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ORIGINAL ARTICLE

Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients

Russell K. Portenoy, MD; William Raffaeli, MD; Luis M. Torres, MD; Thomas Sitte, BS; Akhil Chandra Deka, MD; Ileana Gonzalez Herrera, MD; Mark S. Wallace, MD; on behalf of the Fentanyl Nasal Spray Study 045 Investigators Group

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ABSTRACT

Objective: *To assess the long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray (FPNS) in patients with breakthrough cancer pain (BTCP).*
Design: *A multicenter, open-label study.*
Patients: *Patients with chronic cancer pain treated with ≥60 mg/d oral morphine or equivalent experiencing 1-4 episodes per day of BTCP.*
Intervention: *All patients entered into a 16-week treatment phase after undergoing a dose-titration phase with FPNS.*
Main outcome measures: *Safety and tolerability were assessed by adverse events (AEs) and by nasal tolerability assessments. Consistency of effect was monitored through additional rescue medication use and FPNS dose change.*
Results: *Four hundred three patients were included in the safety analyses. Of these, 356 patients entered the treatment phase and 110 patients completed the study. FPNS was self-administered for 42,227 episodes. During the treatment phase, 99 patients (24.6 percent) reported treatment-related AEs; most were mild or moderate and typical of opioids. Serious AEs were reported by 61 patients (15.1 percent), but only five were considered related to study drug. Of the 80 deaths that occurred during this study, one was assessed as possibly related to study drug. Nasal assessments revealed no significant local effects. No additional rescue medication was required after 94 percent of FPNS-treated episodes. More than 90 percent of patients required no increase in their initial dose of FPNS.*
Conclusions: *FPNS use for BTCP was associated with AEs, typical of opioids, with no evidence of nasal toxicity. A large proportion of BTCP episodes were treated with a single dose, and doses remained stable over the 4-month period.*

INTRODUCTION

Breakthrough cancer pain (BTCP) has been defined as a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.[1] It has a prevalence that ranges from 33 to 95 percent depending on the severity of illness and the setting of care,[2,3] and it has been associated with relatively more severe chronic pain, functional impairment, psychological distress, and impaired quality of life.[4-6] Some surveys have linked BTCP to increased healthcare costs.[7-9] These data affirm that BTCP is a clinically important phenomenon and support efforts to improve its recognition and management.

Although the phenomenology of BTCP episodes is highly variable, the most common temporal pattern is characterized by a rapid onset and relatively short duration; the time to peak pain intensity generally is measured in minutes, and the duration is usually less than an hour.[3] Most patients with cancer

pain and breakthrough episodes report that severe or excruciating BTCP episodes may occur three to four times per day and about half report that these pains occur without warning.[2,3]

The usual clinical approach to the management of BTCP involves prescription of a so-called rescue dose, a short-acting opioid drug offered as needed for episodic severe pain. The usual rescue drugs are oral formulations, such as immediate-release morphine sulfate (IRMS) or oxycodone.[10] These drugs have a time-action relationship that does not closely match the typical time course of a BTCP episode. With an onset of effect at least 20 minutes after the dose and a peak effect more than 1 hour later, oral rescue drugs may be unable to provide optimal relief for painful episodes that peak and then resolve far earlier. This mismatch has provided the rationale for the development of new methods of opioid drug delivery intended to improve the management of BTCP by providing a more rapid onset of effect. Methods to provide reliable transmucosal delivery of lipophilic opioids, such as fentanyl, have received the greatest attention. Several oral transmucosal fentanyl citrate (OTFC) formulations have already been commercialized for the treatment of BTCP,[11-14] and other formulations are in development. The aim of these new products is to increase the rapidity of onset and consistency of effect and to improve the ease, acceptability, and tolerability of treatment.

Intranasal delivery of opioids may offer a simple and acceptable strategy for new formulations that target BTCP. Tolerability of oral formulations may be a concern for some patients with cancer with oral problems such as xerostomia.[15-17] A recent survey found that the existence of oral mucosal disease is one reason for limited prescribing of OTFC.[18] The intranasal route eliminates this concern and may offer a method for relatively rapid and efficient drug absorption because the nasal tissues are highly vascularized, have good permeability, and avoid first-pass metabolism.[19,20] Intranasal sprays may also be well accepted by patients because they are familiar with their use as over-the-counter decongestants.

