Original Article

Fentanyl Buccal Tablet vs. Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Randomized, Crossover, Comparison Study

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Abstract

Context. Fentanyl products have shown superiority to oral opioids for the management of breakthrough cancer pain (BTcP). However, these studies did not use appropriate patient selection, and drugs have been compared by using different rationales.

Objectives. The aim of this randomized, crossover, controlled study was to compare efficacy and safety of fentanyl buccal tablets (FBTs) and oral morphine (OM), given in doses proportional to opioid daily doses.

Methods. Cancer patients with pain receiving ≥60 mg or more of oral morphine equivalents per day and presenting with ≤3 episodes of BTcP per day were included. In a randomized, crossover manner, patients received FBT or OM at doses proportional to the daily opioid regimen in four consecutive episodes of BTcP. Pain intensity was measured before (T0) and 15 (T15) and 30 minutes (T30), after study drugs.

Results. In total, 263 episodes of BTcP were treated. A statistical difference in changes in pain intensity—decrease of ≥33% and ≥50%—between the two groups was observed at T15 and T30 ($P < 0.0005$). No severe adverse effects after study drug administration were observed.

Conclusion. When used in doses proportional to the basal opioid regimen, FBT showed a clear superiority and was well tolerated when compared with OM during the first 30 minutes, which is the approximate target for a timely intervention required for a BTcP medication. J Pain Symptom Manage 2015;■:■−■. © *2015 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Cancer pain, breakthrough pain, fentanyl buccal tablet, oral morphine

Introduction

Breakthrough cancer pain (BTcP) has been defined as a transitory increase in pain intensity that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.[1] BTcP is a common problem in patients with cancer and is associated with significant morbidity. In a recent report in which a pragmatic definition of BTcP was used,[2] the prevalence of BTcP was 75%.[3]

Oral morphine (OM) has been traditionally offered as a BTcP medication in doses of about 1/6 of the daily opioid regimen, although this approach has never been supported by any evidence.[4] Different

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technologies have been developed to provide a rapid onset of effect with potent opioid drugs such as fentanyl (rapid onset opioids [ROOs]) delivered by noninvasive routes. It has been suggested that the dose of fentanyl should be individually titrated to enable effective analgesia to be delivered while minimizing the risk of clinically significant adverse effects.[2] However, there is no evidence for dose titration as these studies were aimed to demonstrate superiority of ROOs over placebo or OM. [5] The need for dose titration with ROOs has never been appropriately assessed, as evidenced by a series of weaknesses in articles published for regulatory reasons.[6,7] Indeed, the only existing study comparing dose titration and proportional doses reported that proportional doses of fentanyl buccal tablets (FBTs) are more effective and safer than a dose titration method, particularly in patients receiving higher doses of opioids for background pain[8]; this confirms data reported with different fentanyl products, at home, in high doses, and in the elderly.[9–14]

From a practical point of view, the need to titrate opioid doses for BTcP may make the practical use of ROOs difficult in daily practice, particularly at home or in outpatient setting, and most patients could prefer, in the end, to use OM. [15]

All the studies have shown the superiority of the different ROOs over OM. [16–25] NICE guidelines, however, did not provide evidence for that, at least at certain time intervals after administration.[26] To scientifically compare ROOs and OM, a similar approach should be used, while using a strict selection of patients, according to a more specific algorithm for a diagnosis of BTcP.[3,27,28] The aim of this randomized, crossover, controlled study was to compare the efficacy and safety of FBT and OM, both given in doses proportional to daily opioid doses, for the management of BTcP. The primary outcomes were the changes in pain intensity, and the number of episodes with a decrease in pain intensity of ≥33% and ≥50%, recorded 15 and 30 minutes after study medication. The secondary outcome was the number of episodes in which patients reported adverse effects attributed to study medication and the level of satisfaction with the treatments.

Methods

This was a multicenter, randomized, crossover, controlled study, performed in acute palliative care or pain therapy units. The study was approved by Institutional Review Board of the University of Palermo, and all participating patients provided informed consent.

Participants

Adults were eligible if they had a diagnosis of cancer, were receiving opioids at doses that were ≥60 mg oral morphine equivalents (OMEs) per day for background pain, had stable well-controlled pain, with background of mild intensity (≤4 on a 0–10 numerical rating scale [NRS]), and had one to three episodes of BTcP per day.

Patients with unstable or uncontrolled pain (>4 on a 0–10 NRS) were not eligible for the study. Exclusion criteria also included past inability to tolerate the study drugs, treatment with monoamine oxidase inhibitors, recent antineoplastic treatment, history of alcohol or substance abuse, an expected short survival, and cognitive impairment. Other pharmacologic treatments were maintained if administered for at least two weeks. Patients with relevant problems of the oral mucosa also were not eligible.

Interventions

Consenting patients who met the inclusion criteria were assessed for four consecutive BTcP episodes. Patients were treated according to a routine protocol. After establishing around-the-clock opioid medication according to an opioid titration process and achieving a stable analgesia, with a mean pain intensity ≤4/10 on a 0–10 NRS for two consecutive days, patients were instructed to call for a BTcP medication when their pain got severe or was clearly distinguishable from their background pain. The study period was three days. Patients randomly received FBT or OM in a crossover design (two episodes for each study drug), in doses proportional to those used for background analgesia for two episodes. For example, the minimal existing dose of 100 μg of FBT or OM 10 mg was given to patients receiving 60 mg of OME; 200 μg of FBT or 20 mg of OM were given to patients receiving 120 mg of OME; 300 μg of FBT or 30 mg of OM were given to patients receiving 180 mg of OME and so on. Intermediate dosing was done with the lower rounded dose. The choice of the doses was based on previous experiences, the availability of FBT and OM, and studies comparing BTcP medications.[10,28,29] For example, 100 μg of FBT and 10 mg of OM are commonly suggested for patients receiving 60 mg OME, and the same approach was used for higher doses.

For each BTcP episode, nurses recorded pain intensity (0–10 NRS) and severe enough adverse effects intensity to require medical intervention, just before (T0) and 15 minutes (T15) and 30 minutes (T30) after starting the FBT or OM medication. Patients who were not satisfied with the treatment could stop the procedure and ask for their previous effective BTcP medication.

Outcomes

The principal outcome was the change in pain intensity of events treated with study medications, and