

Oral transmucosal fentanyl citrate in cancer pain management: a practical application of nanotechnology

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Abstract: Pain is experienced by most cancer patients and represents an important issue in the clinical setting. Breakthrough pain is a transitory flare of pain that occurs in most cancer patients on a background of otherwise controlled persistent pain. Treatment of breakthrough pain is a challenging phenomenon. Oral transmucosal fentanyl citrate (OTFC; Actiq®, Cephalon, UK), a new opioid formulation with a unique delivery system, utilizing the advantages that nanotechnology offers, reflects the characteristics of breakthrough pain (rapid onset of action and short duration), which makes it an effective treatment to cancer patients who are already receiving opioids and continue to experience such flares of pain. Oral transmucosal fentanyl citrate is specifically developed and approved for the management of breakthrough pain in cancer patients and it has the potential to be a useful tool for clinicians.

Keywords: oral transmucosal fentanyl citrate, cancer pain, breakthrough pain

Introduction

Pain is often an undertreated symptom in cancer and highly affects patients' quality of life. Seventy-four percent of patients with advanced cancer report pain which is usually controlled in these patients sufficiently with a fixed-scheduled, around-the-clock opioid regimen. Apart from this chronic and persistent pain, up to two thirds of patients also experience transient flares of severe pain that occur on a background of otherwise controlled and tolerated chronic pain (Portenoy and Hagen 1990; Portenoy et al 1999a). These transitory flares are commonly described as "breakthrough pains" and are characterized by rapid onset (within 3 minutes), moderate to severe intensity, and relatively short duration (average 30 minutes) (Portenoy et al 1993; Simmonds 1999; McMenamin and Farrar 2002). Moreover, breakthrough pain is associated with more severe pain, higher distress, and lower quality of life (Portenoy et al 1999b; Hwang et al 2003).

Nanotechnology is a multidisciplinary field involving the design and engineering of objects <500 nanometers (nm) in size. Over the last two decades, nanotechnology has offered a variety of nanoscale tools specifically designed for therapeutic use in cancer. For drug-delivery systems, nanotechnology offers the potential to optimize drug delivery and minimize side-effects. Recently, novel nanotechnology-based methods, such as implantable drug delivery devices, and transdermal and transmucosal delivery systems, have been engineered (Csaba et al 2006). Oral transmucosal drug delivery is a method of systemic drug delivery that offers several advantages over traditional parenteral or enteral methods (Sprintz et al 2005; Cuenca et al 2006).

Nanotechnology and cancer pain

Moderate to severe pain is experienced by one third of cancer patients receiving active therapy and by 60%–90% of patients with advanced disease (Daut and Cleeland 1982;

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Twycross and Fairfield 1982). Advances in the diagnosis and treatment of cancer, coupled with advances in our understanding of anatomy, physiology, pharmacology, and pain perception, have led to improved care of the patient with pain (Foley 1999). Such patients are managed most effectively by the use of many analgesic agents, such as opioids, non-steroidal anti-inflammatory drugs, and corticosteroids, in the form of pill, oral solution, or injection, providing additional benefit in the adjuvant setting. Opioid analgesics remain the cornerstone of pharmacotherapy for pain, with morphine long being the gold standard for cancer-associated pain. Short-lived drugs are generally favored because they are easier to titrate than those with a long half-life. The optimal route of administration of opioids is oral; however, bowel obstruction, severe vomiting, or coma may preclude this route.

Breakthrough pain is a transitory flare of pain that occurs in most cancer patients on a background of otherwise controlled persistent pain. Treatment of breakthrough pain is a challenging phenomenon. In cancer patients, immediate release, short-acting oral opioids, such as morphine sulfate, oxycodone, and hydromorphone, taken as needed, are commonly used to treat breakthrough pain.