Conventional intranasal products are simple aqueous solutions delivered as sprays. These formulations may not be optimal because of the risk of dose-to-dose variability in absorption related to the extent of drainage from the nose. When the drug delivered is a potent opioid, such as fentanyl, there is relatively a greater concern that fluctuations in absorption may lead to variability of response.

To reduce this risk of fluctuation, a fentanyl pectin nasal spray (FPNS) was developed to control the absorption profile of fentanyl across the nasal mucosa. With intranasal administration, the pectin in each droplet of the FPNS solution interacts with calcium ions found in the nasal mucosa and forms a thin layer of flexible gel that adheres to the mucosa. This gelling diminishes the risk of runoff or swallowing of the solution, which in turn may promote consistent delivery of doses that yield a drug concentration-time relationship designed to mirror the time course of a typical BTCP episode.[21] Pharmacokinetic studies have reported significantly faster fentanyl absorption with FPNS (T_{max}, 20 minutes) than with oral transmucosal fentanyl citrate (T_{max}, 90 minutes) and enhanced bioavailability.[21] Furthermore, although not a direct comparison, the rapid absorption of FPNS also compares favorably with reported T_{max} values of around 40 to 60 minutes for fast-dissolving buccal fentanyl tablets.[22]

Two randomized, controlled, double-blind phase 3 studies, conducted in a total of 224 patients (831 FPNS-treated episodes), have confirmed that FPNS (100-800 μg) provides pain relief that is superior to placebo or an oral morphine rescue dose, statistically separates from the comparator at only 5 minutes, and is more likely to be at a level associated with a clinically meaningful response from 10 minutes onward.[23,24]

An open-label trial was undertaken to provide additional information about the long-term safety, tolerability, and consistency of FPNS effectiveness and dose. The 16-week duration of the study was considered sufficient to evaluate the long-term safety and tolerability of a nasally administered product intended for use in a population with limited life expectancy. This study accrued patients who completed either of the phase 3 randomized controlled trials and others with BTCP who had not been previously exposed to FPNS.

METHODS

Study design

This was a multicenter, prospective, open-label study of FPNS in the treatment of BTCP in patients receiving regular opioid therapy. The study was conducted at 91 centers in Argentina, Costa Rica, the Czech Republic, France, Germany, the United Kingdom, India, Italy, the Netherlands, Poland, Spain, and the United States. The study protocol was

approved by the institutional review boards at the participating institutions, and all patients provided signed informed consent.

Patients

Patients who completed one of the two controlled FPNS trials[23,24] and had ongoing BTCP episodes, and intended to continue opioid therapy for chronic cancer pain, and met other study entry criteria at the end of the controlled trial (see later) were informed about their eligibility for this study. The controlled trials included the placebo-controlled study CP043 (maximum 10 BTCP episodes treated per patient [seven with FPNS and three with placebo]),[23] which was conducted in the United States, Argentina, and Costa Rica, and the double-blind, double-dummy, active controlled study CP044 (maximum 10 BTCP episodes treated per patient [five with FPNS and placebo oral morphine and five with immediate-release oral morphine and placebo nasal spray]),[24] which was conducted in the European Union and India.

Eligible patients who had not participated in a controlled trial included men and women aged 18 years and older who had a histologically confirmed diagnosis of cancer were receiving a fixed-schedule opioid regimen at a total daily dose equivalent to or greater than 60 mg/d oral morphine and had one to four episodes of moderate to severe BTCP per day. Patients who had uncontrolled or rapidly escalating background pain and those who were medically unstable were not eligible. Other exclusion criteria included breakthrough pain not primarily related to cancer, past inability to tolerate fentanyl or other opioids, history of alcohol or substance abuse, treatment with monoamine oxidase inhibitors within the previous 30 days, and treatment with any other investigational drug within the previous 30 days. Additionally, patients with any disorder or medication use likely to adversely affect the normal functioning of the nasal mucosa were not eligible.

Procedures

Patients who consented to this open-label trial following completion of a controlled trial underwent screening and directly entered the 16-week treatment phase using the FPNS dose taken during the earlier trial. This was followed by an end-of-treatment phase (1 to 14 days after the last dose) during which patients returned to the clinic for final acceptability and safety assessments. Patients who requested continuation of FPNS were allowed to enter a discretionary extension period. The frequency of review during the extension period was at the discretion of the investigator and only safety data (adverse events [AEs] and serious AEs) were collected during this phase (data not presented).

