Oral Transmucosal Fentanyl Citrate for Cancer Breakthrough Pain: A Review

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This article has been chosen as being particularly suitable for reading and discussion in a Journal Club format. The following questions are posed to stimulate thoughtful critique and exchange of opinions, possibly leading to changes on your unit. Formulate your answers as you read the article. Photocopying of this article for group discussion purposes is permitted.

1. Is the article evidence based? Can we assess the level of evidence being presented?
2. Identify at least one patient for whom breakthrough pain was a significant problem.
3. What strategies do our physicians typically use to address breakthrough pain? Is oral transmucosal fentanyl ever ordered?
4. What patient teaching strategies have been employed when this formulation of pain medicine is ordered?
5. Identify three ways to increase the possibility that this formulation of analgesia could be introduced into our setting and, if effective, its use could be encouraged.
6. What management resources would be needed to effectively incorporate the use of this drug in our setting?

At the end of the session, take time to recap the discussion and make plans to follow through with suggested strategies.

Purpose/Objectives: To review the dose titration, efficacy, and safety of oral transmucosal fentanyl citrate (OTFC).

Data Sources: Phase I and II clinical trial abstracts and evidence-based review articles.

Data Synthesis: OTFC has an onset, peak, and duration of action similar to that of an IV dose of an opioid and has been demonstrated to be effective and well tolerated for the management of breakthrough pain in patients with cancer.

Conclusions: Studies of OTFC demonstrate that it is easy to use, noninvasive, effective, safe, and acceptable to patients, caregivers, and healthcare providers. However, OTFC is expensive and approved for use only in opioid-tolerant patients with cancer.

Implications for Nursing: Breakthrough pain in patients with cancer is a common problem with characteristics that make it difficult to treat. Oncology nurses should familiarize themselves with OTFC's unique characteristics to be able to best help patients manage their therapy.

Key Points . . .

- Oral transmucosal fentanyl citrate (OTFC) is the only opioid specifically formulated for transmucosal delivery.
- OTFC may work best for breakthrough pain that is paroxysmal, severe, and brief.
- A successful dose of OTFC has no predictors, so each patient should be titrated individually.

Breakthrough pain is a term used to describe a transitory exacerbation of pain that occurs on a background of otherwise stable pain in patients receiving chronic opioid therapy (Portenoy & Hagen, 1990). By definition, breakthrough pain is typically of rapid and paroxysmal onset and brief duration, reaching peak intensity in 3–52 minutes (Fine & Busch, 1998; Portenoy & Hagen; Portenoy, Payne, & Jacobsen, 1999). Although some debate remains about the precise methods of assessment and diagnosis of breakthrough pain (Bennett et al., 2005a; Mercadante et al., 2002), the prevalence of breakthrough pain is reported to be 51%–86% in patients with cancer (Ashby et al., 1992; Bruera, Fainsinger, MacEachern, & Hanson, 1992; Gomez-Batiste et al., 2002). Three subtypes of breakthrough pain have been defined and include incident pain, idiopathic pain, and end-of-dose failure (see Table 1). The characteristics of breakthrough

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Table 1. Subtypes of Breakthrough Pain

Subtype	Characteristics
Incident, predictable	Consistent temporal causal relationship with predictable motor activity, such as movement, defecation, micturition, breathing, or coughing
Incident, unpredictable	Inconsistent temporal causal relationship with motor activity, such as sneezing, bladder spasm, or coughing
Idiopathic	Not associated with a known cause: generally of longer duration than incident pain
End of dose	Occurring before a scheduled dose of an around-the-clock analgesic; more gradual onset and longer duration than incident or idiopathic breakthrough pain

Note. From "Consensus Panel Recommendations for the Assessment and Management of Breakthrough Pain, Part 1, Assessment," by D. Bennett, A.W. Burton, S. Fishman, B. Fortner, B. McCarberg, C. Miaskowski, et al., 2005, *Pharmacy and Therapeutics, 30,* p. 297. Copyright 2005 by MediMedia USA, Inc. Adapted with permission.

pain (pathophysiology, predictability, onset, intensity, and duration) have been shown to vary widely, making the condition difficult to treat. The presence of breakthrough pain is associated with increased pain-related functional impairment, psychological distress, and use of medical resources (Portenoy, Payne, & Jacobsen). In a survey of 1,000 patients with cancer, those with breakthrough pain had higher costs associated with pain-related hospitalizations and physician office visits, with total annual cost estimates of $1.9 million for patients with breakthrough pain compared with $227,000 for those without the symptom ($12,000 per year for a patient with breakthrough pain and $2,400 per year for a patient without breakthrough pain) (Fortner, Okon, & Portenoy, 2002).

