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Original Reports

Intranasal Fentanyl Versus Fentanyl Pectin Nasal Spray for the Management of Breakthrough Cancer Pain in Doses Proportional to Basal Opioid Regimen

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Abstract: The aim of this randomized, crossover, comparison study was to assess the analgesic and adverse effects of 2 nasal preparations, intranasal fentanyl (INFS) and fentanyl pectin nasal spray (FPNS), for breakthrough pain, given in doses proportional to opioid basal regimen. Each patient randomly received INFS or FPNS in doses proportional to opioid dosages used for background analgesia for 2 pairs of episodes. For each episode of breakthrough pain, pain intensity and adverse effects intensity were recorded just before starting the INFS or FPNS (T0) and 5 minutes (T5), 10 minutes (T10), and 20 minutes (T20) after the administration of the nasal drugs. Sixty-nine patients were studied. The mean age was 63.4 years, and 37 patients were males. For the present analysis, 188 episodes were considered. A statistical decrease in pain intensity was observed with both nasal drugs after 5, 10, and 20 minutes. A decrease in pain intensity of >33% was observed in 16, 102, and 159 treated episodes at T5, T10, and T20, respectively. Adverse effects were of mild nature in most cases or were preexistent because of basal opioid therapy. No differences were found in summed pain intensity difference 20 minutes after dosing. Most of patients did not find substantial preferences. INFS and FPNS were effective and well-tolerated treatments for breakthrough pain management. Both delivery systems, in doses proportional to the basal opioid regimen, provided significant analgesia within 10 minutes, without producing relevant adverse effects.

Perspective:* *This article showed that INFS and FPNS in doses proportional to basal opioid regimen are equally safe and effective for the management of breakthrough pain in cancer patients. These data provide new insights on the use of nasal preparations of fentanyl.

Key words: *Cancer pain, breakthrough pain, rapid-onset opioids, intranasal fentanyl, fentanyl pectin nasal spray.*

Breakthrough cancer pain (BTP) has been defined as a transitory increase in pain intensity on a baseline pain of moderate intensity in patients on analgesic treatment regularly administered.[1,26] More recently, it has been underlined that background pain should be of mild intensity.[3] Many transmucosal fentanyl products have been licensed for BTP in opioid-tolerant patients.[21] These preparations, named rapid-onset opioids (ROOs), have some advantages such as ease of administration, rapid onset of action, and avoidance of first-pass metabolism, which consequently offer an interesting alternative to intravenous, subcutaneous, oral, and rectal administration in the management of BTP. A recent meta-analysis of the efficacy of opioid analgesics in the management of BTP episodes has reported that these fentanyl preparations achieved a greater level of pain

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relief in a shorter time frame than placebo and oral opioids.[11]

Intranasal administration is a noninvasive route for drug delivery, which is widely used for many drugs. Because drugs can be absorbed into the systemic circulation through the nasal mucosa, this route may also be used in patients with buccal problems, including mucositis or dry mouth.[8] There are 2 approved nasal fentanyl products. Intranasal fentanyl (INFS) comprises an aqueous-buffered solution containing fentanyl citrate equivalent to .5, 1, or 2 mg/mL of fentanyl base.[7,8] The product provides fentanyl doses of 50, 100, and 200 μg. Fentanyl pectin nasal spray (FPNS) is an aqueous solution that is based on a delivery system to provide in situ gelling of the formulation, which reduces the potential for drip, modulating fentanyl release compared to a simple solution.[12,28] Two strengths are available containing either 100 or 400 μg fentanyl citrate equivalent.

Preliminary registration studies were performed with the lowest dose to be titrated against the effect, showing that both nasal fentanyl preparations provide rapid and efficient analgesia in comparison with placebo, oral morphine, or oral transmucosal fentanyl citrate.[2,5,9,13,27]

These products have different pharmacokinetic profiles and availabilities. Although a pharmacokinetic study has not been performed in which FPNS has been compared against a simple (non-gelling) nasal solution, by comparing the pharmacokinetic data from the FPNS studies to those reported with simple solutions and to a non-gelling chitosan formulation, on an equivalent dose basis, FPNS generates a lower Cmax and has a lower availability, about 60%,[29] in comparison with that of INFS, which is 80 to 90%.[6] This means that a 100-μg dose of INFS will generate a higher Cmax than 100 μg of FPNS. However, the minimal commercially available strength of FPNS is 100 μg, which is double that of INFS, that is, 50 μg. Indeed, these dosages have been similarly suggested to start the treatment in patients tolerant to 60 mg of oral morphine equivalents, as they would be equivalents.