For patients without prior exposure to FPNS, the study consisted of a screening phase, an open dose-titration phase, the 16-week open-label treatment phase, the end-of-treatment phase, and the extension period if appropriate. During the titration phase, the approach used in the controlled trials was applied: Patients were initially treated with the lowest FPNS dose (100 μg) and gradually uptitrated, 1 dose of FPNS per episode of pain, to a maximum of 800 μg per dose. The effective dose was defined by the successful (defined as pain relief within 30 minutes without unacceptable AEs) treatment of two consecutive episodes of BTCP.

During the treatment phase, all patients were given up to a 4-week supply of FPNS and were instructed to self-administer the effective dose of FPNS for a maximum of four episodes of BTCP per day. If pain relief was inadequate after 30 minutes, the prestudy rescue medication could be taken. Stepwise adjustments in the dose of FPNS were permitted for all patients based on the patient's report of efficacy and side effects, in consultation with the prescribing clinician. However, a dose of FPNS between 100 and 800 μg had to be identified as satisfactory for the patient to continue in the study.

Assessments and outcome measures

This open-label study was designed to evaluate the 4-month safety and tolerability of FPNS and did not collect data on pain intensity or pain relief. These data were collected in the randomized, controlled studies, which are better designed to show clinical efficacy.

Most patients were treated in the outpatient setting. Patients were contacted by telephone at least weekly; more frequent contacts were made during the titration period. The calls were used to review appropriate use, discuss the need for dose adjustments, and obtain information about dosing and safety.

Electronic diaries (e-diaries) were used to collect information at the time of a treated BTCP episode during both the dose-titration phase (for patients

who required titration) and the treatment phase. AEs, patient nasal symptom scores, and use of additional rescue medication were recorded.

Objective (clinical) and subjective nasal assessments were performed at screening and at weeks 8 and 16. Objective nasal assessment by the study physician graded obstruction and inflammation using 4-point scales (0 = absent to 3 = severe) and the presence of discharge on a scale of none, mild, moderate, or severe. The side of the nose most affected by changes (if any) and the color of nasal mucosa were also recorded. Subjective nasal assessments were performed by the patient using a 10-item questionnaire. Each item was rated on a 4-point scale, from 0 = absent to 3 = severe, before the first use of study drug, 1 hour after each dose of study medication for the first week only, and during weeks 4, 8, 12, and 16. The items rated were stuffy/blocked nose, runny nose, itching/sneezing, crusting/dryness, burning/discomfort, bleeding of nose, cough, postnasal drip, sore throat, and taste disturbance.

Statistical analysis

Safety analyses were performed on the safety population, which included all patients—those previously enrolled in studies CP043 or CP044 and those who were newly enrolled—who had received at least one dose of study drug. Treatment-emergent AEs (TEAEs) were considered to be AEs that began after study drug administration and were either not present at baseline or increased in intensity or frequency during treatments when compared with baseline. Both the nature and number of TEAEs were tabulated. Each TEAE was graded by the investigator in terms of severity and the likelihood of a relationship with the study drug. The number of study withdrawals due to TEAEs was also noted. All changes in FPNS dose were similarly summarized. The percentage of BTCP episodes after which additional rescue medication was taken within 60 minutes after the FPNS dose was tabulated for weeks 0 and 4, weeks 5 and 8, weeks 9 and 12, and weeks 13 and 16. Nasal examinations and subjective symptom assessments were recorded.

RESULTS

Patient disposition and baseline demographics

Patient disposition is depicted in Figure 1. Information about safety and tolerability could be collected from all patients who received at least one dose of FPNS—a total of 403 patients. This included