Treatment of breakthrough pain depends on a comprehensive pain assessment, including patients' prior experiences and responses to analgesics as well as their medical history, to determine the presence of comorbidities that increase the risk of adverse effects of analgesic therapy. Nurses play a pivotal role in pain assessment as well as counseling and patient education on how to use analgesics. The purpose of this article is to review the dose titration, efficacy, and safety of a unique opioid formulation, oral transmucosal fentanyl citrate (OTFC) (marketed as Actiq®, Cephalon, West Chester, PA), that was approved specifically as an option for the treatment of cancer-related breakthrough pain.

Treatment of Breakthrough Pain

The World Health Organization (1996) recommended a sequential treatment approach to pain based on intensity using the least invasive and most convenient route of drug delivery (oral). The management of breakthrough pain always should be tailored to best meet patient factors uncovered during pain assessment and include a wide variety of nonpharmacologic and pharmacologic techniques (Bennett et al., 2005b). Although combination pharmacotherapy often is more effective than opioid therapy alone to treat persistent pain, immediate-release morphine, oxycodone, hydrocodone, and oral nonsteroidal anti-inflammatory analgesics are the mainstay of rescue analgesics (American Pain Society [APS], 2003; Colleau, 2004). The use of as-needed rescue doses of pain medicine is an accepted treatment approach for cancer-related breakthrough pain. However, treatment with conventional oral analgesics may be insufficient at times because of the relative mismatch between the onset, peak, and duration of breakthrough pain and that of the oral opioid preparations commonly used to treat it. Additionally, the enteral route may be contraindicated at times.

Ideally, drugs used to treat breakthrough pain should provide rapid onset and peak with a relatively short duration of action (Bennett et al., 2005b; Colleau, 2004). Additionally, providing patients with a rescue medication that possesses capacity for rapid titration would be helpful to meet the varying characteristics of different breakthrough pain episodes. Oral ingestion, the most convenient, least invasive, and commonly used route of administration for rescue medications, may be too slow in onset and peak to relieve breakthrough pain adequately. Following oral administration, drug action is slowed (compared to parenteral administration) because of variation in absorption within the gastrointestinal tract and retention, inactivation, or partial destruction by the liver before entering general circulation (first-pass phenomena). The IV route provides the most rapid onset of effect but generally is reserved for rapid titration in carefully monitored settings (APS, 2003).

Sublingual Morphine for Breakthrough Pain

The large surface area, uniform temperature, stable pH, high permeability, and extensive vascularization of the human mouth make it an ideal environment for rapid, noninvasive delivery of systemic drugs. Several forms of short-acting oral morphine suitable for sublingual administration are available on the market, including soluble tablets and oral solution. Sublingual administration of morphine often is used to treat breakthrough pain in an attempt to hasten analgesic onset and peak; however, available data do not support more rapid absorption of morphine through the sublingual mucosa when compared with the oral route (Coluzzi, 1998; Davis et al., 1993; Osborne, Joel, Trew, & Slevin, 1990). Mean time to maximum concentration has been shown to be shorter following oral morphine (0.8 + 0.35 hours) compared with sublingual (1.75 + 1.30 hours), indicating that sublingual morphine is likely swallowed and absorbed gastrointestinally rather than through the oral mucosa (Coluzzi). The bioavailability (amount of drug eventually made available to the systemic circulation) of sublingual morphine has been shown to be only 9% (Weinberg et al., 1988) compared with 24% after an oral solution (Micromedex, 2004).

