CASE REPORT

A descriptive case series: Oral transmucosal fentanyl use in patients with noncancerous pain

Anthony H. Guarino, MD
Jennifer Myers, RN, MSN, ANP
Martha E. Cornell, RN, BSN

ABSTRACT

Transmucosal fentanyl is indicated for patients with cancer who are opioid tolerant, but it is also used for the treatment of noncancerous pain. The following is a survey study of the use of transmucosal fentanyl in 29 patients with noncancerous pain in an academic, community-based pain management practice. Transmucosal fentanyl was found to be safe and efficacious in the patients studied.

Key words: Transmucosal fentanyl, Actiq, noncancerous pain, breakthrough pain, opioid

INTRODUCTION

Oral transmucosal fentanyl (OTFC) is currently approved solely for the management of breakthrough cancer pain in patients who are already receiving and tolerating opioid therapy for underlying persistent pain. The package insert for OTFC (Actiq) has a black box warning stating that this is the only indication approved by the Food and Drug Administration.[1] Despite this warning, clinicians have greatly expanded OTFC's use in the management of noncancerous pain over the last several years. We report the experiences of 29 patients prescribed OTFC for noncancerous breakthrough pain.

OTFC has proven efficacy in the management of cancer pain.[2-8] The clinical significance of the change in a patient's perception of pain with this medication has been addressed.[9] The clinical safety for the use of OTFC in patients without cancer has been established.[10,11] Patients who have chronic pain, regardless of the cause, commonly have transient pain flares, referred to as breakthrough pain (BTP).[12-16] Even in a noncancerous pain state, BTP is common despite the long-term use of opioids.

Patients who present to our pain management clinic traditionally have pain states that are chronic, meaning pain that has persisted for six months or longer. While we utilize the World Health Organization's Analgesic Ladder as a reference, it is not our treatment algorithm. We routinely tailor our treatment plans to the needs of the patients and the nature of their pain conditions. If a patient is presenting to our clinic for the first time, a detailed medication history is obtained, including medications that have not worked in the past. This information is used to determine what level of pain management is needed in order to improve the patient's quality of life. For example, if a patient presents with a pain flare but the underlying pain condition (e.g. low back pain) has not changed, these patients may be treated conservatively with nonsteroidal anti-inflammatory medications. If the pain state is moderate to severe, a stepwise approach to medication management is taken. If the patient has tried a short-acting medication (e.g. hydrocodone or oxycodone) and has been taking the medication every four hours around the clock, we provide the patient with a long-acting opioid (e.g. morphine or oxycodone). Our intent is to obtain a steady concentration of medication with a lower yield of BTP that may require additional short-acting medication.

Despite a maintenance dose that provides effective management of chronic pain, patients will experience BTP episodes. OTFC has been tested and approved in patients with cancer who experience BTP episodes. Pain specialists frequently prescribe OTFC off-label to treat BTP episodes in patients that do not have cancer. OTFC dosing in these patients is individualized according to the premise that the dose should be approximately equivalent to the dose of other short-acting BTP medications that a patient has previously taken. Equivalent dosing is not an exact science with OTFC because 25 percent of the dose is absorbed through the mucosal tissue, and only 25 percent of the swallowed dose is absorbed through the stomach. Thus dosing becomes an educated guess that is based on the assumption that only 50 percent of the dose is absorbed. Using the number of BTP episodes, the severity of the episodes, and the patient's