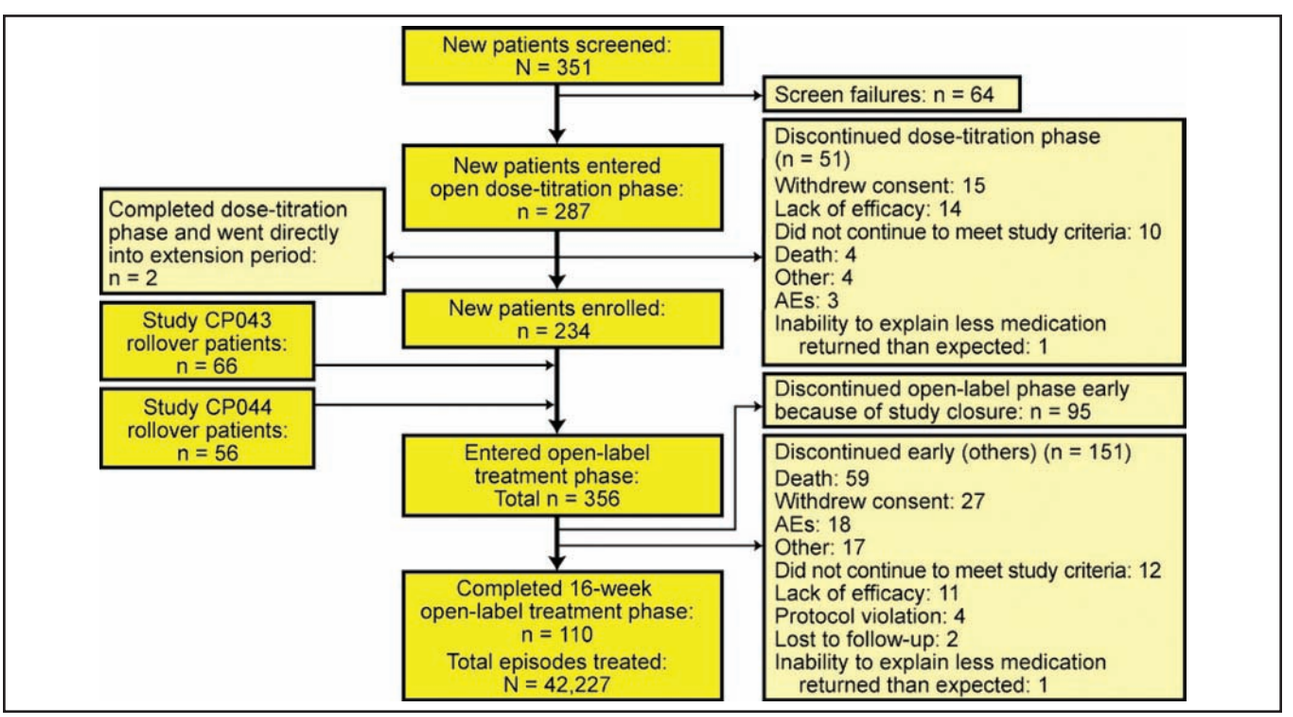

Figure 1. Study disposition.

the patients who entered the titration phase without those who did not receive any doses of FPNS after screening (N = 281), plus those who rolled over from the controlled trials and entered the treatment phase without titration (N = 122). The mean age (±SD) of the safety population was 53.8 (±12.23) years; 53.1 percent were male and 53.1 percent were Caucasian (Table 1).

In addition to information about safety, additional information about dosing and other outcomes was collected from the 356 patients who entered the treatment phase. These patients included 122 patients who had previously participated in a controlled trial (66 patients from study CP043 [FPNS vs placebo] and 56 patients from study CP044 [FPNS vs IRMS study]) and 234 newly treated patients. The latter group included 67 percent of the 351 new patients screened for the study and 81.5 percent of the 287 patients who began dose titration; six of the 51 patients who withdrew during dose titration (Figure 1 details reasons for withdrawal) never took any doses of FPNS.

In addition to the 356 patients who entered the treatment phase, two patients were successfully titrated but directly entered the extension phase because recruitment to the treatment phase had closed by the time they completed dose adjustment. These patients were included only in the safety population.

Of the 356 patients who entered the treatment phase, 246 discontinued the study before completing 16 weeks of therapy. The main reasons for early discontinuation were study closure (95 patients; 26.7 percent) and death (59 patients, 16.6 percent). The distribution of early discontinuations was as follows: 1-7 days, n = 63; 8-14 days, n = 18; 15-28 days, n = 49; 29-90 days; n = 129; >90 days, n = 138. A total of 110 patients (30.9 percent) successfully completed 16 weeks of treatment.

The e-diary was given to all patients who directly entered the treatment phase after completing a controlled trial and to the patients without prior FPNS exposure who entered the titration phase. A total of 397 patients provided information on the e-diary. Among these patients, the mean duration of FPNS exposure was 60.4 days.