Agents are absorbed most readily through the oral mucosa when they are potent, nonionized at physiologic pH, and lipid soluble. Potency refers to the intensity of analgesic effect for a given dose and is based on access to the receptor and binding affinity at the receptor site (Ferrante, 1996). The more soluble a drug, the more rapidly it will be absorbed. Because cell membranes contain a fatty acid layer, lipid solubility is a valuable attribute of a drug that is to be absorbed. Morphine has a relatively low potency for an opioid, is 90% ionized at the pH of the mouth, and is one of the least lipid-soluble opioids, providing an explanation for its low bioavailability and poor choice as a sublingual or buccal medication (Coluzzi, 1998). Indeed, a number of clinical studies have found no substantial advantage to the use of sublingual morphine over the oral form (Pannuti et al., 1982; Robison, Wilkie, & Campbell, 1995; Weinberg et al., 1988).

Oral Transmucosal Fentanyl Citrate

Fentanyl generally is considered 100 times more potent and 800 times more lipid soluble than morphine (Streisand et al., 1991). The relative potency of OTFC and IV morphine was determined to be approximately 10:1 (range = 8–14:1) (Lichtor et al., 1999). In other words, 20 mcg of IV fentanyl is approximately equianalgesic to 200 mcg of OTFC, 2–4 mg of IV morphine, or 6–12 mg of oral morphine. Under normal conditions of the mouth, fentanyl is 80% nonionized, making it conducive to absorption through the mucosa (Mather & Denson, 2000). OTFC first gained approval for use in 1993 as premedication for surgery and painful procedures (not requiring general anesthesia) in children (Ashburn et al., 1990; Nelson, Streisand, Mulder, Pace, & Stanley, 1989; Zimmer & Ashburn, 2001). A dosage unit resembles a lollipop or lozenge on a stick. It contains fentanyl, sugar, dye, and an artificial flavor to hide the taste of the medication. The novel formulation was greeted with high hopes by clinicians, parents, and children as a convenient alternative to less accepted oral, rectal, or intramuscular delivery routes in children. Unfortunately, nausea and vomiting was seen in 6% of pediatric patients who used OTFC preoperatively and in 11% during the first 90 minutes postoperatively (Ashburn & Streisand, 1994). The high incidence of nausea may be explained by the fact that the children were likely opioid naive, unlike most patients with cancer. Pretreatment with an antiemetic did not appear to reduce the unacceptable incidence of nausea and vomiting.

However, information obtained from experience with and studies of OTFC for breakthrough pain in opioid-tolerant patients with cancer (Christie et al., 1998; Coluzzi et al., 2001; Portenoy, Payne, Coluzzi, et al., 1999) led to U.S. Food and Drug Administration (FDA) approval in 1998 of OTFC. Because of the uniqueness of the dosage form and because fentanyl is a potent schedule II narcotic, the FDA advisory committee members were concerned that OTFC be packaged and marketed to minimize the opportunity for diversion, abuse, access, and accidental overdose, particularly in children. Although OTFC is clinically used off label for a variety of pain problems, the FDA approved it (on the basis of the data submitted) only for breakthrough pain in patients with malignancies who already are receiving and who are tolerant to opioid therapy for their underlying cancer pain (FDA, 1998). Life-threatening hypoventilation can occur at any dose in patienta who are not tolerant to opioids. The development of tolerance to opioid side effects is well recognized clinically and experimentally and can occur over a period of days to weeks (Foley, 1993). Patients can be considered opioid tolerant if they take at least 60 mg oral morphine per day, 50 mcg transdermal fentanyl per hour, or an equianalgesic dose of another opioid for a week or longer (Cephalon, 2004).

Compared with orally ingested fentanyl, OTFC produces a higher maximum plasma fentanyl concentration (3.0 versus 1.2 ng/ml), faster time to peak plasma concentration (22 minutes versus 101 minutes), and greater bioavailability (52% versus 32%) (Streisand et al., 1991). When administered transmucosally over 15 minutes, approximately 25% of fentanyl goes directly into the bloodstream through mucosal absorption. The remaining fentanyl that is eventually swallowed (75%) is absorbed more slowly from the gut; 50% of this amount goes through the first-pass effect metabolism in the liver, and 25% becomes bioavailable (Chandler, 1999). OTFC has been shown to produce an onset of analgesia as quickly as 6 minutes, with peak effect occurring approximately 20–30 minutes after completion of the OTFC unit and duration of action of two to five hours (Basskin, 1999; Fine & Streisand, 1998; Mock et al., 1986).