The aim of this randomized, crossover study was to assess analgesia and adverse effects of these 2 nasal preparations for the BTP management. The secondary outcome was to assess the efficacy and safety of the 2 fentanyl delivery systems by using doses proportional to the background opioid doses.

Methods

Study Design

This randomized, crossover, open-label study was conducted in a high-volume pain relief and supportive care unit. The study was approved by ethical committee of University of Palermo, and all patients provided their informed consent.

Patients

Adults were eligible if they had a diagnosis of cancer, were receiving opioids at doses equivalent to or greater than 60 mg oral morphine equivalents per day for background pain, had a background analgesia of mild intensity (≤4 on a numerical scale of 0–10), and were presenting 1 to 3 episodes of BTP per day.

Patients with unstable or uncontrolled pain (having a background pain intensity >4 on a numerical scale of 0–10) were not eligible for the study. Exclusion criteria were BTP not primarily related to cancer, past inability to tolerate fentanyl, treatment with monoamine oxidase inhibitors, history of alcohol or substance abuse, an expected short survival, and cognitive impairment. Other pharmacologic treatments were maintained if administered for at least 2 weeks. Patients with local problems of the nasal mucosa were also not eligible.

Procedures

Consenting patients who met inclusion criteria were assessed for the first 4 consecutive BTP episodes for 4 consecutive days. Patients admitted to inpatient setting were treated according to a routine protocol. After establishing around-the-clock opioid medication, according to the opioid titration process, and achieving a stable analgesia—with mean pain intensity equal to or less than 4/10 on a numerical pain rating scale from 0 to 10—for 2 consecutive days, patients were instructed to call for a BTP medication when their pain got severe or clearly distinguished from their background pain. BTP type was described as idiopathic or predictable.

Consecutive episodes were recorded during admission time. Each patient randomly received INFS or FPNS in doses proportional to opioids used for background analgesia for 2 pairs of consecutive episodes. For example, the minimum existing dose of 100 μg of FPNS was given to patients receiving 60 mg of oral morphine equivalents, 200 μg was given to patients receiving 120 mg of oral morphine equivalents, and so on. Similarly, in episodes treated with INFS, patients were administered 50 μg, 100 μg, and so on. For each episode of BTP, nurses recorded pain intensity (numerical scale of 0–10) and adverse effects intensity on a scale ranging from 0 to 3 (absent, mild, moderate, and severe) just before starting INFS or FPNS (T0) and then 5 (T5), 10 (T10), and 20 (T20) minutes after administration of the nasal drugs. Patients who were unsatisfied with the treatment could ask to stop the procedure and opt for their previous effective BTP medication (mainly intravenous morphine).

Efficacy Measures

The principal outcome was the evaluation of the number of episodes that benefited from the use of INFS or FPNS by using proportional doses of the basal opioid dosage at different point intervals. The administration of the BTP medication was considered successful whenever the decrease in pain intensity was more than 33% of baseline pain measurement. Secondary end points were the patient-averaged summed pain intensity difference 20 minutes after dosing (SPID20), defined as the cumulative sum of the recorded difference between pain intensity and baseline at each time point from 5 to 20 minutes post dose. Moreover, patients who received both treatments were asked about their preference.

Safety and Tolerability Assessment

Intensity of adverse effects at each point interval was recorded on a scale from 0 to 3. The occurrence of adverse effects of moderate to severe intensity (intensity of 2–3 on a verbal scale) or requiring a medical intervention was recorded.

Statistical Analysis

A sample size of 65 evaluable patients (considering at least 1 pair of episodes of BTP for a patient to achieve in a total of 65 pairs of episodes of BTP) yielded a statistical power of 80% with type I error of .05 and would allow the detection of a difference of 15% in pain intensity score reduction from a baseline of ≥33% or ≥50% between 2 treatment groups with BTP episodes. Statistical analysis of quantitative data, including descriptive statistics, was performed for all the items. All continuous data are expressed as mean ± standard deviation of the mean. Frequency analysis was performed using the Pearson's chi-square and Fisher exact tests as needed. One-way analysis of variance and Kruskal-Wallis statistical test were used to compare the different parametric or nonparametric variables between the treatment groups. One-way and mixed-model analyses of variance were used to examine within- and between-group effects, respectively, at the different time intervals. Data were analyzed by using the Epi Info software, version 3.2.2 (Centers for Disease Control and Prevention, Atlanta, GA), and SPSS, version 21.0 (SPSS, Inc, Chicago, IL). All *P* values were 2 sided, and *P* values less than .05 were considered statistically significant.