Table 1. Baseline patient demographics (N = 403)*

Age, y	
Mean (SD)	53.8 (12.23)
≤60 n (percent)	298 (73.9)
>60 n (percent)	105 (26.1)
Minimum-maximum	21-84
Race, n (percent)	
Caucasian	214 (53.1)
Black	15 (3.7)
Asian	135 (33.5)
American Indian	1 (0.2)
Hispanic	38 (9.4)
Gender, n (percent)	
Men	214 (53.1)
Women	189 (46.9)
Opioid use,† n (percent)	
Morphine	241 (59.8)
Fentanyl	127 (31.5)
Oxycodone	58 (14.4)
Methadone	37 (9.2)
Hydromorphone	18 (4.5)
Other opioids	17 (4.2)
Codeine/hydrocodone	6 (1.5)
Buprenorphine	4 (1.0)
Tramadol	4 (1.0)

*Patients exposed to ≥1 dose of fentanyl pectin nasal spray (safety population).
†Patients could be on more than one opioid.

Safety

A total of 99 (24.6 percent) of 403 patients reported TEAEs, the most common of which were dizziness (5.2 percent), vomiting (3.7 percent), constipation (3.5 percent), and somnolence (3.5 percent; Table 2). Of the 403 patients, TEAEs were reported as mild in 80 patients (19.9 percent), moderate in 104 patients (25.8 percent), and severe in 126 patients (31.3 percent). The proportion of patients reporting at least one AE after taking FPNS was higher following the 800-μg dose (20.1 percent) than the lower doses (11.2

Table 2. Treatment-emergent adverse events by type (all phases), n (percent)*

Event type	Dose of fentanyl pectin nasal spray				
	100 μg (n = 276)	200 μg (n = 242)	400 μg (n = 216)	800 μg (n = 144)	All (N = 403)
Dizziness	5 (1.8)	7 (2.9)	4 (1.9)	7 (4.9)	21 (5.2)
Vomiting	3 (1.1)	5 (2.1)	3 (1.4)	4 (2.8)	15 (3.7)
Constipation	4 (1.4)	2 (0.8)	6 (2.8)	2 (1.4)	14 (3.5)
Somnolence	4 (1.4)	2 (0.8)	4 (1.9)	4 (2.8)	14 (3.5)
Nausea	2 (0.7)	2 (0.8)	3 (1.4)	3 (2.1)	10 (2.5)
Nasal discomfort	4 (1.4)	2 (0.8)	4 (1.9)	0 (0)	9 (2.2)
Headache	1 (0.4)	2 (0.8)	1 (0.5)	2 (1.4)	5 (1.2)
Rhinorrhea	4 (1.4)	0 (0)	9 (4.2)	6 (4.2)	5 (1.2)
Pruritus	0 (0)	0 (0)	1 (0.5)	3 (2.1)	4 (1.0)
Confusional state	0 (0)	0 (0)	1 (0.5)	2 (1.4)	3 (0.7)
Euphoric mood	0 (0)	0 (0)	0 (0)	2 (1.4)	2 (0.5)
Overall (all terms)	31 (11.2)	23 (9.5)	29 (13.4)	29 (20.1)	99 (24.6)

*Patients having at least one treatment-emergent adverse event.

percent at 100 μg, 9.5 percent at 200 μg, and 13.4 percent at 400 μg). However, analysis by episodes did not show the same increase at the higher dose (2.73 percent at 100 μg, 2.16 percent at 200 μg, 1.75 percent at 400 μg, and 1.46 percent at 800 μg).

A total of 80 deaths occurred during this open-label trial. Four occurred during the dose-titration phase, 59 during the treatment period, 14 during the extension phase, and three immediately after study completion. Of these 80 deaths, 33 were attributed directly to disease progression, and all but two others were caused by expected complications of advanced cancer (noted by an investigator to be anemia, bradycardia, cardiorespiratory arrest, hemorrhage, increased intracranial pressure, multiorgan failure, myocardial infarction, pulmonary failure, septic shock, urinary tract infection, vascular injury). Of the two deaths assessed as related to the study drug, one was considered by an investigator to be possibly related and the other remotely related. The former was a patient who died after peritonitis complicated bowel perforation, which was believed to be related to opioid-induced constipation. The latter was a patient whose cause of death was noted to be septic shock.

Nonfatal secondary adverse events (SAEs) were reported in 61 (15.1 percent) patients overall. Fifty-six of these SAEs were considered not related to study drug. Of the remaining five patients with SAEs, one had severe dyspnea (breathlessness) that was considered by the investigator as being probably related to the study drug; three had events (one cyanosis, loss of consciousness, and upper airway obstruction; one constipation; and one nausea and vomiting) that were considered possibly related; and one had nausea and vomiting that was considered to be remotely related.