The rate of consumption affects how quickly fentanyl travels across the oral mucosa (Streisand et al., 1991). Chewing or sucking the OTFC unit may result in more drug being swallowed, which will limit the amount absorbed transmucosally and reduce efficacy (Mystakidou, Katsouda, Parpa, Tsiatas, & Vlahos, 2005). Fifteen minutes is recommended as the ideal amount of time to consume a unit to get the desired onset and peak effect (Cephalon, 2004; Simmonds, 1997; Stanley et al., 1989). Peak blood levels with OTFC occur 5–10 minutes after the unit is dissolved completely. Patients with little saliva may not be able to dissolve the OTFC unit within the desired time. Absorption also depends on the amount of saliva swallowed without adequate exposure to the mucosal surface. In other words, patients should be told to swirl saliva produced from the dissolving unit around their mouths prior to swallowing it. Positioning of the OTFC unit in the mouth also affects the absorption. Drug permeability is lowest in the gingiva and tongue (Squier & Johnson, 1975). Ideally, the unit matrix should be swabbed across the inside of the cheek and not placed on the tongue. Patients should be instructed to avoid drinking fluids such as coffee, cola, or citrus fruit juices before drug administration because they may reduce the pH of the mouth and decrease fentanyl absorption (Rees, 2002). Additional patient information is outlined in Figure 1.

No change in dosing because of altered pharmacokinetics in older adults appears to be necessary (Kharasch, Hoffer, & Whittington, 2004). However, older adult patients have been shown to be twice as sensitive to the effects of fentanyl when administered via IV as compared to the younger population (Cephalon, 2004), and caution is warranted. The reason for the increased sensitivity is not entirely understood but may be caused, in part, by more rapid uptake of fentanyl into the central nervous system (Lu & Bailey, 2003) and prolonged elimination of opioids from plasma (diminished elimination clearance) in older adults (Kharasch et al.).

The amount of fentanyl absorbed remains stable over multiple administrations, reducing the risk of cumulative increases in serum levels with repetitive doses (Streisand, Busch, Gaylord, Gay, & East, 1996; Streisand et al., 1993, 1998). This means that, as with other opioids, the peak concentration of drug in the bloodstream is dependent on the total dose delivered, not the number of doses. However, two simultaneously administered doses should be considered equivalent to administration of a single total identical dose. In other words, two simultaneously consumed 400 mcg OTFC were found to be equivalent to one 800 mcg OTFC with no differences in time to peak concentration or exposure time of the drug in the body (mean residence time) (Lee, Kern, Kisicki, & Egan, 2003).

Studies in volunteers (Egan, Kern, & Vadiei, 2002), children (Moore et al., 2000), and patients with cancer (Coluzzi et al., 2001; Portenoy, Payne, Coluzzi, et al., 1999) have reported typical opioid dose-related side effects, including somnolence, nausea, and dizziness. Use of OTFC may result in oral mucosal ulceration; however, OTFC has been well tolerated in patients with radiation-induced oral mucositis (Danjoux et al., 2000; Portenoy et al., 2002; Shaiova et al., 2004). Frequent use of OTFC may increase the risk of dental caries despite routine oral hygiene (Cephalon, 2004). Patients with diabetes

Oral Transmucosal Fentanyl Citrate—OTFC (Actiq®)

Oral transmucosal fentanyl citrate (OTFC) is a solid formulation of fentanyl that resembles a lozenge on a handle and is intended for oral transmucosal administration. Fentanyl is one of the most lipid-soluble opioids and when placed in saliva under normal conditions of the mouth is 80% nonionized making it the only opioid suitable for transmucosal absorption.

Fentanyl is generally considered 100 times more potent than morphine. However, bioavailability of OTFC depends on the fraction of the dose that is absorbed through the oral mucosa and the fraction that is swallowed. OTFC has been shown to produce an onset of analgesia while consuming the unit (fentanyl begins to cross the blood-brain barrier in as little as 3–5 minutes), with peak effect at approximately 45 minutes after the start of administration, and duration of action of 2–3 hours.

An easy way to conceptualize the profile of OTFC is that it is comparable to an IV bolus of opioid in terms of its onset, peak, and duration.

