CLINICAL REPORT

Fentanyl in a pectin gel treating breakthrough pain in vertebral compression fracture due to multiple myeloma: A descriptive study of three cases

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ARTICLE INFO

Keywords:
fentanyl breakthrough pain multiple myeloma cancer pain

ABSTRACT

Breakthrough pain (BTP) currently represents a challenge for health professionals dedicated to the treatment of pain. In this descriptive 1-year follow-up study on three patients with BTP from vertebral crush, in the context of multiple myeloma, the authors have observed the great either efficacy or tolerability profile of fentanyl pectin nasal spray. The most relevant findings in this study were better adherence to treatment compared to previously opioids and also great personal satisfaction. Because of common pathophysiological mechanism for noncancerous pain of bone origin, these good results could open the door to investigation of the use of this drug in this patient's group.

INTRODUCTION

Chronic pain is one of the largest health challenges of the twenty-first century. This fact is due to its high prevalence, which is around 20 percent in Europe, and that it consumes healthcare resources at a similar level as cardiovascular diseases. It is a disease in and of itself but needs a multimodal treatment strategy, involving analgesic drugs, surgical interventions, rehabilitation, and social and professional management. The objective of any treatment is to alleviate the pain, improve the patient's quality of life, and reduce their psychological suffering.

Breakthrough pain (BTP) was defined in 1990 by Portenoy and Hagen as a temporary increase in pain to greater than moderate intensity (severe or excruciating), which occurred on a baseline pain of moderate intensity or less. They defined baseline pain as that reported by the patient as the average pain intensity experienced for more than 12 hours during the whole day before the interview. An international survey of cancer pain characteristics indicated that BTP's definition varied from country to country. BTP is an English term, which has no literal translation in many languages, including Spanish and Italian, among others. Further, to avoid confusion, some experts have advocated the use of broader terms like episodic pain or transient pain in place of BTP, whereas some have listed types of BTP depending on its predictability and precipitating factors. European Guidelines were published in 2002 which define BTP as "a sudden intense transitory exacerbation of pain (Visual Analog Scale VAS > 7) of short duration (usually shorter than 20-30 minutes) that appears as an increase of persistent stable pain, which is maintained at a tolerable level (VAS < 5) using major opioids." Three factors form the basis for the appropriate management of BTP: prevention, anticipation, and the use of the appropriate medication. Opioid formulations exist that have a rapid onset and short action time (ROOs), which are specially adapted to this kind of pain. All of them contain fentanyl citrate and must be administered through either the oral or the nasal mucosa. They all have a rapid onset of between 5 and 15 minutes after administration, action over 2-4 hours and high bioavailability that can vary between 50 and 80 percent depending on the formulation.

The intranasal fentanyl citrate in pectin spray available in Spain uses a patented technology of...
trans-mucosal administration (PecSys™), in which pectin is used to modulate the delivery and absorption of fentanyl. It is administered as a fine mist of small drops, which jellify on contact with the calcium ions found in mucosal secretions. Fentanyl in a pectin gel presents advantages over other formulations with faster onset and higher bioavailability than fentanyl administered through the mucosa into the mouth. It does not need saliva to be absorbed as do the formulations aimed at passing the active ingredient through the oral mucosa. It has a longer duration of action and results in less nasal dripping than intranasal aqueous formulations.\(^7\)

In our study, it was chosen to control incidental predictable BTP caused by lifting, walking, or strenuous activity as well as crisis of mixed nociceptive/neuropathic pain. We present in this article, a 1-year descriptive follow-up study of the efficacy of this drug in three cases. The results show high efficacy and excellent tolerability in patients suffering BTP in vertebral compression fracture due to multiple myeloma (MM).

**MATERIALS AND METHODS**

**Inclusion criteria**

Fentanyl pectin nasal spray is indicated for the treatment of BTP in adults who were receiving treatment with major opioids for chronic oncological pain. We recruited three patients who were referred to the chronic pain unit, between January and June 2014 (n = 3) with BTP originating in bone due to compression fractures secondary to MM. The patients included had nociceptive BTP and/or neuropathic BTP with basal inflammatory pain well controlled by opioids.

