

Fentanyl Nasal Spray: A New Option for Breakthrough Cancer Pain

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Author's disclosures of potential conflict of interest are found at the end of this article.

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Fentanyl nasal spray (Lazanda) was recently approved for breakthrough cancer pain (BTCP) in patients 18 years and older who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain. Breakthrough cancer pain is defined as a transitory exacerbation of pain to greater than moderate intensity, which occurs within a background of otherwise-controlled, persistent pain in a patient receiving opioid therapy (Leppert, 2010; Taylor et al., 2010). It is estimated to occur in 23% to 93% of patients with cancer (Fine & Busch, 1998; Fortner, Okon, & Portenoy, 2002; Portenoy & Hagen, 1990; Portenoy, Payne, & Jacobsen, 1999; Swannick, Haworth, & Lennard, 2001; Taylor et al., 2010; Zeppetella, 2000). The typical episode has a rapid onset (mean time from onset to peak pain intensity, approximately 1 to 3 minutes) and brief duration (mean duration, 30 to 60 minutes; Davies et al., 2011; Portenoy & Hagen, 1990).

Breakthrough cancer pain can have a profound impact on both patients' and caregivers' quality of life (Panagiotou & Mystakidou, 2010). Patients with BTCP are more likely to have severe pain, psychological distress, impaired function, and poorer quality of life (Portenoy, Burton, Gabrail, & Taylor, 2010).

Opioids are the cornerstone of pharmacotherapy for pain, and opioids such as controlled-release morphine and oxycodone, as well as transdermal fentanyl, have long been the "gold standard" for persistent pain related to

cancer. Short-acting oral opioids such as morphine sulfate immediate release, oxycodone immediate release, hydro-morphine, and hydrocodone are often employed in addition to a fixed around-the-clock regimen as "supplemental" or "rescue" medications for BTCP. One limitation of oral immediate-release agents is the delayed onset of action for BTCP, which is greater than 30 minutes with a peak in 1 to 2 hours. In other words, these oral medications peak after the BTCP abates. The agent can then accumulate and contribute to sedation. Because of this limitation, novel opioid analgesics have evolved, primarily fentanyl due to its lipophilicity and pharmacokinetic profile (Panagiotou & Mystakidou, 2010).

Fentanyl is a highly lipid-soluble, potent (50 to 100 times more potent than morphine), and synthetic pure opiate with a selective activity on μ receptors in the spinal cord, brain, and other tissues (Panagiotou & Mystakidou, 2010). Fentanyl's onset of action is variable and dependent upon the route of administration. When administered transdermally, fentanyl has a slow onset of approximately 12 hours; however, its onset is rapid (within minutes) when administered via the transmucosal or nasal route, which makes it an excellent choice for BTCP. Rapid onset fentanyl is currently available for BTCP as a buccal tablet, buccal film, transmucosal lozenge or troche, sublingual tablet, IV formulations, and now the nasal route (Micromedex, 2011). The nasal route

may be especially useful for patients who suffer from dry mouth, mucositis, or nausea and vomiting (Leppert, 2010).

Nasal Route of Administration

The nasal route of administration shows potential advantages in the treatment of BTCP. Blood flow to the nasal mucosa is extensive and considered to be greater per cubic centimeter of tissue than in muscle, brain, and liver. One study compared the relative bioavailability of fentanyl nasal spray and an oral transmucosal fentanyl citrate product, and found the bioavailability of fentanyl nasal spray to be approximately 20% higher than that of the oral transmucosal fentanyl citrate product (Fisher, Watling, Smith, & Knight, 2010). This results in the rapid onset of fentanyl nasal spray in as little as 5 minutes, and time to maximal plasma concentration is 15 to 21 minutes.

However, nasal administration of pharmacologic agents can be extremely challenging. First, agents must be administered in very small volumes to prevent irritation to the nasal mucosal membranes. Second, uptake and distribution of the medication in the nasal passages require attention so that medication will not run out of the nose before it is absorbed. Archimedes Pharma, the manufacturer of fentanyl nasal spray, uses a pectin-based technology to modulate the medication's profile. When the drug comes into contact with mucosal surfaces (the nasal mucosa in this situation), the drug forms a gel that allows rapid absorption while it controls the spike in the blood concentration (C_{max}). The technology also aids in reduced runoff (Archimedes Pharma, 2011).

Clinical Studies

The following studies reflect those used in the approval of fentanyl nasal spray. A multicenter, randomized, placebo-controlled, double-blind crossover study by Portenoy et al. (2010a) assessed the efficacy and tolerability of fentanyl nasal spray

for BTCP. Out of 114 patients who entered the study and who experienced one to four BTCP episodes per day while taking approximately 60 mg/day of oral morphine or an equivalent dose of another opioid, 83 successfully identified an effective dose of fentanyl nasal spray during a titration phase. The 83 successful patients then entered a double-blind phase in which 10 BTCP episodes were randomly treated with the nasal fentanyl (7 episodes) or placebo (3 episodes).