Approximate equivalents

Parenteral morphine 2 mg	Parenteral fentanyl 20 mcg (0.02 mg)	Transmucosal fentanyl 200 mcg

Prescribing Information

- OTFC is available in 200, 400, 600, 800, 1,200, and 1,600 mcg dosage strengths.
- No predictive relationships were seen between patient, pain episode, around-the-clock or rescue analgesic factors and the successful dose of OTFC in either titration or long-term efficacy studies. This means, OTFC should always be started at 200 mcg and then individually titrated based on patient response. If the first dose of 200 mcg is inadequate in providing relief, the patient should wait for 15 minutes and take a second unit. If pain is relieved after the second dose of 200 mcg, the dose to use for the next episode of breakthrough pain would be 400 mcg. The patient should be instructed not to take more than two units per pain episode during the initial titration period.
- The amount of fentanyl absorbed from each single dose remains stable over multiple administrations. This fact, combined with fentanyl's short half-life, reduces the risk of a cumulative increase in serum level with repetitive doses.
- Studies in opioid tolerant patients with cancer have shown typical opioid dose-related side effects including somnolence, nausea, and dizziness.

Important Patient Information on Consumption Technique and Storage

- The OTFC is administered by placing it between the cheek and gums next to the buccal mucosa, moving the unit gently from side to side. Chewing or sucking OTFC may result in more drug being swallowed, which will limit the amount absorbed and reduce efficacy. In clinical studies, 15 minutes seemed to be the ideal amount of time to consume a unit to achieve the desired onset and peak effect.
- Peak blood level with OTFC occurs 20–40 minutes from the beginning of consumption of the OTFC unit.
- Patients with little saliva may not be able to dissolve the unit within the desired time. Absorption likely also depends on the amount of saliva swallowed without adequate exposure of the OTFC unit to the mucosal surface. In other words, patients should be told to swirl saliva produced from the dissolving unit around their mouth prior to swallowing it.
- Positioning of the matrix in the mouth also affects the absorption. Drug permeability is lowest through the gums and tongue. Ideally the matrix should be swabbed across the inside of the cheek and not placed on the tongue. Patients should be instructed to avoid drinking fluids such as coffee, cola, or citrus fruit juices prior to drug administration which may reduce the pH of the mouth and decrease fentanyl absorption. Patients may, however, moisten their mouths with water prior to medicine use to increase saliva.
- Actiq units are designed for one time administration. However, patients should be instructed to remove the unit from their mouth if usage results in excessive opioid-related side effects.
- Instruct patients to utilize the manufacturer's safety containers to store the dosage units, and discard any unused portion of the OTFC by dissolving it under hot tap water. The drug should be stored under room temperature, and not be frozen.

References

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Portenoy, R.K., Payne, R., Coluzzi, P., Raschko, J.W., Lyss, A., Busch, M.A., Frigerio, V., Ingham, J., Loseth, D.B., Nordbrock, E., & Rhiner, M. (1999). Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: A controlled dose titration study. *Pain, 79,* 303–312.

Figure 1. Fast Facts Five-Minute In-Service

Note. From the University of Wisconsin Hospital and Clinics in Madison. Reprinted with permission.

should be advised that each OTFC unit contains approximately 2 grams of sugar (hydrated dextrates). In September 2005, Cephalon received FDA approval to market a sugar-free formulation of Actiq that is bioequivalent to the original formulation and will use the same name. The company also submitted a new drug application to the FDA seeking approval to market a fentanyl effervescent buccal tablet (Oravescent® fentanyl, Cephalon) that is easier to administer.

Titration of Oral Transmucosal Fentanyl Citrate to Treat Cancer Pain

Two multicenter studies initially were performed to establish a safe and effective dose titration process for OTFC in patients with cancer (see Table 2). The same two-stage design was used in studies with different adult patient populations. Christie et al. (1998) included 62 patients using transdermal fentanyl to control their pain, whereas Portenoy, Payne, Coluzzi, et al. (1999) included 65 patients using oral opioids as an around-the-clock opioid. Stage one involved evaluation of patients' breakthrough pain and the performance of their usual rescue pain medication. In stage two, OTFC was titrated using all available dosage forms (200, 400, 600, 800, 1,200, and 1,600 mcg) to determine a successful dose, defined as a single OTFC dosage unit that provided adequate analgesia with acceptable side effects. Investigators and patients were blinded to doses, and patients were randomly assigned to start at 200 or 400 mcg (except all patients using less than 100 mcg transdermal fentanyl were started at 200 mcg OTFC for safety purposes). Patients were instructed on how to properly consume a dosage unit and to treat up to two episodes of pain per day using as