The patient who had the SAE of severe cyanosis, loss of consciousness, and upper airway obstruction considered possibly related to study drug developed this problem following the use of more than one dose of FPNS for a single episode of BTCP what was not according to the protocol. This occurred during the first week of treatment and was associated with multiple reports from the patient that the bottles in the carton in use were failing to deliver study drug. It became apparent that the patient had misinterpreted a lack of sensation of drug delivery as nondelivery and had administered additional sprays (probably five, instead of the intended single spray), leading to the overdose. Following his rapid recovery from the effects of this event, the patient was again instructed about the appropriate use of the study drug and admonished never to administer additional sprays even if drug did not appear to have been delivered.

He subsequently continued to use FPNS through 16 weeks of the treatment phase and through an additional 126 days in the extension period. There were no further incidents of possible overuse or overdose, and the patient's overall correlation between drug used and episodes reported in the e-diary was appropriate.

Withdrawals due to AEs were distributed across FPNS dose groups (100 μg: three patients; 200 μg: six patients; 400 μg: four patients; 800 μg: seven patients). Of the 20 patients who discontinued treatment due to an AE, 11 of these AEs were not considered to be related to study drug. Of the remaining nine patients, withdrawal was due to an AE considered to be related to the study drug (severe urticaria, moderate nausea, severe intestinal perforation, and mild headache were considered possibly related; moderate intentional drug misuse, moderate mouth ulceration, moderate nausea, and severe dyspnea [breathlessness] were considered probably related; and moderate constipation was considered definitely related). No treatment-emergent changes in laboratory or clinical safety parameters suggested safety issues associated with short- or long-term FPNS treatment.

Nasal tolerability

Objective nasal examinations were undertaken to determine treatment effect on the nasal mucosa. Most patients had normal findings of the nasal examination at screening and at the end-of-treatment visits. There was no consistent pattern of findings from these examinations that would indicate FPNS is associated with changes in nasal obstruction, inflammation, discharge, or color of mucosa, even after more than 4 months of treatment. In the subjective symptom assessments (Table 3), no consistent patterns of abnormal nasal symptoms such as stuffy/blocked nose, runny nose, itching/sneezing, nasal crusting/dryness, burning/discomfort, nasal bleeding, cough, postnasal drip, sore throat, or taste disturbance were reported.

FPNS dosing

A total of 42,227 BTCP episodes were treated during the treatment phase. Of these, 5,338 episodes (12.6 percent) in 276 patients were treated with FPNS 100 μg, 6,711 episodes (15.9 percent) in 242 patients were treated with FPNS 200 μg, 13,897 episodes (32.9 percent) in 216 patients were treated with FPNS 400 μg, and 16,281 episodes (38.6 percent) in 144 patients were treated with FPNS 800 μg.

After selection of a satisfactory FPNS dose, either through participation in an earlier controlled trial or through a formal dose titration phase preceding the treatment phase, there were few dose changes. More than 90 percent of patients who entered the 16-week

Table 3. Nasal tolerability at end of treatment, n (percent)

Parameter*	Absent	Mild	Moderate	Severe
Stuffy/blocked nose	210 (92.9)	13 (5.8)	3 (1.3)	0 (0)
Runny nose	200 (88.5)	22 (9.7)	2 (0.9)	2 (0.9)
Itching or sneezing	217 (96.0)	9 (4.0)	0 (0)	0 (0)
Nasal rusting or dryness	206 (91.2)	18 (8.0)	1 (0.4)	1 (0.4)
Burning or discomfort	218 (96.5)	5 (2.2)	3 (1.3)	0 (0)
Nasal bleeding	223 (98.7)	3 (1.3)	0 (0)	0 (0)
Cough	196 (86.7)	29 (12.8)	1 (0.4)	0 (0)
Postnasal drip	203 (89.8)	20 (8.8)	2 (0.9)	1 (0.4)
Sore throat	212 (93.8)	11 (4.9)	2 (0.9)	1 (0.4)
Taste disturbance	197 (87.2)	26 (11.5)	2 (0.9)	1 (0.4)

*End of treatment: n = 312; missing data: n = 86; percentage representing evaluable data: n = 226.

