Original Research

Effect of Modulated Electrohyperthermia on the Pharmacokinetics of Oral Transmucosal Fentanyl Citrate in Healthy Volunteers

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ABSTRACT

Purpose: This study aimed to determine whether changes occur in fentanyl absorption and disposition when administered in conjunction with modulated electrohyperthermia (mEHT) treatment.

Methods: A randomized, single-dose, crossover, open-label study was used to investigate the effect of mEHT on the pharmacokinetic properties of fentanyl in 12 healthy volunteers. The 12 healthy volunteers were each administered a single dose of oral transmucosal fentanyl citrate (OTFC) or a single dose of OTFC with mEHT. mEHT was performed on the abdomen for 1 hour. Blood samples were collected for 24 hours after dosing. The temperature of the abdominal skin surface was assessed before dosing and at 10, 20, and 60 minutes after dosing.

Findings: Geometric mean ratios (ratio of fentanyl with mEHT to fentanyl alone) for the C_{max} and AUC_{0-last} were 1.20 (90% CI, 1.09–1.32) and 1.15 (90% CI, 0.99–1.33), respectively. The mean temperature of the abdominal skin surface increased by approximately 4°C.

Implications: There was an increase in the overall exposure to the drug without implications of any clinical significance. OTFC can be administered without limitations in combination with mEHT, and it is not necessary to modify the dosing regimen. cris.nih.go,kr Identifier: KCT0001286. (*Clin Ther.* 2016;38:2548–2554)

Key words: clinical trial, electrohyperthermia, fentanyl, pharmacokinetics, temperature of the abdominal skin surface.

INTRODUCTION

Hyperthermia has long been used for pain management, even in ancient medical practices.[1] A higher local tissue temperature induces vasodilation, which enables greater oxygen transfer due to increased local blood flow and reduces pain.[2] A higher blood flow increases the delivery of nutrients and eliminates carbon dioxide, metabolic waste, and inflammatory chemical mediators. Increased local blood flow also affects the treatment efficacy of the heated target.

Modulated electrohyperthermia (mEHT) is the next-generation medical innovation that delivers selective, controlled, and deep energy treatments using the capacitive-coupled energy of 13.56-MHz amplitude-modulated radiofrequency for cancer therapy.[3,4] Malignant cells are selectively heated, affecting the cell membranes[5] and inducing apoptosis at mild temperatures ($\leq$42°C).[4,6] This treatment promotes immunogenic cell death.[7,8] The mEHT does not cause pain and causes few adverse effects (AEs), resulting in improved efficacy and quality of life.[9] Moreover, patients treated with mEHT have reported pain relief[10] and, as a result, have used decreased doses of analgesics.[11]

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia.[12] Fentanyl binds to μ-opioid receptors in various locations of the central nervous system and relieves pain by increasing pain

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thresholds, changing pain sensations, and inhibiting ascending pain pathways.[13] Fentanyl is generally considered 50 to 100 times more potent than morphine.[13]

The fentanyl citrate oral transmucosal lozenge* is a solid formulation of fentanyl citrate delivered on a plastic stick. Generic fentanyl citrate is a form of oral transmucosal fentanyl citrate (OTFC). The absorption pharmacokinetic properties of OTFC works via initial rapid absorption through the buccal mucosa and prolonged absorption through the gastrointestinal (GI) tract.[14] The peak blood concentration is observed 20 to 40 minutes after the initiation of OTFC application.[13] Thus, OTFC is used to treat breakthrough pain in patients with cancer who already received and are tolerant to around-the-clock opioid therapies for underlying persistent cancer pain.[14,15] The analgesic effect of OTFC is related to the blood concentration of fentanyl at a range of 0.3 to 1.2 ng/mL, and levels in excess of 10 to 20 ng/mL are associated with surgical anesthesia and respiratory depression.[16]

OTFC is often consumed during mEHT therapy. The heat with radiation would be influenced by the heat-induced changes in regional blood flow.[17] mEHT may affect the pharmacokinetic properties of fentanyl because of changes in the regional blood flow. The unexpected AEs can be caused by changes in the fentanyl concentration. Therefore, we examined the effects of mEHT on the pharmacokinetic properties of fentanyl in healthy volunteers.

SUBJECTS AND METHODS

This study was approved by the Ministry of Food and Drug Safety and the Institutional Review Board of Chonbuk National University Hospital. This study was conducted according to the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki and according to the Good Clinical Practice guidelines. Written informed consent was obtained from each participant before screening, and a detailed explanation of the study was provided.

Healthy male and female volunteers aged 19 to 55 years with body mass indexes ranging from 17.5 to 30.5 kg/m^2 were enrolled in the study. The health of each subject was confirmed via physical examinations, measurements of vital signs, and clinical laboratory assessments (ie, hematology, biochemistry, serology, urinalysis, and urine human chorionic gonadotropin tests for females of childbearing potential). Subjects were excluded if they had taken any prescription medications or over-the-counter drugs within 10 days before the first administration of OTFC. Subjects were also excluded if their sitting blood pressure decreased in the following ranges during the screening procedure: systolic blood pressure $\geq$140 mm Hg and diastolic blood pressure $\geq$90 mm Hg. Subjects were required to abstain from taking any medication without prior consent of the investigator and from drinking alcohol, smoking, and consuming food or beverages that contained caffeine during the study period. All subjects were asked to abstain from taking food or beverages that contained grapefruit for 7 days before the first administration to the discharge of the second admission.

This study was conducted as an open-label, randomized-sequence, 2-period, 2-treatment, single-dose, 2-way crossover trial at the Clinical Trial Center of Chonbuk National University Hospital, Jeonju, Republic of Korea. All subjects were randomly assigned to 1 of 2 treatment sequence groups: AB or BA. The 2 treatments were as follows: (A) 0.3142 mg of OTFC (Hyundai Pharmaceutical Inc, Seoul, Republic of Korea), which is equivalent to 0.2 mg of fentanyl free base and (B) 0.3142 mg of OTFC with mEHT. Each sequence group consisted of 6 subjects. Each period was followed by a 1-week washout period.

On the first day of each period, all subjects were administered OTFC on day 1 at the clinical facility. OTFC was presented as a sweetened lozenge with an integral oromucosal applicator (unit) for oral administration by sucking not chewing. A unit dose of OTFC, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed because the generally observed 50% bioavailability of OTFC is divided equally between rapid transmucosal and slower GI absorption. Subjects should place the OTFC unit in their mouths between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. Subjects were instructed to consume the total dose within 15 minutes. All subjects received OTFC within 15 minutes. The unit was not to be bitten, chewed, or swallowed. Each

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