Table 2. Key Titration[a] Trials for Oral Transmucosal Fentanyl Citrate (OTFC)

Study	N	Around-the-Clock Opioid Dose	Patients Titrated to Successful Dose of OTFC		$\bar{X}$ Pain Relief Scores[b]	Dose (mcg) of OTFC Following Successful Titration		Adverse Side Effects (Incidence)	$\bar{X}$ Medication Performance Rating[c]
			n	%		$\bar{X}$	SD		
Christie et al., 1998	62	50–300 mcg per hour transdermal fentanyl	47	76	1.90	587	335	Somnolence (18%) Nausea (11%) Dizziness (10%) Vomiting (5%)	2.6 versus 2.0 for usual supplemental pain medicine, p = 0.0001
Portenoy, Payne, Coluzzi, et al., 1999	65	60–1,000 mg per day oral morphine	48	74	2.1 after 15 minutes 2.5 after 30 minutes	640	374	Somnolence (28%) Dizziness (14%) Nausea (10%) Headache (5%)	2.7 versus 2.1 for usual supplemental pain medicine, p = 0.0001

[a] The goal is to demonstrate a process that can identify a dose of OTFC that is safe and effective in patients with cancer receiving around-the-clock opioids.

[b] 0 = none to 4 = complete

[c] 0 = poor to 4 = excellent

many as four OTFC units per episode. Patients were titrated until one unit of OTFC was effective on two consecutive days. Range of around-the-clock opioids for the oral study was 60–1,000 mg per day (oral morphine equivalents) and 50–300 mcg per hour for the patients receiving transdermal fentanyl. For comparison purposes, all doses of all opioids were converted to oral morphine equivalency milligrams. Prior rescue medication in both studies ranged widely from 5–100 mg per episode, with similar means (26 ± 22 mg oral study and 21 ± 20 mg per episode transdermal study).

More than 70% of patients in both studies were titrated to a successful dose. The average successful titration dose in both studies was 600 mcg. Interestingly, no relationship was found between the successful dose of OTFC and the starting (titration) dose of OTFC, a patient's 24-hour dose of around-the-clock opioid, or a patient's prior successful dose of rescue drug. Additionally, neither age, gender, route of around-the-clock medication, nor pain pathophysiology (nociceptive versus neuropathic) were found to be helpful in predicting the successful OTFC dose. These data suggest that the effective dose of OTFC cannot be predicted based on a patient's around-the-clock opioid used to manage persistent pain and that all patients should be titrated individually beginning at 200 mcg OTFC. Adverse events in both studies included commonly reported opioid side effects such as somnolence, dizziness, nausea, and vomiting with relatively low incidence.

Patients were asked to evaluate the performance of the study medication to treat pain using a scale that ranged from 0 (poor) to 4 (excellent). Patients in both studies (Christie et al., 1998; Portenoy, Payne, Coluzzi, et al., 1999) provided significantly higher medication performance ratings of OTFC compared with their previous rescue medication (oral study 2.7 versus 2.1, p = 0.0002; transdermal study 2.6 versus 2.0, p = 0.0001), and 91% chose to enter a long-term study that followed, indicating high acceptance of OTFC.

Efficacy of Oral Transmucosal Fentanyl Citrate in Cancer Pain

To better determine the effectiveness of OTFC and compare it to immediate-release morphine sulfate for breakthrough pain, 89 patients who had been titrated to a successful OTFC dose were enrolled in a double-blind, placebo-controlled crossover study (Coluzzi et al., 2001). Table 3 summarizes the data from the efficacy trial. Patients were given 10 prenumbered sets of OTFC units and capsules. Each set had one unit and several capsules. Five of the sets contained the successful OTFC dose paired with placebo capsules, and five of the sets were placebo OTFC paired with enough capsules to provide a patient's successful dose of immediate-release morphine (15–60 mg). Patients were instructed to take one full set in sequential order for each episode of pain and to record information about pain intensity and amount of pain relief at varying points of time following an episode of treated pain and to again evaluate medication performance (scale of 0 [poor] to 4 [excellent]).

