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Is Fentanyl Pectin Nasal Spray Safe and Effective for Patients with Breakthrough Cancer Pain?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

OBJECTIVE: The objective of this systematic review is to determine whether fentanyl pectin nasal spray (FPNS) is safe and effective treatment for patients with breakthrough cancer pain.

STUDY DESIGN: Review of three English language primary randomized controlled trials published 2010-2011.

DATA SOURCES: Multicenter, randomized, double-blind, double-dummy, placebo-controlled trials comparing fentanyl pectin nasal spray, immediate-release morphine sulfate, and/or nasal spray placebo were found using PubMed, COCHRANE, and Medline databases.

OUTCOME MEASURED: All three studies essentially used similar parameters to measure effectiveness and safety of fentanyl pectin nasal spray compared to oral immediate-release morphine sulfate and/or placebo. Baseline pain intensity was scored 0-10. Pain intensity (PI) and pain relief (PR) were measured at 5, 10, 15, 30, 45, 60 minutes in order to assess time intervals clinically meaningful pain relief and maximum pain relief has been achieved. Adverse events were also recorded through all phases of the studies, and objective nasal tolerability assessments were performed.

RESULTS: Collectively, the results demonstrated that clinically meaningful pain relief was achieved by fentanyl pectin nasal spray in as early as 10 minutes when compared to the control. Furthermore, approximately half the breakthrough cancer pain episodes achieved maximum pain relief at 60 minutes with FPNS compared to just over one-third of patients with immediate-release morphine sulfate. No significant nasal effects were reported, and there were no nasal tolerability parameters reported at moderate to severe intensity.

CONCLUSION: The three randomized-controlled trials demonstrate that fentanyl pectin nasal spray is both safe and effective for the treatment of BTCP episodes compared to the current gold standard of treatment and placebo. The efforts of the studies used have contributed to the FDA approval of this first intranasal option in 2011for cancer patients suffering from inadequately managed breakthrough cancer pain.

KEY WORDS: fentanyl, intranasal, patient acceptability, breakthrough cancer pain

INTRODUCTION

The pain experienced by patients suffering from cancer can often be categorized as one of two types. Persistent pain, also known as background pain, can be described as constant, having a gradual onset, and can last up to 12 hours a day.[1] This kind of pain can be attributed to mass effects (cancerous tumors pressing on surrounding bones, nerves, and/or organs), an activated inflammatory response, or in response to chemotherapy/radiation.[1] Conversely, breakthrough cancer pain (BTCP) strikes suddenly, is unpredictable, peaks at an average of 5 minutes, and lasts an average of 45 minutes. It is characterized as sharp, shooting, and radiating.[1] Although there is no widely accepted definition, classification system, or assessment tool for this cancer pain syndrome, it is diagnosed based on the history of several key features such as high intensity pain, temporal features, precipitating events, and predictability despite otherwise well controlled background pain.[2] These acute episodes of moderate-severe pain "break through" what would otherwise be tolerated as background pain.

Palliative care is an integral component of care for any cancer patient. BTCP management presents a challenge for patients and health care providers, because it occurs even when the patient is taking an appropriate dose of long-acting opioid analgesics on a fixed schedule. BTCP has been reported to affect up to 80% of all cancer patients with pain.[5] Most patients with BTCP report having pain of severe to excruciating intensity; studies have reported patients experiencing a median of 1.5-6 episodes per day[1], and a maximum of 50 episodes per day.[1] Furthermore, there are 28.2 million primary diagnoses of cancer per year, and the average inpatient length of stay is 6.3 days.[6] Although an exact amount has not been identified regarding the national expenses related to cancer-related pain management, greater patient satisfaction with

pain control ultimately results in taking less medications, less office visits, and less medical debt for the patient.