The study subjects included had to be receiving opioid maintenance therapy. The daily total opioid dose required was described in the fentanyl pectin nasal spray Summary of Product Characteristics (PSPC)\(^8\) as follows: “The patients must be taking at least 60 mg of oral morphine daily, 30 mg of oxycodone daily, 8 mg of oral hydromorphone daily, 25 μg of transdermal fentanyl per hour, or an equianalgesic dose of another opioid for longer than a week as specified by the manufacturers.” The maintenance dose of opioids was higher than these for all the patients recruited.

**Study procedure**

Treatment with fentanyl pectin nasal spray was started by and followed up by a physician experienced in treating patients with chronic pain with opioids. The physician warned the patient of the possibility of abuse of the intranasal fentanyl. Patients were followed up by a daily phone call by a nurse from treatment initiation until an effective dose was reached and confirmed for two consecutively treated episodes of BTP. A telephone number was provided to the patients, which they could call to ask any question at any time during the study period. Follow-up during 1 year was made in all three cases at day fifteenth, first month, third month, sixth month, and twelfth month. All three patients recruited completed the study.

**Recommendations of use to the study patients: PSPC**

Fentanyl pectin nasal spray should be titrated to an effective dose that provides adequate analgesia without causing intolerable adverse effects, for two consecutively treated episodes of BTP.\(^8\) The efficacy of a given dose should be evaluated over the ensuing 30 minutes period.

**Initial dose.**

- The initial dose of fentanyl pectin nasal spray to treat episodes of BTP always was one-spray 100 μg, even in patients switching from other fentanyl containing products for their BTP.

- Patients had to wait at least 4 hours before treating another episode of BTP with fentanyl pectin nasal spray.

**Method of titration.**

- All patients were prescribed an initial titration supply of one bottle that contained eight sprays, of fentanyl pectin nasal spray 100 μg/spray.

- Patients who needed to titrate to a higher dose due to a lack of effect were instructed to use two 100-μg sprays for their next BTP episode (one in each nostril). If this dose was not successful, the patient was prescribed a bottle of fentanyl pectin nasal spray 400 μg/spray and instructed to change to one 400-μg spray for their next episode of pain. If this dose was not successful, the patient was instructed to increase to two 400-μg sprays (one in each nostril).
Clinical cases

1. A 72-year-old man with cancer pain resulting from a vertebral compression fracture (tenth and twelfth thoracic vertebra) related to MM. The basal pain was controlled with a transdermal fentanyl matrix patch 50 μg/h/3 d, celecoxib 200 mg/d, paracetamol 1 g/8 h, pregabalin 75 mg/12 h, and lormetazepam 2 mg per night. The patient's incidental BTP was badly controlled with oral trans-mucosal fentanyl 200 μg (VAS = 8). After third month of titrating the dose, the patients BTP was adequately controlled (VAS < 3) with two daily 400-μg fentanyl pectin nasal sprays.

2. A 68-year-old man with axial pain related to a vertebral compression fracture at first lumbar level in a MM context. The basal pain was well controlled with slow release morphine at 30 mg/12 h, paracetamol 1 g/8 h, and trazodone 100 mg at night. Occasional BTP was poorly controlled with 10 mg fast-release morphine (VAS 7-9) but was improved to a tolerable level during daily activities (VAS < 3) with one daily 200-μg fentanyl pectin nasal spray.

3. A 65-year-old woman with low back pain due to a vertebral compression fracture in the twelfth dorsal vertebra with underlying MM. The basal pain was controlled with paracetamol 1 g/8 h and oxycodone/naloxone 20/10 mg/12 h. The occasional BTP scored VAS > 8 and was badly controlled with 10 mg fast-release oxycodone. The BTP improved to VAS < 3 after changing the treatment to a single daily 400-μg fentanyl pectin nasal spray.

RESULTS

In this descriptive study, the main limitation is the number of patients included (n = 3), so it is difficult to extrapolate these results to general cancer population. Moreover, the BTP observed in the cases in this study was somatic and/or neuropathic and it was classified both as incidental and predictable in two cases (especially when walking and coughing) and spontaneous in one case. Basal opioid treatment varied a great deal, involving three different drugs at various doses (fentanyl TD 50 μg/h/72 h, morphine oral 60 mg/d, and oxycodone/naloxone oral 40/20 mg/d). Also, three different rescue drugs were used before the patients started using the fentanyl pectin spray nasal: fentanyl oral trans-mucosal 200 μg, rapid release oral morphine (OM) 10 mg, and rapid release oral oxycodone 10 mg.

