ORIGINAL ARTICLE

Oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients: An overview of its pharmacological and clinical characteristics

Kyriaki Mystakidou, MD, PhD
Emmanuela Katsouda, MD
Efi Parpa, BA, MA
Marinos L. Tsiatas, MD, PhD
Lambros Vlahos, MD, PhD

ABSTRACT

Breakthrough pain is a transitory flare of pain occurring in most cancer patients against a background of otherwise controlled persistent pain. Treatment of breakthrough pain is a challenging phenomenon. Oral transmucosal fentanyl citrate (OTFC; brand name Actiq®, Cephalon Inc., West Chester, PA), a new opioid formulation with a unique delivery system, reflects the characteristics of breakthrough pain (rapid onset of action and short duration), making it an effective treatment for cancer patients who already receive opioids and experience flares of pain. This review article aims to present the role of oral transmucosal fentanyl citrate in the management of breakthrough pain in cancer patients. In particular, it is going to discuss the synthesis, clinical pharmacology, pharmacokinetic and pharmacodynamic properties, toxicity, and clinical efficacy of this novel agent.

Key words: oral transmucosal fentanyl citrate, breakthrough pain, cancer

INTRODUCTION

The vast majority of patients with advanced cancer report pain, which is usually controlled sufficiently with a fixed-schedule, around-the-clock opioid regimen. In addition to this chronic and persistent pain, up to two-thirds of cancer patients also experience transient exacerbations of severe pain that occur against a background of otherwise controlled, tolerable pain.[1,2] This transitory exacerbation is commonly described as "breakthrough pain" and characterized by rapid onset (median interval from onset to peak: three minutes; range: one second to 30 minutes), moderate to severe intensity, and relatively short duration (median duration: 30 minutes).[3-5]

Immediate-release, short-acting oral opioids taken as needed are commonly used to treat breakthrough pain. In cancer patients, morphine sulfate, oxycodone, and hydromorphone are commonly used for this purpose. Oral transmucosal fentanyl citrate (OTFC; brand name Actiq®, Cephalon Inc., West Chester, PA) is the first medication developed specifically for the treatment of breakthrough pain. It provides fentanyl, its active ingredient, via a unique oral transmucosal delivery system and offers personal pain control to cancer patients.

PHARMACOLOGICAL CHARACTERISTICS

Synthesis

OTFC is a solid formulation of fentanyl citrate, a potent (50 to 100 times as potent as morphine), short-acting, rapid-onset, lipophilic, synthetic opioid with selective activity for μ-receptors expressed in the brain, spinal cord, and other tissues. OTFC is formulated as a solid drug matrix on a handle, allowing the unit to rotate in the mouth for optimal absorption and the removal of the unit if signs of excessive opioid effects occur during administration. OTFC is available in six strengths equivalent to 200, 400, 600, 800, 1,200, or 1,600 mcg fentanyl base.

Clinical pharmacology

Fentanyl, a pure opioid agonist, acts primarily through interaction with opioid μ-receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS).[5] The most clinically useful pharmacologic effects of fentanyl's interaction with μ-receptors are analgesia and sedation. Other opioid effects—at clinically relevant doses—may

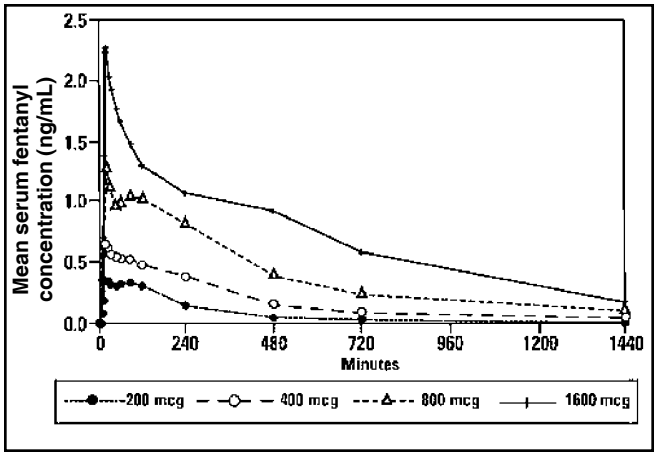

Figure 1. Mean serum fentanyl levels following administration of the four strengths of OTFC (200, 400, 800, and 1,600 mcg units) in adult subjects (*Actiq® Summary of Product Characteristics*).

include somnolence, hypoventilation, bradycardia, postural hypotension, pruritus, dizziness, nausea, diaphoresis, flushing, euphoria, and confusion or difficulty in concentrating.