Results

A total of 70 patients were screened for the study. The mean age was 63.4 years (SD = 10.8, range 28–85), and 37 patients were males. The primary diagnoses were lung (n = 15), genitourinary (n = 12), gastrointestinal (n = 11), pancreas (n = 9), breast (n = 8), and other (n = 15). Information on the type of BTP was available for 46 patients: idiopathic in 28 patients, predictable in 10, and both in 8 patients.

The opioid dose used for background pain, expressed as mean oral morphine equivalents, was 191.6 mg (SD = 111.2, range 490).

A flow diagram of the study is presented in Fig 1. One patient declined to participate. Seven patients did not receive any study medication: 6 did not have episodes of BTP for 4 consecutive days, and 1 had poor compliance. Fifteen patients received only 1 study medication

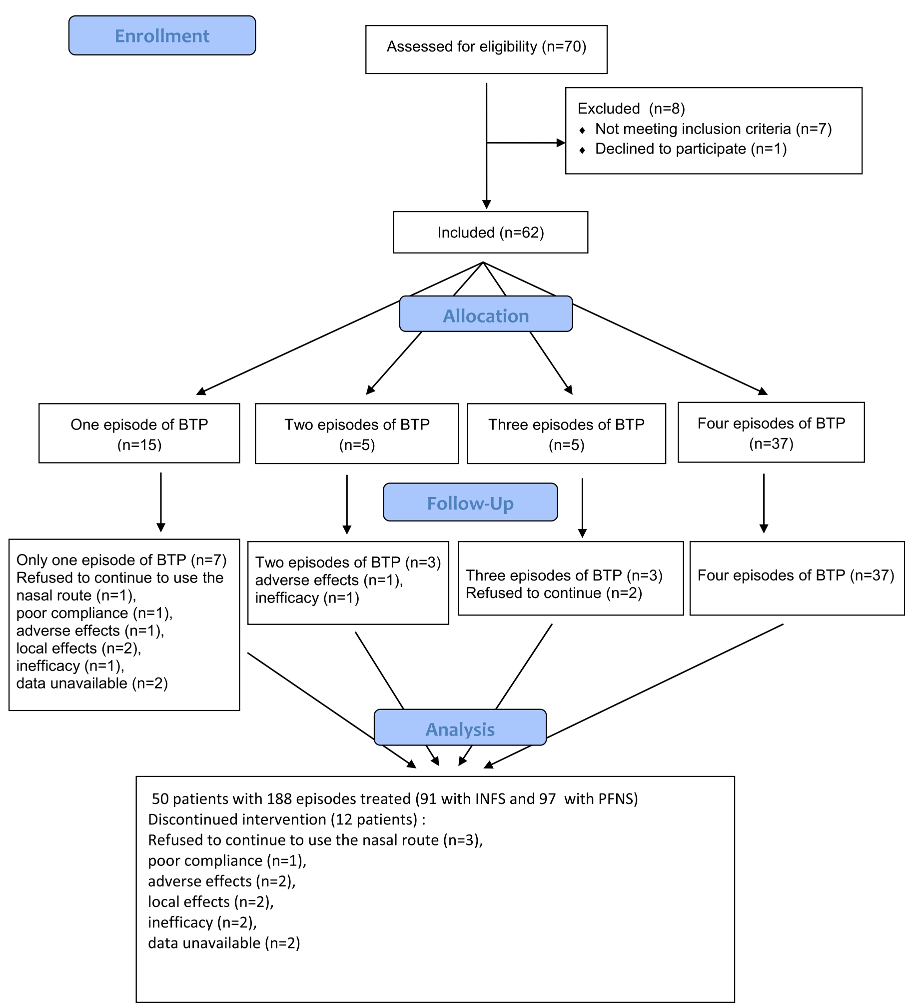

Figure 1. Study flow chart.

because they had only 1 episode of BTP (n = 7) or because they refused to continue to use the nasal route because of poor satisfaction (n = 1), poor compliance (n = 1), adverse effects (n = 1), local effects (n = 2), and inefficacy (n = 1). Data were unavailable in 2 patients. Forty-seven patients took both study medications. Two groups of 5 patients each had 2 and 3 episodes of BTP, respectively, and 37 patients had 4 episodes. Globally there were 84 pairs of episodes of BTP to compare. Intravenous morphine was used 20 minutes after drug administration in 6 and 7 episodes in INFS and PFNS, respectively.