Nanotechnology has exhibited a remarkable progress over the past 20 years in the management of pain in cancer patients. Recent applications at the nanoscale level include novel drug-delivery systems, such implantable drug-delivery devices, transdermal or transmucosal patches, and micro-needles. Oral transmucosal fentanyl citrate (OTFC; Actiq[®], Cephalon, UK) is the first medication developed specifically for the treatment of breakthrough pain and provides its active ingredient, fentanyl, in a unique oral transmucosal delivery system, utilizing microfabrication technology, offering personal pain control for cancer patients (Mystakidou et al 2006).

Oral transmucosal fentanyl citrate and cancer pain

Oral transmucosal fentanyl citrate is a solid formulation of fentanyl citrate, a potent (50- to 100-fold 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 rotation of the unit 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, 1200, or 1600 μ g fentanyl base.

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) (Portenoy et al 1993; Mystakidou 2002). The most clinically useful pharmacological effects of the interaction of fentanyl with μ -receptors are analgesia and sedation. Other opioid effects may include somnolence, hypoventilation, bradycardia, postural hypotension, pruritus, dizziness, nausea, diaphoresis, flushing, euphoria, and confusion or difficulty in concentrating at clinically relevant doses.

In the clinical setting, pharmacological and pharmacokinetic differences have been observed between patients administered fentanyl. The variable binding of serum fentanyl to plasma proteins may be a factor in these observed differences. Approximately 80% of fentanyl is bound to plasma proteins (Mather 1983), such as the acute phase protein α 1-acid glycoprotein (Meuldermans et al 1982), with only free fentanyl able to cross the blood-brain barrier. Variability in cerebrospinal fluid concentrations of endogenous opioids may also contribute to these observed differences (Cohen et al 1982; Tamsen et al 1982). The requirement for higher than estimated blood concentrations typically sufficient to elicit clinically significant analgesia (\sim 1 ng/mL) may result in ventilatory depression (at $>$ 2 ng/mL) (Cartwright et al 1983). This need for additional supportive analgesia without severe respiratory depression led to the development of the oral transmucosal fentanyl delivery system.

This delivery approach offers simple, tolerable, and patient-compliant administration of fentanyl for rapid onset of opioid analgesia specifically for breakthrough pain episodes associated with cancer. The OTFC delivery system incorporates nanoparticle technology for the improvement of transmucosal transport of fentanyl. The achievement of high surface-volume ratios of nanosized drug maximizes drug-mucosal interactions and thus increases the bioavailability of fentanyl compared with the drug administered in larger particles (Csaba et al 2006).

The absorption pharmacokinetics of fentanyl from 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 (Streisand et al 1991). Both the blood fentanyl profile and the bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

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

Dose proportionality among four of the available strengths of OTFC (200, 400, 800, and 1600 µg) has been demonstrated in a balanced crossover design in adult subjects (Streisand et al 1998). Mean serum fentanyl levels following these four doses of OTFC are shown in Figure 1. The curves for each dose level are similar in shape, with increasing dose levels producing 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 (Streisand et al 1998). The median time of maximum plasma concentration (T_{max}) across these four doses of OTFC varied from 20 to 40 minutes (range of 20–480 minutes) as measured after the start of administration. Moreover, studies in healthy donors showed that two smaller doses of OTFC (400 µg) administered simultaneously are pharmacokinetically equivalent to an identical dose administered as a single unit (800 µg) (Lee et al 2003).

Fentanyl is principally (more than 90%) metabolized in the liver and in the intestinal mucosa by the cytochrome P450 3A4 isoenzyme system by oxidative *N*-dealkylation to norfentanyl and other inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% 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/h/kg (range 0.3–0.7 L/h/kg). The terminal elimination half-life after OTFC administration is about 7 hours (Cephalon Inc. 2003; Mystakidou et al 2005). The structural formula of the compound is shown in Figure 2.

OTFC for the management of breakthrough pain has been evaluated in 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 their persistent pain. Two randomized, double-blind, dose titration studies of OTFC have been published ($n = 65, 62$) (Christie

et al 1998; Portenoy et al 1999a). The results demonstrated that 74% and 76% 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 µg. 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. Additionally, OTFC was reported to produce a greater analgesic effect, better global satisfaction, and a more rapid onset of action than the usual breakthrough medication (Christie et al 1998; Portenoy et al 1999a).