Compared with placebo, fentanyl nasal spray significantly improved the mean summed pain intensity difference from 10 min ($p < .05$) until 60 min ($p < .0001$), including the primary endpoint at 30 min ($p < .0001$). Fentanyl nasal spray significantly improved pain intensity scores as early as 5 min ($p < .05$), pain intensity difference from 10 min ($p < .01$), and pain relief scores from 10 min ($p < .01$). Approximately 91% of fentanyl nasal spray-treated BTCP episodes vs. 80% of placebo-treated BTCP episodes did not require rescue medication ($p < .0001$). The most commonly reported adverse effects were consistent with opioid treatment and were mild to moderate in severity. No significant nasal-related symptoms were reported, and the majority of patients found the fentanyl nasal spray convenient and easy to use (Portenoy et al., 2010a).

A second study (Portenoy et al., 2010b) was a multicenter, open-label study. Patients with chronic cancer pain treated with ≥ 60 mg/day oral morphine or an equivalent dose of another opioid and experiencing one through four episodes of BTCP per day were enrolled in a 16-week treatment phase following a dose titration with fentanyl nasal spray. A total of 403 patients were included in the safety analysis; of these, 356 entered the treatment phase and 110 completed the study. Patients treated a total of 42,227 episodes during the study. During the treatment phase, 99 patients (24.6%) reported treatment-related adverse events, but most were mild or moderate and typical of opioids. Nasal assessments revealed no significant local effects. No additional rescue medication was required after 94% of fentanyl nasal spray-treated episodes. More than 90% of patients required no increase in the initial dose of fentanyl nasal spray (Portenoy et al., 2010b).

Adverse Effects and Drug Interactions

The most common adverse effects occur during dose titration. Those seen in more than 5% of patients include nausea, vomiting, dizziness, pyrexia,



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and constipation. Occasional nasal irritation occurred, but in less than 5% of patients.

Metabolized by the cytochrome P450 3A4 liver enzyme system, fentanyl has the potential for drug-drug interaction. Potent inhibitors of this enzyme may increase fentanyl blood levels and produce increased or prolonged fentanyl side effects. Potent inducers of CYP3A4 can cause decreased serum concentrations, thereby decreasing the efficacy of the drug (Prommer & Thompson, 2011). In light of the fact that fentanyl nasal spray is used intermittently and all patients will be opioid tolerant, it is important to be aware of these interactions, but no specific contraindications exist with any CYP3A4-inducing or -inhibiting medications.

Patients on concomitant central nervous system depressants should be monitored for a change in opioid effects, and doses of fentanyl nasal spray should be adjusted as needed. Fentanyl is not recommended to be given within 14 days of monoamine oxidase inhibitor (MAOI) administration, as severe and unpredictable potentiation of MAOIs has been reported with opioid analgesics (Archimedes Pharma, 2011). Patients using vasoconstrictive nasal agents to treat allergic rhinitis may potentially impair fentanyl absorption and lead to a decrease in pain control (Panagiotou & Mystakidou, 2010). Fentanyl nasal spray should be used with caution in patients with impaired renal or hepatic function. Doses should be carefully titrated to clinical effect in patients with severe renal or hepatic disease (Archimedes Pharma, 2011).

Dosage and Administration

Fentanyl nasal spray comes in two strengths: 100 µg and 400 µg. Each unit contains eight doses (or sprays). All patients should start with one spray (100 µg); if pain persists, at the next episode of BTCP the dose can be titrated to two sprays (200 µg; one spray in each nostril). The recommended dose is one or two sprays *no more than every 2 hours*. Table 1 includes a titration table for fentanyl nasal spray. If BTCP persists during any treated episode, a rescue medication may be given.

Because of the potential for misuse, abuse,

Table 1. Titration of Fentanyl Nasal Spray

Dose	Titration steps ^{a,b}
100 µg	1 x 100 µg spray
200 µg	2 x 100 µg spray (1 in each nostril)
400 µg	1 x 400 µg spray
800 µg	2 x 400 µg spray (1 in each nostril)

^aIf adequate analgesia is not achieved with the first 100-µg dose, dose-escalate in a stepwise manner over consecutive episodes of breakthrough pain until adequate analgesia with tolerable side effects is achieved.

^bPatients MUST wait at least 2 hours before treating another episode of breakthrough cancer pain with fentanyl nasal spray.

addiction, and overdose, all rapid-onset fentanyl products are available through a Risk Evaluation and Mitigation Strategy (REMS) program. Under the REMS program, pharmacies, distributors, and health-care professionals who prescribe opioids to outpatients are required to enroll in the program to dispense, distribute, and prescribe fentanyl nasal spray (Archimedes Pharma, 2011).

Conclusions

Fentanyl nasal spray offers unique pharmacokinetic advantages over existing treatment options for BTCP. Oral immediate-release opioids, traditionally used for treatment of BTCP, do not always match the typical characteristics of BTCP. Traditional agents have an onset of action of 30 minutes or more, whereas BTCP may have an onset in minutes and may subside within 30 minutes to 1 hour. Clinical studies have shown that fentanyl nasal spray is effective in the treatment of BTCP with typical opioid-related side effects and few reports of nasal adverse effects. Overall, fentanyl nasal spray provides another good option for the treatment of BTCP, which can have a profound impact on both patients' and caregivers' quality of life.

DISCLOSURE

The author has no conflicts of interest to disclose.

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