vital signs, clinical laboratory test results, ECGs, or adverse events between treatments.

Implications: Concurrent administration of imrecoxib and fluconazole did not seem to change imrecoxib's safety profile. The ratio (imrecoxib + fluconazole/imrecoxib) for AUC_{0-t} was 1.72 (90% CI, 1.41−2.11) and for Cmax it was 1.88 (90% CI, 1.59−2.21). Hence, it is necessary to adjust the imrecoxib dose when it is concurrently used with other CYP2C9 inhibitors. (*Clin Ther.* 2018;40:1347−1356) © 2018 Elsevier Inc. All rights reserved.

Key words: COX-2 inhibitor, drug interaction, fluconazole, imrecoxib, pharmacokinetics, NASID.

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INTRODUCTION

NSAIDs are widely used to relieve pain and treat inflammation, although they have a number of adverse effects such as stomachache, gastritis, and gastrointestinal perforation, which may present a life-threatening condition.[1] The efficacy of these drugs is related to cyclooxygenase (COX)-1 and/or COX-2 inhibition, but inhibition of COX-1 is responsible for the more serious side effects. This issue seriously limits the clinical application of NSAIDs.[2–4] COX-2–targeted inhibitors are expected to be as clinically effective as nonselective ones but with fewer gastrointestinal risks compared with NSAIDs.[5–8] Nonselective NSAIDs exhibit less risk for triggering cardiovascular events than the COX-2–selective NSAIDs when they are used in the therapeutic process.[9–12] Thus, NSAIDs with moderate COX-2 selectivity might show more promising applications.[13–15]

Imrecoxib[4-(4-methane-sulfonyl-phenyl)-1-propyl-3-p-tolyl-1,5-dihydro-pyrrol-2-one], a novel and moderately selective COX-2 inhibitor recently developed by a Chinese pharmaceutical group, has an inhibitory effect on COX-1 and COX-2 in which the mean IC_{50} values for COX-1 and COX-2 are 18 (4) and 115 (28) nmol/L, respectively.[1,16] It has been proven that imrecoxib can relieve osteoarthritis pain as effectively as other NSAIDs, but it has an excellent gastrointestinal tolerability, which makes it a good choice for patients with arthritis. Imrecoxib undergoes a strong first-pass effect and is mainly eliminated by hepatic metabolism in humans with a minimal (<2%) amount of unchanged drug recovered in the urine and feces.[17] Imrecoxib's metabolism in the body occurs via several steps: (1) it is metabolized to the 4′-hydroxymethyl metabolite (M1); (2) it is further oxidized to the 4′-carboxylic acid metabolite (M2); and (3) it is mainly excreted in the feces as its major metabolite (M2) or the glucuronide conjugate of M2 in feces. Previous heterologous expression human cytochrome P450 (CYP) study in vitro showed that imrecoxib is metabolized by CYP2C9 (62.5%), CYP2D6 (21.1%), and CYP3A4 (16.4%).[18] CYP2C9 is also reportedly the major isoform involved in imrecoxib (60%) metabolism, with CYP3A4 and CYP2D6 each contributing ~20% in rats.[19,20] In vitro studies of the types and ratios of metabolic enzymes in humans are ongoing.

Fluconazole is widely used for the treatment of fungal infections via intravenous, infective, and/or oral methods. Fluconazole can inhibit CYP2C9, which may result in the active drug concentrations necessary for increased pesticide effects, thereby increasing the toxicity of the concurrent medications.[21] At the same time, fluconazole is also known as a moderate inhibitor of CYP3A4. If fluconazole interacts with imrecoxib, an increase in plasma imrecoxib concentrations and a reduction in the serum concentrations of the M1 and M2 metabolites may occur.[20,22]

To the best of our knowledge, there is currently no report available regarding the effects of fluconazole-mediated enzyme inhibition on imrecoxib's activity. Therefore, it was deemed necessary to assess possible drug–drug interactions (DDIs) between fluconazole and imrecoxib. With this theoretical background, the present study was designed to investigate the pharmacokinetic (PK) effects of fluconazole, a known strong inhibitor of CYP2C9, on an in vivo single oral dose of imrecoxib.

SUBJECTS AND METHODS

Subjects

Healthy Chinese male subjects between 18 and 40 years of age whose weight, height, and frame size were within 20% of the normal level were enrolled in the study. All of the volunteers were in good health according to their medical histories and results of their physical examinations, ECGs, laboratory tests (routine blood tests and blood chemistry, urine analyses, serologic detection, coagulation tests, and thyroid function), chest radiogram (direct and lateral side), and abdominal B-ultrasound examinations (liver, gallbladder, pancreas, spleen, and kidney). All laboratory tests, chest radiograms, and abdomen B-ultrasound examinations were performed at the Second Xiangya Hospital in Hunan Province, China, which is accredited by the Ethics Committee of the School of Pharmaceutical Science, Central South University. No congenital or chronic diseases were diagnosed in any subject, no histories of clinically significant diseases or drug hypersensitivities were identified, and no subject had HIV or hepatitis B or C.

Exclusion criteria for the subjects included several parameters: (1) use of any drugs that influence drug metabolism (eg, barbiturates, ketoconazole, phenytoin) within the 30-day period before receiving the experimental dosages; (2) use of prescription or over-the-counter medications within the 14-day period before dosing; (3) donating blood 60 days before drug