Original Article

Fentanyl Pectin Nasal Spray Versus Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Comparative Study

Sebastiano Mercadante, MD, Federica Aielli, MD, Claudio Adile, MD, Andrea Costanzi, MD, and Alessandra Casuccio, BS

Anesthesia and Intensive Care Unit and Pain Relief and Palliative Care Unit (S.M., C.A.), La Maddalena Cancer Center, Palermo; Department of Biotechnological and Applied Clinical Sciences (F.A.), University of L'Aquila, L'Aquila; Department of Oncology (A.C.), Hospital Sant'Andrea, University of Rome, Rome; and Department of Experimental Biomedicine and Clinical Neuroscience (A.C.), University of Palermo, Palermo, Italy

Abstract

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

Objectives. The aim of this randomized, crossover, controlled study was to compare the efficacy and safety of fentanyl pectin nasal spray (FPNS) and oral morphine (OM), given in doses proportional to opioid daily doses.

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

Results. A total of 167 episodes were treated, 82 with FNPS and 85 with OM. A statistical difference in pain intensity between the two groups was observed at T15, but not at T30 ($P = 0.018$ and $P = 0.204$, respectively). In a greater number of episodes treated with FPNS, there was a pain decrease of ≥33% in comparison with OM after 15 and 30 minutes (76.5% vs. 32.8%, and 89% vs. 54.9%, respectively). Similar differences were found in the decrease in pain intensity of ≥50% after 15 and 30 minutes (52.3% vs. 11.4%, and 75% vs. 45.8%, respectively). The difference was highly significant at T15 ($P < 0.0005$). The mean (SD) pain difference at T15 of FPNS and OM were 3.24 (1.7) and 2.70 (1.2), respectively, whereas the mean (SD) SPIDs30 of FPNS and OM were 4.87 (1.7) and 4.54 (1.5), respectively. The difference was highly significant at T15 ($P = 0.019$). No severe adverse effects after study drug administration were observed.

Conclusion. When used in doses proportional to the basal opioid regimen, FPNS showed a superior analgesic effect over OM for the management of BTcP. Only minor adverse effects were found with both medications. J Pain Symptom Manage 2016;52:27–34.

Key Words

Cancer pain, breakthrough pain, fentanyl pectin nasal spray, oral morphine

Introduction

Breakthrough cancer pain (BTcP) has been traditionally considered as a transitory peak in pain intensity, occurring spontaneously or in relation to a specific trigger, but with the patient reporting stable and well-controlled background pain.[1–6] BTcP is frequently reported in cancer patients and is

Address correspondence to: Sebastiano Mercadante, MD, Anesthesia and Intensive Care Unit and Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Via san Lorenzo 312, 90145 Palermo, Italy. E-mail: terapiadeldolore@lamaddalenanet.it

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associated with a relevant morbidity.[7] Despite different definitions and methodologies that have been used in different surveys,[8] 50%–90% of cancer pain patients experience an increase in pain intensity.

Oral opioids given as needed in addition to the background analgesic medication are commonly used to manage these episodes. The temporal pattern of BTcP is characterized by a rapid onset and a short duration. Accordingly, different technologies have been developed to provide a timely onset of analgesia with potent opioids, such as fentanyl (rapid onset opioids [ROOs]), delivered by noninvasive routes.[9] The dose of fentanyl to be administered should be individually titrated to enable effective analgesia and to minimize the risk of adverse effects.[10] Although this statement has been quoted by evidence "B," no scientific evidence supports this approach. In fact, these studies were designed to demonstrate superiority of ROOs over placebo or OM, after achieving an effective dose with dose titration. This approach has never been appropriately assessed and was based on a series of studies that were designed for regulatory issues.[8,11–13] Indeed, a recent study showed that doses of fentanyl buccal tablet (FBT) given in proportional doses were more effective and safe over doses achieved after dose titration, particularly in patients who were receiving higher doses of opioids for background analgesia.[14] This study confirmed a large experience previously reported with different medications, including intravenous morphine and ROOs, even at home, in high doses, and in the elderly.[15–23]

In daily practice, the need of titrating opioid doses for BTcP may render the use of ROOs problematic, especially in home care patients or in outpatients. Patients may be reluctant to find the dose and could avoid use of the ROO, preferring, at the end, the simplicity of oral dosing of morphine, which is commonly administered in doses proportional to the basal opioid regimen.[24]

Studies comparing the various types of ROOs with OM have been performed by using dose titration up to the effective dose for ROOs and imprecise doses of OM.[8,11,12] All these studies have shown the superiority of the different ROOs over OM.[25] NICE guidelines, however, do not suggest that ROOs are more effective than OM for the management of BTcP, particularly at certain time intervals after drug administration. This consideration also was presumably based on cost impact.[26]

OM is commonly given in doses proportional to the basal opioid regimen.[27] As a consequence, to scientifically compare ROOs and OM, similar approaches should be used. Fentanyl pectin nasal spray (FPNS) is a pectin-based delivery system. The nasal route may allow transmucosal fentanyl delivery in patients with oral problems preventing adequate absorption.[28]

The aim of this comparison randomized, crossover, controlled study was to assess the efficacy and safety of doses of FPNS vs. OM, both given in doses proportional to opioid doses used for background analgesia, for the management of BTcP. The primary outcome was the number of episodes in which there was a decrease in pain intensity of ≥33% and ≥50%, 15 and 30 minutes after drug administration. The secondary outcome was the assessment of adverse effect intensity and the level of patients' satisfaction with the medications.

Methods

This comparison randomized, crossover, open-label study was conducted in two specialistic units of acute pain relief and supportive care. The study was approved by the institutional review board. All participating patients provided informed consent.

Patients

Adults were eligible if they had a cancer diagnosis, presented with a stable background analgesia (more than three days) of ≤4/10 on a 0–10 numerical scale, and were tolerant to stable doses of ≥60 mg OM equivalents/day for the management of background pain, and were presenting one to three episodes of BTcP/day. Patients with unstable or uncontrolled pain (intensity >5 to 10 on a numerical scale) were not eligible for the study. If patients required changes in baseline opioid doses, they discontinued the study. Criteria for exclusion included BTcP not primarily related to cancer, an expected short survival, a past inability to tolerate opioids, a previous or concomitant use of monoamine oxidase inhibitors, concomitant or recent antineoplastic therapy, history of alcohol or substance abuse, and cognitive impairment. Other drugs were continued if they had been administered for at least two weeks. Patients with problems related to the nasal mucosa were excluded.

Procedures

Consenting patients who met inclusion and exclusion criteria were evaluated for four consecutive BTP episodes occurring within three consecutive days. Patients were recruited by a doctor, after examining the inclusion and exclusion criteria. Pain intensity was measured by a 0–10 numerical scale. Patients were treated according to a standard protocol. After achieving an acceptable background analgesia (with a pain intensity of ≤4/10), for two consecutive days, with opioids given around the clock, patients were instructed to call when pain increased and was clearly distinguishable from their baseline pain. Each patient randomly received FNPS or OM by administering