Table 1. Survey questions	
Demographics	Age, weight
General medical information	Nonpain related medical problems requiring continual care
Current pain diagnosis	Diagnosis, length of time of diagnosis
	Pain medications other than OTFC
OTFC information	Dose, start date
Specific questions	How long does your pain relief last after using OTFC? (0, 1, 2, 4, 5, >5 h)
	Rate the amount of pain reduction you experience using OTFC (none, slight, good, very good, excellent)
	Rate your level of sleepiness after using OTFC (none, slight, somewhat, very, cannot stay awake)
	Rate your level of nausea after using OTFC (none, slight, some, very, extreme)
	Rate your level of dizziness after using OTFC (none, slight, some, very, extreme)
	Rate your level of constipation after using OTFC (none, slight, some, very, extreme)
	Rate your level of breathing difficulty after using OTFC (none, slight, some, very, extreme)
Comparison of OTFC with medications used to control pain	Darvocet-N, Vicodin, Lortab, Norco, Demerol, other
	Tylenol with codeine, Talwin, Fiorinal, Percocet, morphine and Dilaudid (better, same, not as good, not applicable)
Miscellaneous questions	How many episodes of BKP do you have each day? (none, 1, 2, 3, 4, 5, >5)
	In general, how long have you been taking pain medications for this condition?
	How often do you feel impaired from taking OTFC? (never, sometimes, most of the time, always)
	How often do you feel impaired from any other pain medications? (never, sometimes, most of the time, always)
BTP, breakthrough pain; OTFC, transmucosal fentanyl	

history with the use of other BTP medications, the physician determines the best dose. Therefore, the intent of this study was to report one physician's off-label use of OTFC for BTP in 29 patients who had chronic noncancerous pain that was being managed with opioids.

METHODS

This study was a retrospective survey of patients with chronic noncancerous pain who experienced BTP episodes. The Washington University Human Studies Committee gave approval to administer the survey. The 29 patients, with a variety of pain diagnoses, attended a community-based academic pain management clinic. Patients asked to complete the survey 1) had chronic pain; 2) were using optimized dosages of opioids, either long-acting or around-the-clock short-acting, for chronic pain management; 3) indicated that current chronic pain management had resulted in a 50 percent or greater reduction in the original pain level, and 4) had BTP episodes that had been treated with a stable dose of OTFC for a minimum of one month.

Survey instrument

To facilitate the gathering of information, the investigator developed a questionnaire to collect both subjective and objective information from the patient. Collected information included 1) demographics, 2) current medical information, 3) current pain diagnosis, 4) information on current OTFC usage, 5) known side effects experienced, 6) length of pain relief, and 7) perception of impairment from OTFC and other pain medications (Table 1). All patients seen from July 2003 through October 2003 who met the inclusion criteria were asked to complete the questionnaire.

Statistical methods

The data were analyzed with SPSS for Windows (SPSS 12.0; SPSS Inc., Chicago, Illinois). Both descriptive and inferential statistical methods were used. All testing was based on determining statistical significance at a two-sided α level of 0.05. The study sample was described with measures of central tendency (mean and median) and dispersion (standard deviation and range) for continuous variables and frequency and percentage for categorical variables. The Spearman's rho statistic was used to evaluate the association between continuous and ordinal-scaled variables. The Mann-Whitney U test was used to compare the distribution of continuous and ordinal-scaled variables between two categories of categorical variables. The Kruskal-Wallis test was used to compare the distribution of continuous and ordinal-scaled variables among three or more categories of categorical variables.

RESULTS

Patient characteristics

Patient characteristics are presented in Table 2. The patients represented a middle-aged or older white (93 percent) population who had used pain medications for an average length of 5.4 years. The patients' pain was attributed to a variety of diagnoses, but it was predominantly due to spine-related disorders. Fifteen patients reported a pain diagnosis related only to the spine, seven reported only a nonspine-related pain diagnosis, and seven reported both a spine-related and nonspine-related diagnosis for pain.

Long-acting pain medications

The subjects were taking a variety of long-acting or around-the-clock opioids to maintain their chronic pain states at an acceptable level (Table 3). Fourteen (48 percent) of the subjects were using a fentanyl patch alone for chronic pain management, four (14 percent) were using a fentanyl patch and short-acting around-the-clock opioids, nine (31 percent) were using only short-acting around-the-clock opioids, and two (7 percent) were using another form of long-acting opioid medication for chronic pain management. The doses of the chronic pain medications had been stabilized before OTFC was prescribed for BTP. The average daily dose of long-acting opioid medication was 285 (± 235) morphine equivalents (mg).[17]

Side effects experienced

The patients' perceptions of several known side effects related to the use of OTFC are presented in Table 4. The most common side effects experienced were sleepiness and constipation. The least common side effects were breathing difficulties, nausea, and dizziness. None of the patients reported the side effects as being severe, although three patients reported they were very constipated, one was very sleepy, and one was very dizzy. No information was obtained to determine whether the subjects had been experiencing any of the side effects before the start of OTFC.

