An Assessment of the Pharmacokinetics of a Sustained-Release Formulation of a Tramadol/Acetaminophen Combination in Healthy Subjects

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ABSTRACT

Purpose: To provide consistent pain relief and improve convenient sustained release (SR), a fixed-dose combination tramadol/acetaminophen tablet was formulated. This study aimed to evaluate the pharmacokinetic profiles of an SR 75-mg tramadol/650-mg acetaminophen formulation after a single dose compared with an immediate release (IR) 37.5-mg tramadol/325-mg acetaminophen formulation after 2 doses and at steady state and to assess the effect of food on the pharmacokinetic SR formulation profile after a single dose.

Methods: Two clinical trials were conducted: (1) an open-label, randomized, 3-period, 3-treatment, crossover study to assess the pharmacokinetic SR (one 75-mg tramadol/650-mg acetaminophen combination tablet) formulation profiles after a single dose and IR (one 37.5-mg tramadol/325-mg acetaminophen combination tablet q6h for 2 doses) formulation profiles after 2 doses and the effect of food intake on healthy male subjects and (2) an open, randomized, 2-period, 2-treatment multiple dose crossover study to evaluate the steady-state pharmacokinetic SR and IR formulation profiles. Safety assessments were performed.

Findings: Forty-three subjects completed each study protocol. The SR combination tramadol/acetaminophen formulation was clinically and statistically equivalent to the IR combination formulation in the fasting state. When tramadol and acetaminophen tablets were administered with food, the time to peak plasma concentrations and the tramadol/acetaminophen absorption were unaffected. There was no serious adverse event reported.

Implications: The SR combination tramadol/acetaminophen tablet exhibited similar exposure and absorption rates compared with those of the IR formulation of tramadol, O-desmethyltramadol, and acetaminophen. The SR formulation may be more convenient for patients and has the potential to enhance compliance and pain control. ClinicalTrials.gov identifier: NCT01880125 (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: acetaminophen, food effect, pharmacokinetics, sustained release, tramadol.

INTRODUCTION

Conventional analgesics are classified as either opioids or nonopioids. Opioid analgesics relieve pain by acting directly on the central nervous system, whereas nonopioid analgesics are often used for treating acute postoperative pain. Nonopioids act on peripheral and central sites and interfere with pain mechanisms that are functionally different from the opioid pathway.[1]

Tramadol is a centrally acting opioid analgesic that is used as its racemate, (−)-tramadol and (+)-tramadol, both of which act synergistically to alleviate pain.[2,3] Tramadol binds weakly to μ-opioid receptors and

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inhibits the reuptake of norepinephrine and serotonin (5-hydroxytryptamine).[4,5] Tramadol is extensively metabolized in the liver. The O-desmethyltramadol metabolite (M1) of tramadol contributes to the opioid component of tramadol-induced analgesia, with an ~200-fold increased affinity for opioid receptors than the parent drug.[2,3]

Acetaminophen, a nonopioid analgesic, is widely used for pain management as an alternative to nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors. Although the mechanism of action is unclear, acetaminophen appears to act centrally by inhibiting either *N*-methyl-D-aspartate or substance P–mediated nitric oxide synthesis.[6] It may also inhibit the release of prostaglandin E_2 in the central nervous system.[2,7]

Combining agents that have complementary modes of action and target multiple sites, such as tramadol and acetaminophen, may potentially provide a better analgesic effect in several types and sources of pain.[4,5] In clinical trials, tramadol plus acetaminophen provided effective pain relief in both acute and chronic pain management.[8–10]

A fixed-dose combination tablet of 37.5 mg tramadol and 325 mg acetaminophen is marketed worldwide. The recommended dose of this combination is 2 tablets q4h or q6h as needed for pain relief up to a maximum of 8 tablets per day.[11] However, such multiple dosing regimens are inconvenient. To provide consistent pain relief and improve convenient, sustained release (SR) formulation of 75 mg tramadol and 650 mg acetaminophen combination (YJAT-SR) is being developed by Yungjin Pharmaceutical Co Ltd (Seoul, Republic of Korea). This new formulation, which includes an immediate-release (IR) portion and a SR portion, provides rapid-onset and long-lasting pain relief.

The coadministration of food with oral drugs can alter drug bioavailability through various means, including delayed gastric emptying, stimulation of bile flow, altered gastrointestinal pH, increased splanchnic blood flow, and physical or chemical interactions with the formulation.[12] Generally, SR drug formulations are designed to prolong the duration of efficacy and have higher drug contents compared with conventional formulations. Food consumption may have a marked effect on the systemic availability of a drug, including a serious and prolonged effect on circulating drug levels.[13] Therefore, a food-effect study should be conducted for an SR formulation.

The aim of this study was to evaluate the pharmacokinetic profile of an SR formulation of 75 mg tramadol and 650 mg acetaminophen combination after a single dose compared with an IR formulation of 37.5 mg tramadol and 325 mg acetaminophen combination after 2 doses and at steady state, as well as to assess the effect of food on the pharmacokinetic profile of the SR formulation of 75 mg tramadol and 650 mg acetaminophen combination after a single dose. Bioequivalence is concluded if the average bioavailability of the SR formulation is within 80% to 125% that of the IR formulation, with a certain assurance.

SUBJECTS AND METHODS

Two clinical studies were designed to assess the pharmacokinetics of tramadol/acetaminophen under various conditions. Part I was a Phase I study evaluating the pharmacokinetic profile of the SR formulation after a single dose compared with the IR formulation after 2 doses and an assessment of the effect of food on the SR formulation after a single dose. Part II was a Phase I study evaluating the pharmacokinetic profile of the SR formulation compared with the IR formulation after steady-state administration. This study was approved by the Korea Food and Drug Administration and the Institutional Review Board of Chonbuk National University Hospital (Jeonju, Republic of Korea) and was conducted according to the Declaration of Helsinki for biomedical research involving human subjects and the Guidelines for Good Clinical Practice. Written informed consent was obtained from all participants before screening.

Subjects

The study enrolled healthy Korean male volunteers 20 to 45 years of age who weighed ≥45 kg and were within 20% of their ideal body weights (based on height). The subjects were screened to confirm their health status by physical examination, vital sign measurement, 12-lead ECG, and routine laboratory assessments (ie, hematology, chemistry, urinalysis, serology, and urine drug screening) performed during the 3 weeks before the first administration of the study drug.

The following exclusion criteria were applied: hypersensitivity or history of sensitivity to either tramadol or acetaminophen; evidence or history of

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