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a three- to five-minute half-life). In individuals who are not opioid-tolerant, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/ml to surgical anesthesia and profound respiratory depression at levels of 10 to 20 ng/ml.[6]

In the clinical setting, pharmacological and pharmacokinetic differences have been observed among patients who have been administered fentanyl. The variable binding of serum fentanyl to plasma proteins may be a factor in these observed differences. Approximately 80 percent of fentanyl is bound to plasma proteins,[7] such as the acute phase protein α1-acid glycoprotein,[8] with only free fentanyl able to cross the blood-brain barrier. Variability in endogenous opioid concentrations in cerebrospinal fluid may also contribute to these observed differences.[9,10] The requirement for higher-than-estimated blood concentrations typically sufficient to elicit clinically significant analgesia (~1 ng/ml) may result in ventilatory depression (at > 2 ng/ml).[11] This need for additional supportive analgesia without severe respiratory depression led to the development of the oral transmucosal fentanyl delivery system.

Pharmacokinetics

The absorption pharmacokinetics of fentanyl in the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the gastrointestinal tract.[12] Both the blood fentanyl profile and the bioavailability of fentanyl will vary, depending on the fraction of the dose absorbed through the oral mucosa and the fraction swallowed.

Under normal conditions, approximately 25 percent of the total OTFC dose are rapidly absorbed from the buccal mucosa and become systemically available. The remaining 75 percent of the total dose are swallowed with the saliva and then slowly absorbed from the gastrointestinal tract. About one-third of this amount (25 percent of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50 percent bioavailability of OTFC is divided equally between rapid transmucosal absorption and slower gastrointestinal absorption.

Dose proportionality among four of the available strengths of OTFC (200, 400, 800, and 1,600 mcg) has been demonstrated in a balanced crossover design in adult subjects.[13] Figure 1 shows the mean serum fentanyl levels following these four doses of OTFC. The curves for each dose level are similar in shape to increasing dose levels that produce increasing serum fentanyl levels.

The pharmacokinetic parameters of the four strengths of OTFC tested in the dose proportionality study are shown in Table 1. The mean C_{max} ranged from 0.39 to 2.51 ng/ml.[13] The median time of maximum plasma concentration (T_{max}) across these four doses of OTFC varied from 20 to 40 minutes (a range of 20 to 480 minutes) as measured after the start of administration. Moreover, studies in healthy donors showed that two smaller doses of OTFC (400 mcg) administered simultaneously are pharmacokinetically equivalent to an identical dose administered as a single unit (800 mcg).[14]

Metabolism and elimination

Fentanyl is principally (more than 90 percent) metabolized into norfentanyl and other inactive metabolites in the liver and intestinal mucosa by the cytochrome P450 3A4 isoenzyme system and oxidative μ-dealkylation. Less than 7 percent of the dose is excreted unchanged in the urine, and only about 1 percent is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl is 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about seven hours.[6]

Dosage and administration

OTFC is presented as a sweetened lozenge with an integral oromucosal applicator (unit) intended for oral administration by sucking. Each dosage unit contains 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,200 mcg, or 1,600

Table 1. The pharmacokinetic parameters of the four strengths of OTFC (200, 400, 800, and 1,600 mcg units) tested in the dose-proportionality study (*Actiq® Summary of Product Characteristics*)

	Pharmacokinetic parameter			
	T_{max}, minute median (range)	C_{max}, ng/ml mean (% CV)	AUC_{0-1440}, ng/ml minute mean (% CV)	$t_{½}$, minute mean (% CV)
200 mcg	40 (20 – 120)	0.39 (23)	102 (65)	193 (48)
400 mcg	25 (20 – 240)	0.75 (33)	243 (67)	386 (115)
800 mcg	25 (20 – 120)	1.55 (30)	573 (64)	381 (55)
1,600 mcg	20 (20 – 480)	2.51 (23)	1,026 (67)	358 (45)

mcg fentanyl citrate. To minimize opioid-related side effects, it is necessary to identify a "successful" dose via closely supervised titration. Titration is considered necessary, as clinical trials could not establish a predictable relationship between a daily dose of around-the-clock medication and an OTFC dose. Before titration with OTFC, persistent background pain should be controlled with opioid therapy, and patients should typically experience no more than four episodes of breakthrough pain per day. The initial dose of OTFC should be 200 mcg, titrating upwards as necessary.