Effectiveness of transmucosal fentanyl

Patients were asked to rate their perception of the effectiveness of OTFC in the reduction of the pain from their BTP episodes in terms of no effect, slightly effective, good, very good, and excellent. Six patients (21 percent) rated OTFC as excellent, 12 (41 percent) rated it very good, 10 (34 percent) rated it good, and one (3 percent) rated it slightly effective. None of the patients indicated that OTFC had no effect on reducing pain.

Table 2. Patient characteristics (N = 29)	
Sex	
Male	12 (41.4)
Female	17 (58.6)
Race	
White	27 (93.1)
African American	2 (6.9)
Age (years)	50.4 ± 11.8
Body Mass Index	28.2 ± 7.1
Pain medication usage (years)	5.5 ± 5.4
Medical diagnosis related to pain (multiple diagnosis present in 16 patients)	
Spine-related disorders	
Degenerative disc disease (n = 5)	17.2
Failed back surgery (n = 5)	17.2
Lumbago (n = 6)	20.7
Radiculopathy (cervical and lumbosacral) (n = 7)	24.1
Spinal enthesopathy (n = 2)	6.9
Spinal stenosis (n = 4)	13.8
Other: Spondylosis, compression fracture, scoliosis, CRPS (n = 4)	13.8
Nonspine-related disorders	
Degenerative joint disease (n = 6)	20.7
Fibromyalgia (n = 3)	10.3
Other: Intestinal cystitis, peripheral neuropathy, esophageal spasms, pancreatitis, polyneuropathy, rectal pain, Shy-Drager syndrome (Total n = 7; n = 1 for each disorder)	24.1
Values are mean (± SD) or frequency (percentage); CRPS, complex regional pain syndrome.	

Table 3. Long-term pain medications	
Opioids	**n (percent)***
None	3 (9)
Fentanyl	18 (57)
Oxycodone	5 (16)
Morphine	4 (13)
Methadone	3 (9)
Nonopioid medications used for pain	**n (percent)***
Muscle relaxants	8 (25)
Anticonvulsants	5 (16)
Nonsteroidal anti-inflammatories	4 (13)
Hydrocodone	2 (6)
Other analgesics	4 (13)
Antidepressants	1 (3)
* Percentages do not total 100 because several patients were taking more than one long-acting medication.	

When patients were asked to compare OTFC with other BTP medications they had used, OTFC was rated better by 80 percent or more patients, except in the case of morphine, in which only 41 percent of the patients rated OTFC better. The results of these comparisons are presented in Table 5.

Transmucosal fentanyl dose relationships

To determine whether side effects were associated with higher daily doses of OTFC, we compared the distribution of the daily OTFC dose and the patients' perceptions of each side effect (none, slight, somewhat, very, and severe). When compared with the daily dose of OTFC, the responses were not significant for any of the side effects. The results of these comparisons are presented in Table 6.

The correlation between the total daily OTFC dose and the number of BTP episodes resulted in a Spearman's rho of 0.520 (rho = 0.002). The average total daily dose of OTFC was 1710 ± 967 μg, and the average number of breakthrough episodes was 3.7 ± 1.6. The correlation between a single dose of OTFC and the length of pain relief resulted in a Spearman's rho of -0.384 (rho = 0.030). The average single dose of OTFC was 600 ± 251 μg, and the average length of pain relief was 3.3 ± 1.5 hours. Thus, a moderately strong positive association was present between dose and number of BTP episodes, and a moderately strong negative correlation was present between dose and the length of pain relief.