Initial adverse effects were moderate light; headache, unsteadiness, nausea, headache, or dizziness, but the treatment was well tolerated at 3 months. The patients no. 1 and no. 3 showed neuropathic symptoms and they needed higher fentanyl pectin nasal spray doses than patient no. 2, which showed only somatic pain. All of them had improved either their pain intensity or quality of life with the new intranasal fentanyl rescue regimen after 12 months follow-up. Patient general well-being perception was also improved along the study and was described as very good or excellent at the end of the study. These results are summarized in Table 1.

DISCUSSION

Characteristics of BTP in cancer versus noncancer patients

The underlying mechanism of BTP in cancer pain may be a nociceptive, neuropathic, or mixed pain. Nociceptive pain may be somatic due to an involvement of structures like bone or muscle, or visceral if due to an involvement of underlying solid or hollow viscus. Neuropathic pain is due to an involvement of peripheral or central afferent neural pathways. The incidence of various types of pain has been described as nociceptive in 38-53 percent, neuropathic in 10-54 percent, and mixed pain in about 20-52 percent of patients in cancer pain. The estimated prevalence of all types of BTP is 64-70 percent in MM patients. Even though BTP was originally defined for this patient group, the same kind of pain was later identified in nononcological patients. Both groups have similar characteristics: around 60-75 percent of the patients suffering 2–4 daily episodes of BTP with similar duration of 30-60 minutes. The main difference that has been observed is that nononcological patients more often have incidental BTP. Therefore, these patients are much more likely to have more pain related to their physical activity than cancer patients who experience more often spontaneous BTP. The location and the physiopathology of the pain are fairly similar in the two groups: high incidence of somatic...
Table 1. Results from the three-case observational study treating breakthrough pain in vertebral compression fracture due to multiple myeloma with fentanyl in a pectin gel

<table>
<thead>
<tr>
<th></th>
<th>Patient no. 1</th>
<th>Patient no. 2</th>
<th>Patient no. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal VAS</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Basal opioid</td>
<td>Fentanyl TD 50 μg/h/72 h</td>
<td>Morphine oral 60 mg/d</td>
<td>Oxycodone/naloxone 40/20 mg/d</td>
</tr>
<tr>
<td>BTP type</td>
<td>Somatic and neuropathic</td>
<td>Somatic</td>
<td>Somatic and neuropathic</td>
</tr>
<tr>
<td>BTP classification</td>
<td>Incidental predictable</td>
<td>Incidental predictable</td>
<td>Incidental predictable and spontaneous</td>
</tr>
<tr>
<td>BTP location</td>
<td>T-10, T-12</td>
<td>L-1</td>
<td>T-12</td>
</tr>
<tr>
<td>Initial BTP VAS</td>
<td>8</td>
<td>7-9</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Opioid used for BTP (on demand)</td>
<td>Fentanyl oral trans-mucosal 200 μg</td>
<td>Rapid release morphine 10 mg</td>
<td>Rapid release oxycodone 10 mg</td>
</tr>
<tr>
<td>Initial dose fentanyl pectin nasal spray</td>
<td>100 μg/d</td>
<td>100 μg/d</td>
<td>100 μg/d</td>
</tr>
</tbody>
</table>

Reevaluation 15 days later

| BTP VAS              | 7             | 6             | 6             |
| Secondary effects    | No            | Lightheadedness, unsteadiness | Nausea, headache |
| Adjusted dose        | 200 μg/d      | 200 μg/d      | 200 μg/d      |

Reevaluation first month

| BTP VAS              | 6             | 4             | 4             |
| Secondary effects    | No            | Dizziness     | Nauseas       |
| Adjusted dose        | 400 μg/d      | No            | 400 μg/h      |

Reevaluation third month

| BTP VAS              | 5             | <3            | <3            |
| Secondary effects    | Unstable walking | No          | No            |
| Adjusted dose        | 800 μg/d      | No            | No            |

Reevaluation sixth month

| BTP VAS              | <3            | <3            | <3            |
| Secondary effects    | No            | No            | No            |
| Adjusted dose        | No            | No            | No            |

Reevaluation twelfth month

| BTP VAS              | <3            | <3            | <3            |
| Secondary effects    | No            | No            | No            |
| Adjusted dose        | No            | No            | No            |
| Lattinen index       | Start 15/end 9 | Start 14/end 7 | Start 13/end 8 |
| Patient perception   | Very good     | Excellent     | Very good     |
pain, nociceptive and also neuropathic pain as well as many patients with mixed pain, particularly in the nononcological group.\textsuperscript{11,12}