Short-acting opioid "rescue medications", such as morphine or oxycodone, are common pharmacologic agents used in the management of BTCP that are used adjunctively to a fixed-schedule opioid regimen. Among these medications, the current gold standard is oral immediate-release morphine sulfate tablets (IRMS).[2] However, the discrepancy between the pharmacodynamics of such rescue medications and the very nature of a BTCP episode is a commonplace dilemma that hinders adequate pain control and has been well noted throughout literature. For example, the onset of a typical morphine or oxycodone formulation is at least 20 minutes, with a peak effect at 1 hour; meanwhile, a typical BTCP episode peaks at 5 minutes and can last about 3 minutes.[1] More studies are needed to determine more effective treatments to alleviate this type of pain in a more timely and patient satisfactory manner.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not fentanyl pectin nasal spray is safe and effective for the treatment of breakthrough cancer pain.

METHODS

Regarding the literature search, the keywords used in the databases PubMed, Medline, and Cochrane were limited to fentanyl, intranasal, breakthrough pain, and patient acceptability. All articles were published in English and peer reviewed journals between the years 2010 and 2011. The author selected the three articles on the basis of featuring patient-oriented outcomes, rather than disease-oriented outcomes. Table 1 summarizes characteristics of the studies used in this systematic review.

All three randomized controlled trials used in this systematic review used the following criteria to select participants. Patients had to be over the age of 18 with a histologically confirmed diagnosis of cancer. Also, patients must be receiving a fixed-schedule opioid regimen at a total daily dose ≥60g/day for background cancer pain, and experience at least 1-4 episodes of BTCP per day.[2,3,4]

In these studies, the treatment groups receiving intervention drug, fentanyl pectin nasal spray (FPNS), were compared to those receiving a control treatment of immediate-release morphine sulfate (IRMS) and/or nasal spray placebo. The most common opioids used by participant for background pain control were morphine, fentanyl, oxycodone, and methadone.[4] The studies were essentially conducted in four phases: a screening phase, an open-label titration phase (titration of FPNS to an effective dose between 100µg-800 µg that can successfully treat two consecutive BTCP episodes without unacceptable adverse events), a double-blind, placebo-controlled, randomized, cross over phase, and post double-blind treatment phase.

Several considerations rendering exclusion of participants from the study included uncontrolled or rapidly escalating background pain, medical instability, past history of inability to tolerate fentanyl or other opioids, and any disorder or medication use likely to adversely affect normal functioning of nasal mucosa. Other exclusion criteria include breakthrough pain not related to cancer, history of alcohol/substance abuse, treatment with MAOIs, anticipated treatment with any treatment that may affect pain levels (eg. chemotherapy), and treatment with another investigational drug within 30 days.[2,3,4] The statistics utilized to interpret the data include relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT), and *p*-values.

Table 1. Study Demographics for the Analysis of FPNS in the Treatment of BTCP

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Davies[2] (2011)	DB RCT	110	18+	Histologically confirmed diagnosis of cancer; receiving a fixed schedule opioid regimen at a total daily dose ≥60mg oral morphine/day for background pain; have 1-4 episodes of moderate-severe BTCP/day	Uncontrolled or rapidly escalating background pain; medically unstable; past inability to tolerate fentanyl or opioids; history of EtOH or substance abuse; treatment with MAOIs; any disorder or medication use likely to adversely affect normal functioning of nasal mucosa	11	Titrated dose of fentanyl pectin nasal spray between 100-800µg
Portenoy[3] (2010)	DB/DD RCT	114	18+	Histologically confirmed diagnosis of cancer; receiving a fixed schedule opioid regimen at a total daily dose ≥60mg oral morphine/day for background pain; have 1-4 episodes of moderate-severe BTCP/day	Uncontrolled or rapidly escalating background pain; medically unstable; past inability to tolerate fentanyl or opioids; history of EtOH or substance abuse; treatment with MAOIs; any disorder or medication use likely to adversely affect normal functioning of nasal mucosa	7	Titrated dose of fentanyl pectin nasal spray between 100-800µg
Fallon[4] (2011)	DB/DD RCT	84	18+	Histologically confirmed diagnosis of cancer; receiving a fixed schedule opioid regimen at a total daily dose ≥60mg oral morphine/day for background pain; have 1-4 episodes of moderate-severe BTCP/day	Uncontrolled or rapidly escalating background pain; medically unstable; past inability to tolerate fentanyl or opioids; history of EtOH or substance abuse; treatment with MAOIs; any disorder or medication use likely to adversely affect normal functioning of nasal mucosa	5	Titrated dose of fentanyl pectin nasal spray between 100-800µg