DISCUSSION

In this limited population of 29 patients using OTFC for noncancerous BTP, the patients perceived the medication to be effective with a minimum of tolerable side effects. The patients were not opioid naïve and had tried a variety of opioids for BTP before OTFC was prescribed. Ninety-seven percent of the subjects rated OTFC good to excellent in effectively reducing their BTP episodes.

OTFC has an onset of effect at five minutes and a peak effect at 20 minutes.[1] The lasting effect can be several hours. In this study, the pain relief reported lasted an average of 3.3 ± 1.5 hours.

In this study the side effects were minimal. The most common side effects were constipation and sleepiness.

Table 4. Reported side effects of transmucosal fentanyl*					
	None	Slight	Somewhat	Very	Extreme
Sleepiness	13 (45)	6 (21)	9 (31)	1 (3)	0
Nausea	26 (90)	3 (10)	0	0	0
Constipation	18 (62)	3 (10)	5 (17)	3 (10)	0
Dizziness	24 (83)	4 (14)	0	1(3)	0
Breathing problems	28 (97)	0	1 (3)	0	0

* The total for each category is 29. The values reported are frequency (percentage).

None of the patients reported any of the side effects as being severe, although one patient reported being very sleepy, one very dizzy, and three very constipated. No correlation was seen between the daily dose of OTFC taken and the side effects. Side effects are common with opioids, and OTFC is no exception.

The moderately strong positive association between dose and number of BTP episodes and the moderately strong negative correlation between dose and the length of pain relief may indicate that subjects taking higher doses of OTFC are experiencing more BTP with shorter periods of relief, or they may suggest higher doses of OTFC are associated with less effectiveness. This study was not designed to determine the psychosocial behavior of the patients. Therefore, the correlations may represent a finding that is consistent with patients with drug-seeking behavior. The reports of shorter periods of effectiveness and increased numbers of BTP episodes in patients with the higher doses might represent patients who are seeking more opioids. In this clinical practice, patients are asked to sign a contract before starting opioid therapy that states they understand the consequences of opioid therapy and drug-seeking behavior. The physician conducts random drug testing if there are concerns. Even with guidelines in place, however, drug-seeking behavior is not always detected.

Table 5. Comparison of OTFC with other analgesics used by patients				
	n*	Better†	Same†	Not as good†
Propoxyphene acetaminophen	22	22 (100)	0	0
Hydrocodone acetaminophen	26	21 (81)	3 (12)	2 (8)
Meperidine	13	11 (85)	2 (15)	0
Acetaminophen codeine	24	23 (96)	1 (4)	0
Naloxone pentazocine	1	1 (100)	0	0
Butalbital aspirin	5	5 (100)	0	0
Oxycodone acetaminophen	23	21 (91)	2 (9)	0
Morphine	17	7 (41)	5 (29)	5 (29)
Hydromorphone	7	6 (86)	1 (14)	0

* Of the 29 patients completing the questionnaire, n represents the number of patients who had taken the respective medication; † Values represent the number of responses with percentages determined with the total number of patients who have taken the medication (n [percent]); OTFC, transmucosal fentanyl.

Table 6. Comparison results of side effects with daily OTFC dose (μg)					
	None	**Slight**	**Somewhat**	**Very**	**P**
Sleepiness	1,523 (± 847)	1,500 (± 1,010)	2,089 (± 1,141)	*	0.389
Nausea	1,677 (± 973)	2,000 (± 1,058)			0.612
Constipation	1,511 (± 857)	2,200 (± 1,732)	1,680 (± 912)	2,467 (± 702)	0.315
Dizziness	1,825 (± 959)	850 (± 661)		*	0.062
Breathing problems	*		*		
Values are mean ± SD; * Statistical analysis not done when n < 3; OTFC, transmucosal fentanyl.					