There is no unanimous definition of BTP in nononcological pain at present. Consequently, the terms BTP and incident pain have rarely been used in non-malignant situations. End of dose pain may be more common in chronic noncancer pain than in cancer patients, but it does not meet the criteria for BTP. The definition of BTP varies based on authors, their concepts and requirements. This fact makes it difficult for pain physicians to prescribe an adequate treatment for chronic pain patients. It is therefore hard to improve BTP conditions considering the numerous disadvantages of the effectiveness of opioids in managing chronic pain on a long-term basis.\textsuperscript{13}

In our descriptive study, BTP was incidental and predictable in the three clinical cases and also spontaneous in one case. Although all of them had cancer pain, the symptoms description has much in common with BTP characteristics in noncancer patients.

However, the literature for BTP in chronic non-cancer pain including its terminology, prevalence, relevance, characteristics, and treatments have been poorly described and continue to be debated. Consequently, the treatment of BTP in chronic non-cancer pain is not supported by some authors due to the lack of evidence and inherent bias associated with its evaluation, in addition to the escalating use and abuse of opioids.\textsuperscript{14}

**Opioids efficacy for BTP treatment**

A systematic literature review (1996-2007) compared the efficacy of ROOs: intranasal fentanyl spray (INFS), oral trans-mucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT), and OM for the treatment of breakthrough cancer pain (BTCP).\textsuperscript{15} INFS provided the greatest reduction in pain relative to placebo: pain intensity difference 1.7 points (95 percent CrI: 1.4; 1.9) at 15 minutes, 2.0 (1.6; 2.3) at 30 minutes, 2.0 (1.5; 2.4) at 45 minutes, and 1.9 (1.5; 2.4) at 60 minutes. INFS displayed a more than 99 percent probability of providing the greatest pain reduction out of all interventions compared at 15 minutes after intake. It was maintained at any measured time point before 45 minutes when compared to FBT and for any measured time point before 60 minutes when compared to OTFC. Only from 45 minutes onward did OM show a greater pain reduction than placebo. Consequently, based on currently available evidence, INFS is expected to provide the greatest improvement in the treatment of BTCP.\textsuperscript{15} When treating BTP with opioids in a noncancer situation, it is necessary to evaluate and reeducate the patient. It is also necessary to periodically follow up on the patient to evaluate the effectiveness of the treatment and also any undesirable results that can result from it. Not only addiction and increased tolerance but also other risks associated with a prolonged use of opioids like constipation, cognitive deterioration, hyperalgesia, hypogonadism, and sexual dysfunction.\textsuperscript{16}

In a Cochrane revision published in 2013, either oral or nasal trans-mucosal fentanyl formulations were found to be an effective treatment for BTP. When compared with placebo or OM, participants described lower pain intensity and higher pain relief scores for trans-mucosal fentanyl formulations at all time points. Global assessment scores also favored trans-mucosal fentanyl preparations. One study compared intravenous with the trans-mucosal route, and both were effective. There are relatively few Randomized Controlled Trials in the literature for the management of BTP. Given the importance of this subject, more trials, including head-to-head comparisons of the available trans-mucosal fentanyl formulations are needed.\textsuperscript{17}

A recent systematic review, published in 2015, has demonstrated that either oral trans-mucosal or intranasal fentanyl is an effective treatment for the management of BTP episodes in cancer patients due to a potent analgesic effect, rapid onset of action, and sustained effect. Furthermore, it is a reasonably safe treatment, causing mild adverse events, which are not leading to treatment discontinuation.\textsuperscript{18} This fact has been corroborated by our findings presented in this descriptive study. VAS improved from 7-9 at the beginning to <3 at the end of the study 1 year after. Nevertheless, further progress in standardizing methodology, definitions, and criteria used both in research and in clinical practice is needed to generate quality information allowing a better understanding of the comparable efficacy of available formulations of ROOs. A more rigorous assessment of long-term safety is also required to establish a balance between benefits and risks of the available options.