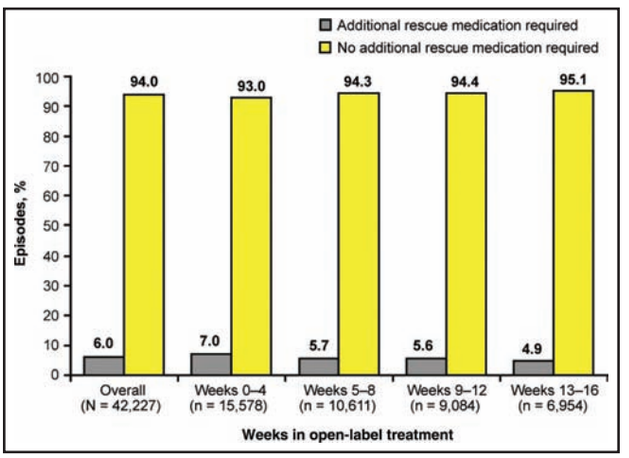

Figure 2. Additional rescue medication use across time.

treatment phase required no increase in their initial dose of FPNS during their participation. After converting the total daily dose of the regularly scheduled opioid into morphine-equivalent milligrams using standard conversion ratios, there was no relationship between the effective FPNS dose and the total daily dose of the opioid used to treat background chronic pain.

Patients seldom required their usual rescue drug after taking a dose of FPNS to treat a BTCP episode. Of the 42,227 BTCP episodes treated with FPNS, 94.0 percent did not require additional rescue medication within 60 minutes (Figure 2). The need for a subsequent dose of the usual rescue drug after FPNS was taken, which declined from 7.0 percent of episodes between weeks 0 and 4 to 4.9 percent of episodes between weeks 13 and 16.

DISCUSSION

The need to improve the recognition and management of BTCP has been established through a series of epidemiologic studies that provide evidence that episodic severe pain is both prevalent and associated with numerous adverse consequences.[2,3,5,6] Use of a short-acting opioid rescue drug is now a widely accepted strategy for the treatment of BTCP.[25] Although clinical observation indicates that many patients benefit from orally administered rescue drugs, there is a clear mismatch between the time-action relationship of these drugs and the time course of a typical episode of BTCP, and this mismatch has generated interest in the development of rapid-onset opioid formulations with relatively early peak effects and potentially shorter durations of action.

FPNS is an intranasal spray that has been developed specifically for BTCP. Two controlled trials have demonstrated efficacy when compared with placebo and oral morphine,[23,24] a relatively rapid onset, and both systemic and local safety and tolerability during short-term dosing. The present open-label trial extends these findings by confirming good safety and tolerability, as well as consistency of effectiveness and dose, during a longer period of drug administration.

The results demonstrate that a large majority of patients with cancer who are able to identify an effective FPNS dose continue with this dose for a prolonged period. As in the studies of other rapid-onset fentanyl formulations, no obvious relationship between the opioid dose taken chronically and the effective FPNS dose was found in this study. This finding supports the conclusion that gradual upward titration from a low initial dose is appropriate whenever FPNS or another transmucosal fentanyl formulation is used for BTCP in clinical practice. In this study, identification of the effective FPNS dose was followed by little use of additional rescue drug (6 percent of FPNS-treated episodes) and a very limited need for further dose escalation (only 10 percent of patients) during a period that extended to 4 months for some patients. The factors that contribute to this dose consistency are not known, and given the open-label design of this study, all findings related to analgesic effects are tentative. Nonetheless, there was no indication that dose escalation was needed routinely, and this observation is reassuring in terms of the clinical need for long-term treatment effectiveness.

Open-label studies provide important data about safety and tolerability. This study demonstrated that nasal tolerability during long-term FPNS dosing is good and there were no treatment-emergent changes in laboratory or clinical safety parameters that raised safety concerns. The side effects during FPNS treatment are generally typical of opioid drugs and mainly mild to moderate. Only nine of the patients who entered the trial withdrew as a result of an AE; most withdrawals were related to study closure or progressive illness. The observation that more patients experienced TEAEs and treatment withdrawals at the 800-μg dose than at the other doses is interesting, but is probably related to the higher number of patients and episodes treated at that dose, as the percentage of treated episodes with associated AEs did not show such an increase.