During titration, if adequate analgesia is not obtained within 15 minutes after the complete consumption of a single lozenge, a second lozenge of the same strength may be consumed. No more than two lozenges should be used to treat an individual pain episode. If treatment of several consecutive breakthrough pain episodes requires more than one dosage unit per episode, an increase to the next available strength should be considered. Patients should be carefully monitored until a successful dose is determined. Once a successful dose has been established, patients should be maintained on this dose and should limit consumption to a maximum of four units per day.[2] If more than four units per day are needed, the dose of fixed-schedule analgesics should be increased or the overall pain management strategy reconsidered.

Adverse events and drug interactions

Adverse events seen with OTFC are typically opioid-related and include somnolence, dizziness, nausea, constipation, asthenia, and confusion. The therapeutic range of fentanyl is between 1 and 3 ng/ml.[16] Overdose may result in hypoventilation and possible respiratory failure. Inappropriate use, either accidental or intentional, may induce fentanyl intoxication. Therefore, all patients must be followed for respiratory depression symptoms.

Because fentanyl is metabolized by the cytochrome P450 3A4 isoform, inhibitors of this enzyme may produce increased or prolonged opioid side effects. The concomitant use of other CNS depressants may produce additive sedative effects. OTFC should not be administered to patients who have received monoamine oxidase inhibitors within the previous 14 days.

CLINICAL CHARACTERISTICS

To date, OTFC for the management of breakthrough pain has been evaluated via small, short-term studies in adult patients with cancer-related pain. In these studies, patients were either taking an oral opioid (usually morphine) or transdermal fentanyl as their around-the-clock medication to control persistent pain.

Two randomized, double-blind dose titration studies of OTFC have been published (n = 65, 62).[2,17] The results demonstrated that 74 percent and 76 percent of patients, respectively, were able to identify a safe and effective dose of OTFC. The mean successful dose of OTFC in these studies was approximately 600 mcg. No relationship was found between the successful dose of OTFC and the total daily dose of around-the-clock opioid in either study, indicating that the optimal dose of OTFC cannot be predicted by the total daily dose of fixed-schedule opioid.

These titration studies also included open-label comparisons of OTFC and the patients' usual oral opioids used for breakthrough pain. Although neither study was designed to validly compare the analgesic efficacy of OTFC to the usual rescue drug, OTFC was reported to produce a greater analgesic effect, better global satisfaction, and a more rapid onset of action than the usual breakthrough medication.[2,17]

The efficacy of OTFC has been evaluated in one randomized, placebo-controlled trial and one randomized, comparative study[18] with immediate release morphine sulphate (MSIR).[19] The placebo-controlled study was a multicenter, crossover study that evaluated the efficacy of individualized doses of OTFC. A total of 130 patients who met the eligibility criteria underwent open-label dose titration to identify their successful dose. Ninety-two patients successfully completed the dose titration phase and consented to participate in the randomized, double-blind phase, during which each patient acted as his/her own control.

Each patient was given 10 units. Seven were OTFC at the same dose found to be effective for the particular patient in the titration phase, and three were identically formulated placebos. All 10 doses were to be taken within a 14-day period. Patients were allowed to take a dose of their usual rescue medication if adequate pain relief was not achieved after 30 minutes. Patients completed a medication diary at 0, 15, 30, 45, and 60 minutes following consumption of a unit.

