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Fentanyl pectin nasal spray as treatment for incident predictable breakthrough pain (BTP) in oral mucositis induced by chemoradiotherapy in head and neck cancer

Paolo Bossi *, Laura Locati, Cristiana Bergamini, Aurora Mirabile, Roberta Granata, Martina Imbimbo, Carlo Resteghini, Lisa Licitra

Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

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SUMMARY

Background: Painful mucositis is one of the most distressing toxicities of chemoradiotherapy (CRT) for head and neck cancer (HNC), with the characteristics of incidental predictable breakthrough pain (BTP) during swallowing. Fentanyl pectin nasal spray (FPNS) could be a good therapeutic option.
Methods: Patients were prospectively considered if receiving basal analgesic therapy with opiates for painful mucositis of grade $\geqslant 4$ on a numerical rating scale from 0 to 10. They were offered FPNS 100 mcg before oral intake. When patients reached the effective dose, they evaluated the basal pain intensity before FPNS use and after 10, 20, 30 and 40 min.
Results: Seventeen HNC patients were offered FPNS before oral intake, with 15 patients completing treatment. Mean reduction of incidental BTP intensity after FPNS was 3.1 points (range 1.2–5.8). Mean time elapsed since FPNS use and highest pain reduction was 26 min.
Conclusions: FPNS demonstrated activity against BTP when swallowing in HNC patients. These data should be considered as hypothesis-generating.

Introduction

Head and neck cancer is diagnosed in about 650,000 patients worldwide each year (about 6% of all cancer in the global population) [1]. Treatments for managing head and neck cancer include radiation therapy, surgery and chemotherapy. A multidisciplinary approach is becoming a cornerstone of head and neck cancer, both in order to improve survival and to promptly recognize and treat adverse events [2]. The evidence suggests that the use of concurrent chemoradiation therapy improves the survival rate and locoregional control [3] at the cost of increasing toxicities, in particular the severity and the mean incidence (about 90%) of oral mucositis (OM) [4–7]. Oral mucositis is painful and may become severe enough to prevent patients from speaking, eating, drinking or swallowing, leading to a worsening of the quality of life and possibly reducing compliance with the treatment and its efficacy [5,8]. The analgesic strategies employed for OM pain treatment vary from local therapies to the administration of systemic drugs with different mechanisms of action such as opiates, anti-inflammatory drugs and anticonvulsants employed to manage neuropathic pain [9–11].

There is insufficient evidence from randomized clinical trials to advise on an optimal intervention specifically for head and neck cancer pain. MASCC/ISOO Guidelines recommend patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain [12]. However, despite individualized approaches, pain control is still often not satisfactory both for the patient and health provider in this care setting, in particular during swallowing [8,10]. Moreover, during chemoradiation, the consequences of a suboptimal pain control could impact on dysphagia, malnourishment, treatment acceptance and compliance, so ultimately influencing chemotherapy dose intensity or radiotherapy treatment continuity.

Breakthrough pain (BTP) is defined as a transitory exacerbation of pain that occurs against a background of stable pain otherwise adequately controlled by around-the-clock opioid therapy. BTP may arise spontaneously in an unpredictable way or it may be related to a specific predictable trigger as incident predictable pain (IP-BTP) [13].

Odynophagia (painful dysphagia or pain with swallowing) due to mucositis can be categorized as incidental predictable BTP,

* Corresponding author. Address: Head and Neck Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milano, Italy. Tel.: +39 0223902150; fax: +39 0223903769.
E-mail address: paolo.bossi@istitutotumori.mi.it (P. Bossi).

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which arises in response to a predictable stimulus that is the act of swallowing. In a prospective cross-sectional study in head and neck cancer patients, the prevalence of BTP was 48% and the majority of pain episodes were associated with some precipitating factor, so these pain episodes were actually predictable [14].

Uncontrolled pain may lead to a decrease in overall swallowing effort as measured by the number of swallow attempts per unit time; it is of particular importance to adequately use analgesics in order to maintain swallowing ability, to reduce aspiration and to more quickly recover adequate oral intake [15]. The optimal control of BTP may allow not to increase the dosage of background drugs employed; in such a way a better control of side effects induced by painkillers could be reached in patients often experiencing poor tolerance of aggressive medications regimens.

A transmucosal intranasal route for the administration of analgesic drugs represents a potentially suitable and practical analgesic treatment method for patients with predictable pain. In fact, in patients with head and neck cancer, oral transmucosal administration could be difficult due to sticky saliva, xerostomia or oral ulcerations. Moreover, intranasal administration appears to have a particularly interesting pharmacokinetic profile.

A recent meta-analysis suggested that rapid onset fentanyl preparations might provide more efficacious treatment options than oral morphine for BTP [16].