**Impact of BTP treatment on quality of life and cost/effectiveness evaluation**

The results of this descriptive three-case study demonstrate the efficiency of fentanyl pectin nasal
spray in treating BTP of bone and articular origin related to compression fractures of the vertebra due to MM. The three patients gained a great improvement in the intensity of the pain as compared to the short acting drugs they were receiving before (rapid release morphine, rapid release oxycodone, and fentanyl citrate trans-mucosal oral). The new rescue drug (fentanyl pectin nasal spray) presented few adverse effects and was on the whole found to be more satisfactory than the drugs previously used by the patients. This fact was evidenced by a subjective improvement in the quality of life of the patients measured by the Lattinen index (LI). LI has been found to be a valid measure of the degree of suffering by patients with chronic pain, and it is a widely used tool for pain assessment in Spanish-speaking countries, both in clinical practice and research. A statistically significant positive correlation was found in between the total LI score (between 0 [best] to 20 [worst]) and the degree of pain measured by VAS. Moreover, the measurements of the individual items in the questionnaire: analgesic consumption, pain frequency, pain intensity, hours of sleep and functional ability, correlated from moderately to strongly with the respective gold standards measurements. In our descriptive study, the time it took to get in the habit of intranasal administering of the drug fentanyl pectin nasal spray was short, and the adoption of the method uncomplicated. All patients expressed a high satisfaction level with this treatment for their BTP episodes.

The quality-adjusted life year (QALY) is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in assessing the value for money of a medical intervention. One QALY equates to 1 year in perfect health. If an individual’s health is below this maximum, QALYs are accrued at a rate of less than 1 per year. A recent study showed a cost-effectiveness analysis of INF citrate as an alternative to morphine for BTCP, selecting three clinical studies that included effectiveness, side effects, hospitalizations, and visits. Utility data were used to differentiate the health status inherent to BTCP. The incremental cost-effectiveness ratio of INF was 10,140 euros/QALY. Sensitivity analysis shows that with a threshold of 30,000 euros/QALY, the treatment of BTCP with INF would have an 86 percent probability of being cost-effective. Moreover, a decision-analysis model was developed a few years ago in Sweden to evaluate the cost-effectiveness of INFS compared with OTFC and FBT for the treatment of BTCP. With INFS, 55 percent of BTCP was avoided (95 percent uncertainty interval [UI]: 46-68 percent), which is greater than expected with OTFC (29 percent; UI 22-38 percent) or FBT (31 percent; UI 25-39 percent). INFS was dominating OTFC (resulting in 0.046 QALY gain and saving 174 euros with a period of 180 days) and cost-effective versus FBT (incremental cost-effectiveness ratio 12,203 euros/QALY). Despite uncertainty in the source data, there was a >99 percent probability that INFS was the most cost-effective intervention. In our descriptive study, we did not make a cost-effectiveness evaluation due to the small sample size so we can make formal comment on this topic.

CONCLUSIONS

BTP (oncologic and nononcologic) has a large socioeconomic impact. It diminishes the patients’ quality of life, and it has a high treatment cost due to its leading of many consultations in emergency wards and hospital stays. It is also one of the aspects of the disease, which has the worst prognosis. The establishment of an appropriate strategy of multimodal treatment has a positive impact on the quality of life of the patients and their families and therefore has a direct impact on medical spending. The last years have seen the introduction of a range of fentanyl-based rapid onset opioids with different administration routes for the management of BTP in opioid-tolerant patients with cancer. Given the absence of data from double-blind, head-to-head trials, it is not currently possible to conclude that any formulation is superior to another. Based on available data, mainly from placebo-controlled trials, the current formulations appear to be comparable concerning in both their efficacy and safety. It is likely that factors such as disease characteristics, patients’ preference, and ease of administration will continue to be key determinants in deciding the most appropriate formulation for individual patients. Fentanyl citrate pectin nasal spray fulfills all of the ideal pharmacokinetics and pharmacodynamics characteristics of the ROOs drugs. It presents an efficiency/tolerability profile, which makes it a good choice drug in treating BTP as shown by this descriptive study of three cases of vertebral compression fracture due to MM. In our study, BTP severity decreased in the three patients over the course of the period of 1-year follow-up. BTP in patients observed in this study showed characteristics and physiopathology similar to BTP for nononcologic patients with bone pathology. It is therefore our
opinion that studies on the efficiency and tolerance of this drug for nononcological BTP patients should be undertaken and could lead to improvements in their treatment. Indeed, a 2-year observational study to measure the effectiveness of fentanyl pectin spray intranasal in elderly patients with breakthrough noncancer pain has proved good results with periodically follow-up.23

ACKNOWLEDGMENT

None of the authors has any conflict of interest.

REFERENCES