DB= double blind, DD=double dummy

OUTCOMES MEASURED

The outcomes measured in the studies were patient-oriented outcomes, which reflect satisfaction with pain management when applying the intervention treatment. The outcomes measured include the need to use a rescue medication, time at which clinically meaningful pain relief and maximum pain relief are achieved, adverse events, objective and subjective nasal tolerability assessments, and patient satisfaction scores.

All three studies collected data via an electronic diary, and objective nasal assessments were performed by a clinician. All three studies use a modified intent-to-treat (m-ITT) method, which included all patients in the randomized population who treated at least one BTCP episode with FPNS and at least one episode with placebo and/or IRMS, and for each of these episodes, had at least one baseline and one post-baseline pain intensity measurement. All three studies used an e-diary system, which prompted the participant to rate various measures on a number scale. Several parameters were used to measure effectiveness; such measures included baseline pain intensity on a scale of 0-10 (0= no pain, 10= worst possible pain), and pain intensity (PI) and pain relief (PR) scored at 5, 10, 15, 30, 45, and 60 minutes. PR was measured on a scale of 0-4 (0= none, 4=complete). Patients were also asked to rate overall satisfaction, satisfaction with speed of onset of PR, satisfaction with reliability, and ease of use and convenience on a scale of 1-4 (1=not satisfied, 4= very satisfied). Also, the need to resort to prescribed rescue medication was recorded.[2,4]

To measure safety, adverse events (AEs) were recorded throughout the study. All AEs that occurred within 24 hours of a FPNS dose were attributed to FPNS use, even though the patient may have been treated with IRMS soon after. Another measure of safety used was nasal assessments to explore possibility of local side effects of FPNS use. The study physician

performed objective nasal assessments to evaluate for nasal obstruction (0=absent; 1= mild mucosal thickening; 2= moderate edema, narrowing of airways; 3=severe obstruction), inflammation (0= absent; 1= mild crusting or blood staining; 2= moderate crusting, fresh blood, pus, or cyanotic mucosa; 3= severe septal perforation or mucosal ulceration), presence of discharge, and color of mucosa. Subjective nasal assessments were completed via a 10 item questionnaire, each item rated 0-3 (0= absent, 3= severe). The items rated were stuffy/blocked nose, runny nose, itching/sneezing, crusting/dryness, burning/discomfort, bleeding nose, cough, post nasal drip, sore throat, and taste disturbance. Participants we asked to perform this survey before the first dose of FPNS, 60 minutes after each dose, and at the final study visit.[3]

RESULTS

All three articles converted continuous data into dichotomous data to adequately assess effectiveness of FPNS. Two studies (Davies et al. and Fallon et al.) were double-blind-double dummy RCTs in which patients were treated with FPNS and oral capsule placebo or IRMS and nasal spray placebo. One RCT (Portenoy et al.) focused on comparing FPNS to a placebo. In these studies, various pain score endpoints were used to assess whether there was clinically meaningful pain relief within in a timely manner for the patient (Table 2). Safety was assessed by the occurrence of AEs and tolerability via nasal assessments.

Of the 110 patients enrolled in the open dose titration phase, 84 patients identified an effective and tolerable dose of FPNS and were randomly assigned to double-blind treatment in the Davies et al. study. Based on a per episode analysis at each time interval, the study demonstrated that FPNS consistently provided statistically significant clinically meaningful pain relief (≥ 2point pain score reduction from baseline) more rapidly than IRMS in as early as the 10 minute interval, which was reflected in the PID_{10} scores ($p < 0.05$).[2] RRR was calculated to be

15.4%, the ABI was 7%, and NNT was 15 patients. The NNT indicates that for every 15 patients treated with FPNS, one more patient would experience a more rapid onset of analgesia than if treated with IRMS.

