Original Article

A Randomized, Double-Blind, Placebo-Controlled Study of Fentanyl Buccal Tablets for Breakthrough Pain: Efficacy and Safety in Japanese Cancer Patients

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Abstract

Context. Rapid-onset opioids for treating breakthrough pain (BTP) in patients with cancer are needed in the Japanese care setting.

Objectives. To examine the efficacy and safety of fentanyl buccal tablets (FBTs) for treating BTP in Japanese cancer patients.

Methods. This was a randomized, double-blinded, placebo-controlled study. In subjects receiving around-the-clock (ATC) opioids at doses of 30 mg or more to less than 60 mg or 60−1000 mg of oral morphine equivalents (low and high ATC groups), dose titration was started from 50 to 100 μg FBT, respectively. Subjects whose effective dose was identified were randomly allocated to a prearranged administration order of nine tablets (six FBTs and three placebos), one tablet each for nine episodes of BTP (double blinded). Efficacy and safety of FBT were assessed for patients overall, and also for the low and high ATC groups.

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Results. A significant difference was observed between FBT and placebo for the primary endpoint of pain intensity difference at 30 minutes. The analgesic onset of FBT was observed from 15 minutes in several secondary variables (e.g., pain relief). Adverse events were somnolence and other events associated with opioids were mostly mild or moderate. Of the low and high ATC group subjects, an effective FBT dose was identified in 72.2% and 73.1%, respectively.

Conclusion. The safety of FBT and its analgesic effect on BTP were confirmed in Japanese cancer patients receiving opioids. Our findings suggest that analgesic onset may occur from 15 minutes after FBT, and that FBT can be administered to patients with low doses of ATC opioids. J Pain Symptom Manage 2014;47:990–1000.

Key Words

Fentanyl buccal tablet, breakthrough pain, cancer pain, rapid-onset opioids, palliative medicine, oral transmucosal opioid

Introduction

Patients with advanced cancer usually have many symptoms that impair their quality of life. Pain can be unbearable and has a great effect on reducing the quality of life. Approximately 80% of patients with cancer experience severe pain until the end of life.[1] In most cases, cancer pain is persistent and requires chronic opioid treatment, so management is extremely important. However, regardless of how persistent pain is controlled, moderate or severe pain occurs abruptly and transiently. The onset or intensification of such pain is referred to as breakthrough pain (BTP). The time from the onset of BTP to its peak ranges from one to three minutes, and the median BTP duration is up to 120 minutes.[2–4] BTP is experienced by 50–60% of hospitalized patients[2,5] and by 89% of those in hospices,[6] occurring at a frequency of one to six times per day.[2–4] The occurrence of BTP is unpredictable in 40–50% of cases regardless of the subtype or cause.[7] Therefore, BTP is treated using rapid-onset opioids as supplemental medication. According to the guidelines of the European Association for Palliative Care, BTP can be effectively managed using immediate-release opioid formulations. In some cases, buccal or intranasal fentanyl formulations are preferable to immediate-release oral opioids because of a more rapid onset of action and shorter duration of effect.[8] In addition, the onset of analgesia of traditional short-acting opioids (including morphine and oxycodone) occurs after the time of peak intensity for many BTP episodes.[3,9,10] Rapid-onset opioids more closely match the profile of a typical BTP episode[11–13] and, therefore, are more useful as supplemental medication. In Japan, however, only morphine, oxycodone, and fentanyl injection are available as supplemental medication. Therefore, easy-to-use rapid-onset opioids such as the fentanyl buccal tablet (FBT) are needed.

Tolerance for opioids is a prerequisite for using FBT as a supplemental medication. In Western countries, patients who receive a fixed-schedule, around-the-clock (ATC) administration of at least 60 mg of oral morphine equivalents per day for at least one week are considered tolerant to opioids. The effective dose of FBT is determined for each patient by titrating from a starting dose of 100 μg to a maximum of 800 μg. However, because Japanese individuals generally weigh less compared with the Western individuals, a lower ATC starting dose may be better tolerated in Japanese cancer patients,[14] and many receive ATC administration at a dose below 60 mg morphine equivalents per day. Therefore, in regard to opioid tolerance, it was assumed that a starting FBT dose of 50 μg would be better for many Japanese cancer patients who receive low ATC doses (between 30 and less than 60 mg/day).

We conducted a double-blinded, placebo-controlled study to examine the efficacy and safety of FBT for treating BTP in Japanese cancer patients. In regard to safety, we titrated the FBT dose from 50 μg in patients who were receiving low ATC doses.