In the primary efficacy analysis (excluding protocol violations; n = 86), analgesic effect in terms of pain-intensity difference (i.e., the difference in pain intensity immediately before consumption of trial medication and at 15, 30, 45, and 60 minutes post-consumption) and pain relief were significantly greater with OTFC than with placebo for all time points ($p < 0.0001$). The mean global performance evaluation values also significantly favored OTFC ($p < 0.0001$). Patients required significantly more additional rescue medication for breakthrough pain episodes treated with placebo than for episodes treated with OTFC—34 percent vs. 15 percent; RR = 2.27 (95 percent CI: 1.51 to 3.26), $p < 0.0001$.[18]

The comparative study was a randomized, double-blind, crossover study assessing the efficacy of successful doses of OTFC with MSIR. Initially, 134 patients who met the eligibility criteria and were using a successful dose of 15 mg, 30 mg, 45 mg, or 60 mg MSIR were entered into an open-label dose titration phase to identify a successful dose of OTFC. Ninety-three of these patients successfully completed the titration phase and entered the randomized, double-blind phase, during which each patient acted as his/her own control. Each patient was given 10 sets of medication (five contained OTFC + placebo capsules; five contained placebo units + MSIR capsules). The patient consumed a full set of study medication at each episode of breakthrough pain, with all 10 doses to be taken within a 14-day period.

In the primary efficacy analysis (for patients who had at least one evaluable episode for each study drug; n = 75), OTFC was statistically significantly superior to MSIR in terms of pain intensity difference ($p < 0.008$) and pain relief ($p < 0.009$) at each time point and global performance rating ($p < 0.001$). In addition, significantly ($p < 0.001$) more pain episodes treated with OTFC had a greater than 33 percent change in pain intensity at 15 minutes than MSIR, implying a faster onset of action with OTFC.[19]

Another open-label study evaluated the long-term safety and tolerability of OTFC in ambulatory cancer patients with breakthrough pain.[20] Participants were patients who had participated in a previous short-term titration trial of OTFC, were experiencing at least one episode per day of breakthrough pain, and had achieved relief of their breakthrough pain with an opioid. In total, 41,766 units of OTFC were used to treat 38,595 episodes of breakthrough pain in 155 patients. Patients averaged 2.9 breakthrough pain episodes per day. About 92 percent of episodes were successfully treated with OTFC, and there was no trend toward decreased effectiveness over time. Most patients (61 percent) did not require dose escalation during treatment. Global satisfaction ratings were consistently above 3 (0 = poor, 4 = excellent), indicating very good to excellent relief. Common adverse events associated with OTFC were somnolence (9 percent), constipation (8 percent), nausea (8 percent), dizziness (8 percent), and vomiting (5 percent). Six patients (4 percent) discontinued therapy due to an OTFC-related adverse event. There were no reports of abuse, and patients and their families raised no concerns about the drug's safety. OTFC was used safely and effectively during long-term treatment of breakthrough pain in cancer patients at home.

Finally, a recent retrospective study evaluated the efficacy of OTFC in the outpatient management of severe cancer patient crises.[21] Prior to OTFC treatment, all patients reported a mean pain intensity of 9.0 (SD = 1.2). After OTFC treatment, patients reported a mean intensity of 3.0 (SD = 1.4), a significant reduction in pain intensity ($p < 0.001$). In most cases, OTFC averted the need for an emergency center visit, parenteral opioids, and hospital admission, which suggests that OTFC could be an effective alternative over intravenous opioids to rapidly titrate analgesia in selected opioid-tolerant cancer patients experiencing severe pain.

CONCLUSION

OTFC is an opioid agonist available in a unique delivery system and is the first opioid analgesic formulation specifically developed and approved for the control of breakthrough pain. The safety profile and pharmacokinetic characteristics (i.e., rapid onset of action and relatively short duration) of this new opioid formulation make it ideal for the management of breakthrough pain in cancer patients already receiving around-the-clock opioid medication for pain.

Kyriaki Mystakidou, MD, PhD, Assistant Professor in Palliative Medicine, Pain Relief & Palliative Care Unit, Department of Radiology, University of Athens, Athens, Greece.
Emmanuela Katsouda, MD, Pneumonologist, Pain Relief & Palliative Care Unit, Department of Radiology, University of Athens, Athens, Greece.
Efi Parpa, BA, MA, Psychologist, Pain Relief & Palliative Care Unit, Department of Radiology, University of Athens, Athens, Greece.
Marinos L. Tsiatas, MD, PhD, Department of Clinical Therapeutics, University of Athens, Athens, Greece.
Lambros Vlahos, MD, PhD, Professor in Radiology, Pain Relief & Palliative Care Unit, Department of Radiology, University of Athens, Athens, Greece.

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