In the Fallon et al. study, 84 patients identified an effective and tolerable FPNS dose of the 110 enrolled in the titration phase. From the79 patients who went on to complete the study, a total of 372 BTCP episodes treated with FPNS and 368 treated with IRMS were mITT-evaluable. Fallon et al. showed that 50.1% of BTCP episodes with FPNS vs. 34.3% BTCP episodes with IRMS use were rated with a maximum PR score of 4 (0=none, 4=complete pain relief) at the endpoint of 60 minutes (PR_{60}). This represents a 46.1% (RBI) improvement in maximal pain relief effectiveness with FPNS use. The NNT conveys that one more patient will experience complete pain relief by 60 minutes for every 7 patients treated with FPNS as compared to IRMS use. According to this study, the number of BTCP episodes achieving the maximum pain relief score of 4 with FPNS was statistically significant from 30 minutes onwards; however, approximately half the BTCP episodes at 60 minutes achieved maximum pain relief with FPNS compared to just over one-third of patients with IRMS.[4]

Another measure relaying effectiveness of FPNS is whether patients needed to use to their usual rescue pain medication the study. Patients were instructed to resort their rescue pain medication for any pain that continued to require treatment after 30 minutes after the dose of the study medication, or any other acute pain other than the target BTCP.[3] Overall, 90.6% of the FPNS-treated versus 80.0% of placebo treated BTCP episodes did not require additional rescue pain medication within 60 minutes ($p<0.001$).[3] The NNT signifies that for every ten people treated with FPNS, one more patient did not need to resort to their rescue medication as compared to the placebo.

Table 2. Summary of Statistically Significant Endpoints Assessing Pain Relief with FPNS

Study	Endpoint	Result	*p*-value	RBI	ABI	NNT
Davies et al.	PID_{10}	EER=52.4% CER=45.4%	<0.05	15.4%	7%	15
Fallon et al.	PR_{60}	EER=50.1% CER=34.3%	<0.0001	46.1%	15.8%	7
Portenoy et al.	No need for rescue med. use	EER=90.6% CER=80%	<0.001	13.25%	10.6%	10

Portenoy et al. assessed the incidence of adverse events (AEs) related to FPNS compared to an identically appearing nasal spray placebo. Expectedly so, more AEs were reported following FPNS treatment than following placebo; however, it is important to note that no dose-dependent trends could be identified (Table 3a).[3] The most commonly reported AEs were appropriate for opioid therapy in general, and were of mild to moderate severity. Four deaths occurred following the administration of FPNS, and investigators have associated them with the progression of disease, rather than the study drug.[3] Only 5.3% of patients withdrew from this study due to adverse events.[3] As seen in Table 3b, the NNH of 3 indicate that for every 3 people treated with FPNS, 1 person will experience an AE when compared to placebo.

Table 3a. Incidence of Common Adverse Events with FPNS in Portenoy et al. Study

FPNS dose:	100µg	200µg	400µg	800µg
Vomiting	6%	1%	4%	1%
Nausea	5%	3%	2%	0%
Dizziness	5%	3%	1%	1%
Epistaxis	1%	2%	2%	2%
Headache	3%	1%	0%	0%

Table 3b. Statistical Significance of AEs in Portenoy et al. Study

	EER	CER	RRI	ARI	NNH
Overall AEs occurrences	51.3%	5.1%	905%	46.2%	3

Another measure conferring the safety of FPNS is the objective assessments by a physician and subjective nasal assessments by the patients. In all the studies, no significant nasal effects were reported. In Davies et al., six patients experienced mild nasal obstruction at screening, which decreased to two by the end of the study. One patient had severe nasal discharge and another acquired pale mucosa at screening; however, no patients exhibited these findings at the study's end. There were no patients with nasal inflammation during any phase of the study.[2] Subjectively, there were no nasal tolerability parameters reported at moderate to severe intensity (>2-3 score). Also, there was not a statistically significant difference between FPNS and IRMS treatments.[2] Table 4 explains the distribution of the positive findings on objective nasal tolerability assessment. There were no findings of moderate to severe rating, so the results were either "absent" or "present" (mild). There were no trends following increasing doses of FPNS administered.