This study was designed only as a point-in-time retrospective survey of patients who were using OTFC for BTP. The study has several limitations. First, the subject-inclusion criteria dictated that only patients who had used OTFC for at least one month were to be studied. Most patients using a medicine tend to discard it fairly quickly if the desired effects are not reached or unwanted side effects are experienced. Second, no standardized tools were used to evaluate the patients' chronic pain or BTP. Third, because all clinic patients with chronic noncancerous pain using OTFC for BTP, regardless of dosage, were asked to participate in this study, the amount of chronic medication prescribed and the amount of OTFC prescribed were not controlled. Fourth, patients were not evaluated for baseline side effects before starting the OTFC. Although the questionnaire asks patients to rate their side effects as related to the OTFC, patients frequently have difficulty separating the two. A prospective study done at the start of OTFC administration would help to clarify this issue. Finally, patients were asked to rate only known side effects. There is a possibility that patients experienced other side effects that did not fit into the categories listed on the survey and thus went unreported.

In summary, in this limited population, OTFC was reported to be effective with a minimum of side effects. We recommend a larger controlled study to support the findings.

Anthony H. Guarino, MD, Washington University in St. Louis, Department of Anesthesiology, St. Louis, Missouri.
Jennifer Myers, RN, MSN, ANP, Washington University in St. Louis, Department of Anesthesiology, St. Louis, Missouri.
Martha E. Cornell, RN, BSN, Washington University in St. Louis, Department of Anesthesiology, St. Louis, Missouri.

REFERENCES

1. Actiq (oral transmucosal fentanyl citrate) [package insert]. Salt Lake City: Cephalon, Inc. 2004.
2. Rhiner M, Kedziera P: Managing breakthrough cancer pain: A new approach. *Home Healthc Nurse.* 1999;17 (suppl.): 1-12; quiz 13-15.
3. Rees E: The role of oral transmucosal fetanyl citrate in the management of breakthrough cancer pain. *Int J Palliat Nurs.* 2002; 8: 304-308.
4. Portenoy RK, Payne R, Coluzzi P, et al.: Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: A controlled dose titration study. *Pain.* 1999; 79: 303-312.
5. Payne R, Coluzzi P, Hart L, et al.: Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain. *J Pain Symptom Manage.* 2001; 22: 575-583.
6. Mercadante S, Fulfaro F: Alternatives to oral opioids for cancer pain. *Oncology (Huntingt).* 1999; 13: 215-220, 225; discussion 226-229.
7. Coluzzi PH, Schwartzberg L, Conroy JD, et al.: Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain.* 2001; 91: 123-130.
8. Oral transmucosal fentanyl for breakthrough cancer pain when morphine fails. *Prescrire Int.* 2002; 11: 106-107.
9. Farrar JT, Portenoy RK, Berlin JA, et al.: Defining the clinically important difference in pain outcome measures. *Pain.* 2000; 88: 287-294.
10. Streisand JB, Busch MA, Egan TD, et al.: Dose proportionality and pharmacokinetics of oral transmucosal fentanyl citrate. *Anesthesiology.* 1998; 88: 305-309.
11. Egan TD, Sharma A, Ashburn MA, et al.: Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers. *Anesthesiology.* 2000; 92: 665-673.
12. Zeppetella G, O'Doherty CA, Collins S: Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *J Pain Symptom Manage.* 2000; 20: 87-92.
13. Portenoy RK, Hagen NA: Breakthrough pain: Definition, prevalence and characteristics. *Pain* 1990; 41: 273-281.
14. Fine PG, Busch MA: Characterization of breakthrough pain by hospice patients and their caregivers. *J Pain Symptom Manage.* 1998; 16: 179-183.
15. Caraceni A, Portenoy RK: An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain.* 1999; 82: 263-274.
16. Ingham J, Seidman A, Yao TJ, et al.: An exploratory study of frequent pain measurement in a cancer clinical trial. *Qual Life Res.* 1996; 5: 503-507.
17. Jacox A, Carr DB, Payne R: New clinical-practice guidelines for the management of pain in patients with cancer. *N Engl J Med.* 1994; 330: 651-655.