Titration to a successful OTFC dose prior to the double-blind placebo stage took, on average, five days (range = 1–22 days). The successful doses of OTFC were distributed evenly, and all OTFC dose levels were used in the study. The mean immediate-release morphine doses used by patients prior to OTFC was 31 mg (SD = 13.5 mg), and the mean successful OTFC dose was 811 mcg (SD = 452 mcg). No relationship was found between the OTFC and morphine dose ($R^2 = 0.065$) or the around-the-clock dose. Patients reported significantly lower pain intensity, greater pain intensity difference, and pain relief (p = 0.001) for OTFC compared with immediate-release morphine.

Seventy-eight percent of patients completed the study, with only seven (8%) patients withdrawing because of adverse events (six were unrelated to study drug and one was itching). Adverse events were similar to those seen in other opioid studies, including dizziness (17%), nausea (13%), somnolence (8%), constipation (5%), asthenia (5%), and confusion (4%). Medication performance ratings also favored OTFC, and again the majority of patients (94%) chose to continue taking OTFC when the study was completed, which indicates high patient acceptance of the formulation.

Long-Term Safety of Oral Transmucosal Fentanyl Citrate in Cancer Pain

To evaluate long-term safety of OTFC in patients with cancer-related breakthrough pain, patients who successfully

Table 3. Efficacy[a] Trial for Oral Transmucosal Fentanyl Citrate (OTFC)

Study	Around-the-Clock Opioid Dose	Patients Titrated to Successful Dose of OTFC		$\bar{X}$ Pain Relief Scores	Dose (mcg) of OTFC Following Successful Titration		Adverse Side Effects (Incidence)	$\bar{X}$ Medication Performance Rating[b]
		n	%		$\bar{X}$	SD		
Coluzzi et al., 2001	60–1,000 mg oral morphine per day or 50–300 mcg per hour transdermal fentanyl	73	82	OTFC produced lower pain intensity and higher pain relief scores at each time point than morphine sulfate immediate relief (MSIR) ($p \leq 0.011$).	811	452	Somnolence (15%) Nausea (13%) Constipation (10%) Dizziness (7%)	2.5 versus 2.1 MSIR, $p < 0.001$ 64 (94%) chose to continue receiving OTFC.

N = 89

[a] The goal is to determine the efficacy of OTFC by comparing it with morphine sulfate immediate relief in a double-blind, placebo-controlled trial.

[b] 0 = poor to 4 = excellent

completed the three prior studies were invited to participate in a fourth study to evaluate long-term safety (Payne et al., 2001). Of 167 eligible patients, 155 (93%) chose to enroll. In that study, patients were instructed not to use more than two OTFC units to treat a single episode of breakthrough pain and not to use more than six OTFC units per day. Patients also were instructed to record the number of breakthrough episodes per day, the number of episodes successfully or unsuccessfully treated, medications used to treat breakthrough pain episodes, medication performance rating, and side effects. In total, patients used 41,766 OTFC units to treat 38,595 episodes of breakthrough pain. The duration of OTFC treatment for individual patients in the study ranged from 1–423 days ($\bar{X}$ = 91 days). The average number of reported breakthrough episodes per day was 2.9, with 2.4 treated successfully with OTFC (unsuccessful meant that an episode was treated with more than one OTFC or an OTFC and a rescue supplemental medication). Sixty-one percent of patients remained on the same OTFC dose throughout their entire study period, indicating that patients do not appear to develop tolerance to analgesia from OTFC. Consistent with the previous three studies, patients provided high global satisfaction ratings (more than 3 or 4 on a scale of 0–4), indicating very good to excellent relief from OTFC with a low incidence of adverse side effects (somnolence [9%], constipation [8%], nausea [8%], dizziness [8%], and vomiting [5%]).

Implications for Nursing

A series of studies has been used to demonstrate that OTFC is safe and efficacious in the treatment of breakthrough pain in patients with cancer. It is the only opioid specifically formulated for transmucosal delivery and may work best for breakthrough pain that is paroxysmal, severe, and brief or in some situations when the oral or IV routes are unavailable or undesirable. For optimal use and effectiveness, nurses must understand the unique characteristics of the opioid formulation and educate patients about how to properly consume and titrate the dosage units (Rhiner & Kedziera, 1999).