Table 4. Nasal Tolerability Assessment in End-of-Treatment Phase for FPNS

Objective parameter	Absent (*n*)	Present (*n*)
Obstruction	87	2
Inflammation	89	0
Nasal d/c	85	4
Color mucosa	89	0

DISCUSSION

Davies et al. and Fallon et al. have proven that FPNS provides more rapid and effective analgesia with a time course more suitable than that of IRMS for treating a BTCP episode. Also, Fallon et al. helped conclude that FPNS can achieve maximum pain relief quicker that IRMS. Also, based on the Portenoy et al. study, the minimal need to use rescue medication in and exceptional nasal tolerability confers effectiveness. All three studies demonstrate safe and effective pain management with FPNS for BTCP episodes.

FPNS, or *PecFent*, is already available in several European countries. The efforts of these studies have contributed to the FDA approval of this intranasal analgesic option for patients suffering from inadequate pain control. The U.S. FDA approved fentanyl nasal spray (*Lazanda*) for patients above 18 years of age with BTCP, and is indicated for patients already receiving opioid therapy, but who have developed resistance to their current regimen. It is contraindicated in patients who are intolerant to opioid therapy (not already taking a fixed-schedule of opioids) due to the possibility of hypoventilation that can occur at any given dose, as well as for patients with severe renal or hepatic failure. According to the manufacturer, the product is made available after the completion of a Risk Evaluation and Mitigation Strategy program (REMS) by healthcare professionals who wish to prescribe or distribute. This measure has been proposed essentially to minimize the risk for abuse, addiction, overdose, and complications due to medication errors.[7]

There are several limitations to all three studies. The short duration of these studies made it difficult to interpret the relationship between AEs, FPNS use, and a patient's fixed-schedule opioid regimen. The complexity of the medical condition of these patients and the differences in each patient's background opioid therapy contribute to the overall AE rate. Regardless of this

flaw, effectiveness of FPNS is suggested by a high percentage of patients opting to continue into an open-label extension phase after the study (for example, 87% in Portenoy et al study). Also, a high placebo response was noted regarding the number of patients who did not need additional rescue medication within the 60 minute interval. A factor complicating this limitation is the possibility of spontaneous resolution of the BTCP episode at various time endpoints.

Patient acceptability is vital when introducing a new route of administration. It was of concern that patients may find it difficult to administer, have a bad taste, or lose efficacy by catching in the back on the throat after administration. However, the subjective patient acceptability ratings in these studies, combined with the results of the objective nasal assessments disprove all these concerns. In fact, this intranasal option is of particular interest to advanced cancer patients who may suffer from mucositis or xerostomia, because they often find oral formulations difficult or uncomfortable to use.[2]

CONCLUSION

The evidence provided in this systematic review demonstrates that FPNS surpassed the therapeutic effects of the gold standard, IRMS, in delivering significantly earlier and clinically meaningful reductions in pain, as well as providing more complete pain relief throughout the duration of the BTCP episode. Unlike oral IRMS, the pharmacokinetics of this intranasal option lends itself to quicker onset of pain relief and quicker total pain relief. Many cancer patients are treated as outpatients in clinical practice today, and studies have shown that patients often receive inadequate pain relief due to improper use of rescue medications, in part due to discouragement of its effectiveness. Proper management of these patients requires a great level of patient compliance and adherence to treatment plans; therefore, it is important that rescue medications are very effective, have a rapid onset, are safe, tolerable, and easy to use.

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