Deaths and serious nonfatal AEs occurred in more than one-third of the patients who entered the

trial. Review of each individual case by the investigators concluded that two of 80 deaths and five of 61 SAEs had any possible relationship to the study drug. The large number of events that were unrelated to the study drug indicates the severity of illness that characterized the study sample and underscores the challenge in treating severe pain in patients with progressive illness, who are expected to experience complications and decline that may complicate treatment. Of the seven events (two deaths and five nonfatal SAEs) determined to have some relationship with the study drug, one was judged to be probably related, four possibly related, and two remotely related. The nonfatal SAE that was determined to be probably related was characterized by dyspnea, a symptom unlikely to occur as a direct effect of opioid toxicity; although other contributing factors are likely, there is no clear explanation for this occurrence. One possibly related nonfatal episode of respiratory depression was due to an unintentional overdose, and the other events considered possibly related were gastrointestinal, including one patient who died after bowel perforation that was most likely related to constipation.

Although occasional drug-related SAEs may be unavoidable when opioids are used to manage severe pain in a population with serious illnesses such as cancer, their occurrence during this study highlights the need for clinician education in the safe use of these drugs, systems of care that allow appropriate monitoring over time, and appropriate instruction of both patients and caregivers about approaches to minimize the risks associated with treatment. To minimize the risks associated with unintentional overdose, the FPNS device has been developed to give an audible click with each spray, and a dose counter is provided to show the number of sprays that remain. In addition, the storage container is child resistant to prevent accidental exposure.

To address concerns about the acceptability of long-term nasal drug administration that may be expressed by patients[26] and the potential for toxicity to nasal mucosa, the treatment phase of this study included repeated assessments of patient outcomes associated with the nasal route of administration and objective evaluations of the nasal cavity. Consistent with the earlier controlled studies,[23,24] there was no evidence that FPNS produced changes in nasal obstruction, inflammation, discharge, or color of mucosa. Patient assessments revealed no pattern of abnormal nasal symptoms such as stuffy/blocked nose, runny nose, itching/sneezing, nasal crusting/dryness, burning/discomfort, nasal bleeding, cough, postnasal drip, sore throat, or taste disturbance. In this subset of patients with cancer with episodic pain, the nasal route of drug administration was well tolerated and acceptable.

This study has important limitations. First, the open-label noncomparative design can only provide limited evidence of analgesic effectiveness, and the entry criteria may have excluded subpopulations of patients with cancer who may be at greater risk from treatment; this could potentially have reduced the occurrence of AEs. Long-term comparative studies against OTFC and other intranasal opioid formulations (including intranasal hydromorphone) would be of interest. Second, the majority of patients did not complete the study. All study patients had malignant solid tumors or a hematologic malignancy, and a relatively high mortality rate during the 16-week open-label treatment period (59 of 356 patients [16.6 percent]) was anticipated. During the following 12-month extension period, another 50 of 166 patients (30.1 percent) died. The low completion rate also reflects the early completion of the study once its predetermined exposure objectives had been met (95 patients completed early, and most continued treatment in the extension period). Nonetheless, the influence of selection bias on the trend to decrease rescue medication use over the 16-week study duration cannot be discounted because some patients might have dropped out because of their need for additional medications. Furthermore, it is important to note that monitoring by the investigators was more intensive than that would be done routinely in clinical practice.

Nevertheless, trials of this type are necessary to provide information about safety, tolerability, and dosing considerations that inform clinical practice. This study demonstrates that FPNS is well tolerated and can be used safely, and at a stable dose, by some patients with cancer for more than 16 weeks. In a population with life-threatening illness, serious AEs occasionally occur, and disease progression commonly leads to medical complications or death during treatment. Similar to other opioid drugs, use of FPNS requires careful monitoring to minimize the risk of adverse outcomes. With appropriate dosing and monitoring over time, FPNS is likely to be safe and yield stable clinical effects during prolonged treatment of BTCP.

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Russell K. Portenoy, MD, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York.

William Raffaeli, MD, Pain Therapy and Palliative Care-Hospice Unit, Infermi Hospital, Rimini, Italy.

Luis M. Torres, MD, Professor of Anesthesia, Anesthesia Department, Puerta del Mar Hospital, Cadiz, Spain.

Thomas Sitte, BS, PalliativNetz Osthessen, Fulda, Germany.

Akhil Chandra Deka, MD, Karnataka Cancer Therapy and Research Institute, Hubli, India.

Ileana Gonzalez Herrera, MD, Hospital Clinica Santa Maria, San Jose, Costa Rica.

Mark S. Wallace, MD, Department of Anesthesia, UCSD Center for Pain Medicine, San Diego, California.

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