A total of 188 episodes were treated, of which 91 and 97 were administered INFS and PFNS, respectively. No differences were found in the number of episodes treated with the 2 drugs and age ($P = .943$), gender ($P = .959$), primary diagnosis ($P = .984$), type of opioids used for background analgesia ($P = .415$), doses of oral morphine equivalents used for background pain ($P = .132$), pain mechanism ($P = .955$), and type of BTP ($P = .983$).

The mean doses of INST and FPNS were 165 μg (SD = 97, range 50–400) and 328 μg (SD = 190, range 100–800), respectively. The changes in pain intensity (numerical scale 0–10) after INFS and FPNS at the different time intervals are shown in Table 1.

The number of episodes in the 2 groups with a decrease in pain intensity >33% and 50%, respectively, at the different time intervals is presented in Fig 2. Globally, a decrease in pain intensity of >33% at T5, T10, and T20 was observed in 16, 102, and 159 treated episodes, respectively. A statistical difference between INFS and FPNS was found 5 minutes after the administration ($P = .016$). A decrease in pain intensity of >50% at T5, T10, and T20 was observed in 4, 40, and 126 treated episodes, respectively. A statistical difference between INFS and FPNS was found 20 minutes after the administration ($P = .043$).

The mean SPID20 values of INFS and FPNS were 6.7 (SD = 3.1) and 7.5 (SD = 4.3), respectively. The difference was not significant ($P = .165$).

No differences in changes in pain intensity were found between episodes treated with ≥200 μg of INST or ≥400 μg of FPNS and episodes treated with lower doses.

Adverse Effects

Adverse effects were evaluated before administering the study drugs. The changes in intensity of the principal adverse effects are shown in Table 2. Adverse effects were of mild entity in the majority of cases or were preexistent because of basal opioid therapy. Only a minority of patients developed adverse effects of moderate or severe intensity. Five patients reported drowsiness of moderate intensity in more BTP episodes (3 patients with doses of INST 100, 200, and 400 μg, and 2 patients with doses of FPNS 400 μg); 2 patients developed nausea of moderate intensity in more BTP episodes (with INST μg 100). Apart from patients who discontinued the study (see above), 2 patients developed nasal pruritus (1 after FPNS, and 1 after INFS).

Table 1. Changes in Pain Intensity (Numerical Scale 0–10) at the Different Time Intervals

	T0	T5	T10	T20
FPNS (n = 97)	6.8 (.98)	5.6 (1.10)*,†	4.4 (1.43)*	3.0 (1.71)*,‡
INST (n = 91)	6.8 (.83)	5.8 (1.03)*	4.6 (1.36)*	3.4 (1.51)*

*$P \leq .0005$ versus T0.
†$P = .016$ versus INFS.
‡$P = .043$ versus INFS.

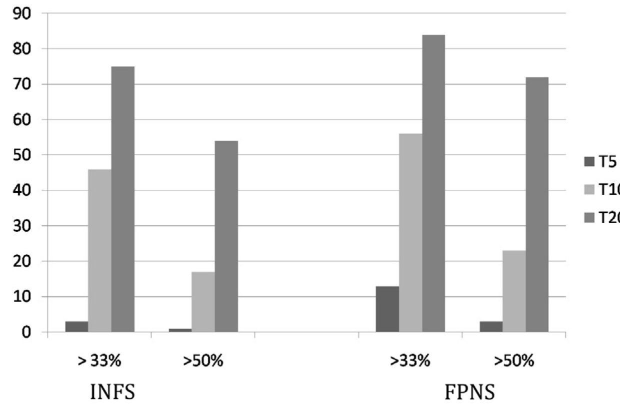

Figure 2. Number of episodes in the 2 groups with a decrease in pain intensity of >33% or 50% at the different time points (T5, T10, and T20).

Preference

Forty-two patients provided information about their preference of the 2 nasal drugs. Most patients did not find substantial differences (indifferent). Seven patients preferred FPNS, and 3 patients preferred INST.