Fentanyl pectin nasal spray (FPNS) is a new formulation of fentanyl citrate that incorporates a proprietary pectin-based gelling agent.

The efficacy and tolerability of FPNS was evaluated in 3 phase III randomized, double-blind trials in comparison with a placebo or immediate-release morphine; FPNS was efficacious and well tolerated providing faster onset of analgesia than immediate-release morphine [17–19].

However, not all the above mentioned studies specifically investigated the ability of FPNS to prevent or reduce the intensity of the IP-BTP related to odynophagia and they did not consider head and neck patients in their inclusion criteria.

Methods

Purpose

This clinical pilot study was designed to assess swallowing BTP reduction in a prospective series of head and neck cancer patients treated with FPNS before eating or drinking and to evaluate compliance with the treatment itself.

Study population

A mono-institutional series of consecutive patients, followed in an outpatient setting was considered. The patients were treated, according to Institutional guidelines for pain treatment during head and neck chemoradiation.

Male and female patients aged 18 years and older with squamous cell cancer of the head and neck treated with both full dose curative and postoperative chemoradiation were considered. They had to be able to receive a nasal spray therapy, with no known hypersensitivity to opioids and to the study drug and/or study medications' formulation ingredients. Patients with known metastatic disease or with impaired hepatic function (total bilirubin >2 times upper normal level) or renal function (serum creatinine >2 times upper normal level) were excluded.

Before the start of radiation treatment, all patients underwent an accurate dental screening. A panoramic radiograph was performed and oral hygiene instructions were given to all the patients. Dental foci were treated in order to remove the causes of any infections. During chemoradiation, mucositis prophylaxis according to Institutional guidelines was prescribed, consisting of an effective oral hygiene, with frequent saline rinses. During each weekly outpatient visit, early identification and treatment of oral infections was considered, but no prophylactic antibiotic or antimycotic drug was employed. Pain due to mucositis was assessed using the numerical rating scale, NRS, from 0 to 10 (where 0 = absence of pain and 10 = the worst experienced pain), as a simple and reliable tool for assessing pain intensity [20,21]. Opioid therapy for background pain started with weak opioids, followed by oral morphine or another strong opioid. Mucositis grading was assessed by the physician at least weekly according to the WHO scale.

Procedures

Patients were considered for the trial when having received basal analgesic therapy with opiates (60 mg oral morphine equivalent doses) they then developed BTP during food or liquid intake, with a stable background pain.

If the patient reported painful dysphagia grade $\geqslant 4$ on the numeric scale during oral intake, they were offered FPNS 100 mcg before eating or drinking. Patients were given FPNS if BTP appeared at least 2 times a day in relation to their oral nutrition. An initial treatment dose of 100 mcg was administered in one nostril with a titration phase until the effective dosage was reached, taking into account the benefit and the tolerability of the drug. Titration was performed in the following way: the patient received a FPNS 100 mcg dose (one dose in one nostril). In cases where this dose was not sufficient to adequately reduce pain (at least 30% intensity reduction), then the patient was given a 200 mcg dose (one 100 mcg dose in each nostril) at the following meal. In cases where this dose was not sufficient to adequately reduce pain (at least 30% intensity reduction), then the patient was instructed to take a 400 mcg dose (one 400 mcg dose in one nostril) at the following meal. Finally, if this dose was not sufficient to adequately reduce pain (at least 30% intensity reduction), then the patient was given an 800 mcg dose (one 400 mcg dose in each nostril) at the following meal. In case the drug at this dosage was not effective in reducing pain, then another drug was chosen according to the physician's preference and, in case of lack of efficacy, a nasogastric feeding tube was inserted.

When patients reached the effective FPNS dose (the dose able to reduce swallowing pain intensity by at least 30%), they were provided with a questionnaire to be filled in 2 times a day for 3 consecutive days in order to evaluate, according to NRS, pain intensity during oral intake before FPNS use and after 10, 20, 30 and 40 min. At the end of the 3-day observational period the questionnaire was collected.

The following data were analyzed: pain intensity at baseline; highest pain intensity change from baseline; time to the highest pain reduction; and mean dose of FPNS employed for each dose (mcg). A decrease in pain from baseline was expressed as a negative number. Descriptive statistics were adopted, considering the mean value for basal pain intensity and the mean pain intensity reduction from basal pain to the lowest value indicated by the patient in the questionnaire. Time to highest pain reduction was calculated as the mean of the collected value. All the adverse events possibly linked to drug intake were registered.

Results

Seventeen patients with head and neck cancer meeting all the inclusion criteria were enrolled between May 2011 and January 2012. They were offered FPNS before eating with a titration