An easy way for nurses to conceptualize the profile of OTFC is that it is comparable to an IV bolus of morphine in terms of onset, peak, and duration of action. OTFC begins to produce analgesia within several minutes and, when consumed properly, peaks approximately 15–20 minutes after completion of the unit and can provide relief for several hours. Patients have the ability to titrate a unit by removing it from their mouths if a partial dosage unit provides adequate pain relief. However, partially used units should not be kept and reused. If the patient does not entirely consume a unit, as a controlled substance, the remaining drug should be dissolved under hot running water or cut from the handle using wire-cutting pliers and flushed down the toilet (Cephalon, 2004).

No predictive relationships were seen among patients, pain episodes, around-the-clock or rescue analgesic factors, and the successful dose of OTFC in either the titration, placebo-controlled, or long-term efficacy studies. That finding indicates that OTFC should always be started at 200 mcg and then individualized based on patient response. During initial dose titration, if the first dose of 200 mcg is inadequate in providing relief, patients should wait for 15 minutes after completing the unit and take a second unit. In general, the OTFC dose should be increased when patients require more than one unit per breakthrough pain episode for several consecutive episodes. For example, if pain is relieved after the second dose of a 200 mcg unit, the dose to use for the next episode of breakthrough pain would be 400 mcg. Patients should be instructed not to take more than two units per breakthrough pain episode during the initial titration period. If pain relief is inadequate after two dosage units at any strength, patients should take their usual dose of previous rescue medication and talk to their healthcare providers. Once titrated to an effective dose, patients should limit consumption to four or fewer units per day. Patients requiring treatment of more than four episodes of breakthrough pain per day should be reevaluated to determine whether the around-the-clock medication doses need to be increased and for possible new sources of breakthrough pain. Patients also must be instructed to use the manufacturer's safety containers to store the dosage units and discard any unused portion of the OTFC carefully. The drug should be stored at room temperature and not be frozen. An Actiq Welcome Kit (an introductory kit containing important safety and educational material, emergency information, and a safe storage container) is available to patients and their caregivers on the drug's Web site (www.actiq.com).

Research is needed to evaluate the cost implications of OTFC. Retail prices per unit of OTFC range from $4–$12. Assuming an average cost of $8 per unit for four units per day, the cost of the drug for one year would be approximately $10,000 or in excess of $7,000 per year more than comparative doses of other oral short-acting opioid formulations (i.e., 20 mg morphine equivalency doses) (Basskin, 1999). However, the cost must be weighed against the cost of uncontrolled breakthrough pain. Use of OTFC has been shown to avert the need for emergency center visits, parenteral opioids, and hospital admissions (Burton, Driver, Mendoza, & Syed, 2004).

Summary

Breakthrough pain in patients with cancer is a common problem with characteristics (e.g., paroxysmal, sudden, brief) that make it difficult to treat. Ideally, drugs used to treat breakthrough pain should provide a rapid onset and peak effect with a relatively short duration of action, similar to that obtained from an IV bolus. The opioid, dose, and route of administration must be tailored to meet an individual's needs (Bennett et al., 2005b). When available and effective, the oral route is the preferred for opioid delivery because of its convenience, flexibility, and cost (APS, 2003). However, commonly used short-acting oral opioid formulations may be too delayed in their onset and peak effect to effectively treat breakthrough pain in all patients. The oral transmucosal route is appealing because it theoretically avoids the first-pass effect of the gut. However, to be absorbed through the oral mucosa, an opioid must have the proper molecular weight and lipid solubility. One opioid that meets these needs is fentanyl. Based on the success and experience with OTFC, a new, improved effervescent fentanyl lozenge is currently in clinical trials (Cephalon, 2005). Initial safety and efficacy studies of OTFC described in this article and other clinical studies (Adelus, Rice, & Bruno, 2002; Burton et al., 2004; Marek et al., 2001) demonstrate that, as a transmucosal delivery formulation, OTFC is relatively easy to use, noninvasive, effective, safe, and acceptable to patients, caregivers, and healthcare providers. However, the cost is prohibitive in many situations, and the drug generally is not considered a first-line therapy. Patient instruction on proper OTFC use, handling, storage, and disposal is critical to safe and effective use. Oncology nurses should familiarize themselves with the OTFC formulation's unique characteristics to be able to best help patients manage cancer breakthrough pain.

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