Discussion

This comparative study has shown that INFS and FPNS are effective and well-tolerated treatments for BTP management. Both delivery systems provided fast and significant analgesia. For example, 50% and 57% of episodes treated with INFS and FPNS, respectively, had a decrease in pain intensity of ≥33% after 10 minutes, and 18% and 23% of episodes treated with INFS and FPNS, respectively, had a more consistent decrease in pain intensity (≥50%). The level of pain intensity 20 minutes after administration was about 50% of the pain intensity of BTP. This change, which mainly corresponded with the background analgesia, is considered clinically meaningful for patients.[24] No preference for 1 of the 2 products was given by patients who received both delivery systems.

Table 2. Changes in Intensity of the Principal Adverse Effects in the 2 Groups

	INFS				FPNS			
	T0	T5	T10	T20	T0	T5	T10	T20
Nausea-vomiting	.15	.13	.08	.07	.08	.07	.05	.17*
Drowsiness	.44	.46	.60	.63*	.43	.49	.53*	.54*
Confusion	.22	.22	.15	.19	.23	.20	.18	.24

*$P < .05$.

The other important finding is that both treatments in doses proportional to the basal opioid dose used for background pain were effective as well as tolerable, confirming experience accumulated through the years and the findings of some controlled studies,[13-24] even when higher doses were used. Finally, despite a similar analgesic trend, FPNS had a major impact at the intervals taken into consideration.

There are some pharmacologic considerations that may explain these observations. The similar onset of action of FPNS could seem to be unexpected, given the characteristics of the products. However, although FPNS generates a lower Cmax for its formulation, modulating fentanyl absorption, the doses given in this study were exactly double those of INFS used as the minimal available strengths commonly employed as starting doses in titration studies, which are 100 and 50 μg, respectively. INFS availability has been shown to be 80 to 90%,[7] whereas FPNS availability is about 60%.[4] At the end, about 60 and 40 μg will be available at dose strengths of FPNS 100 and INFS 50 μg, respectively, with one-third of availability in favor of FPNS. Of interest, a similar analgesic trend was observed at the different dose levels that were given proportional to the basal opioid. Thus, it is likely that patients may benefit from similar but not identical amounts of fentanyl. The presence of a certain level of tolerance may explain this finding, also with respect to the occurrence of adverse effects. In patients responsive to opioids, an opioid dose proportional to the basal opioid regimen has a predictable therapeutic window that provides efficacy with limited toxicity. Thus, opioid tolerance may have a protective role in patients receiving opioids long-term when fentanyl products are given to rapidly relieve BTP.

Most studies of BTP medication have suggested titrating the dose of ROOs given for BTP.[1] However, these randomized trials have never specifically examined this issue, and the information gathered is just consequential to the study design aimed to demonstrate superiority of ROOs over placebo, oral morphine, or usual oral opioids, or to evaluate the safety and efficacy of ascending doses of ROOs in dose-finding studies.[15] Many controversies surround this issue. Dosing proportional to basic opioid regimen has been proposed as an alternative to dose titration.[10] A simulation of a calculation of doses of opioids used for background analgesia and those achieved after individual titration showed mean values of proportional doses very close to those found after titration.[20] In a "real world" study reproducing a clinical scenario of patients receiving opioids for BTP, although the dose of oral opioids used as rescue medication was 18% of the around-the-clock opioid dose, for oral transmucosal fentanyl titrated to determine the effective dose, the rescue dose was about 35% of the around-the-clock dose,[30] suggesting that the titration process may provide even higher doses than those expected by using doses proportional to the basal regimen. For instance, the only existing controlled study performed using a fentanyl buccal tablet has evidenced that proportional doses are more effective than the dose titration approach, without higher risks of adverse effects,[22] confirming a series of open-label studies in which proportional doses were highly effective and well tolerated.[13-25]

Finally, there is clinical legend suggesting that the rescue dose of opioids for BTP should be 10% of the daily dose of scheduled opioids. Several studies of proportional doses have shown that to produce meaningful and clinical analgesic effects, it is necessary to administer 15 to 20% of the daily dose.[13-24]

Limitations of this study lie in the lack of blinding. Moreover, such types of studies are complex and require economic support from the pharmaceutical industry, which was not involved in our case. The study was also designed to assess patients' preferences. Incomplete data are common in such studies. However, the number of pairs of episodes with both treatments was adequate.

In conclusion, INFS and FPNS were effective and well-tolerated treatments for BTP management. Both delivery systems, in doses proportional to the basal opioid regimen, provided significant analgesia within 5 to 10 minutes, achieving a mean decrease of more than 50% in pain intensity 20 minutes after administration, without producing relevant adverse effects.

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