The efficacy of OTFC has been evaluated in one randomized, placebo-controlled trial and one randomized comparative study with immediate-release morphine sulphate (MSIR) (Farrar et al 1998; Coluzzi et al 2001). 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: 7 were OTFC at the same dose found effective for that patient in the titration phase and 3 were identically formulated placebo. 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 (the difference in pain intensity immediately before consumption of trial medication and at 15, 30, 45, and 60 minutes post consumption) and pain relief was significantly greater with OTFC than 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% vs 15%; RR = 2.27 (95% CI: 1.51–3.26), $p < 0.0001$ (Farrar et al 1998).

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,

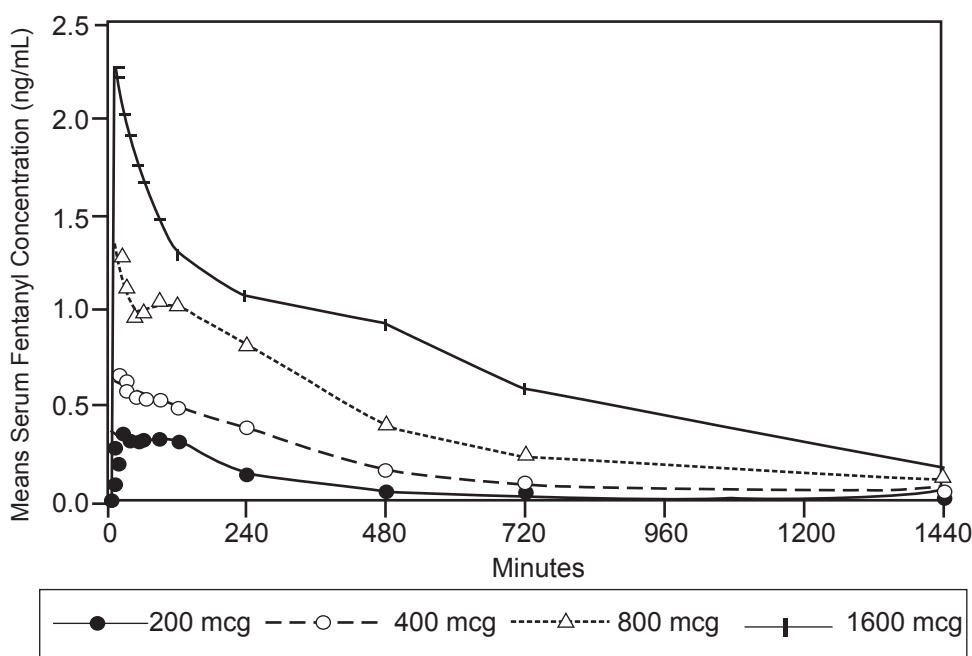


Figure 1 Mean serum fentanyl levels following administration of the four strengths of OTFC (200, 400, 800, and 1600 μ g) in adult subjects. Reproduced with permission from Cephalon Inc. (2003).

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 (5 contained OTFC + placebo capsules; 5 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% change in pain intensity at 15 minutes than MSIR, implying a faster

onset of action with OTFC (Coluzzi et al 2001). Another open-label study evaluated the long-term safety and tolerability of OTFC in ambulatory cancer patients with breakthrough pain (Payne et al 2001). Patients 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% of episodes were successfully treated with OTFC and there was no trend toward decreased effectiveness over time. Most patients (61%) did not require dose escalation during treatment. Global satisfaction ratings were consistently above 3 (0 = poor through 4 = excellent), indicating very good to excellent relief. Common adverse events associated with OTFC were somnolence (9%), constipation (8%), nausea (8%), dizziness (8%), and

Table 1 The pharmacokinetic parameters of the four strengths of OTFC (200, 400, 800, and 1600 μ g) tested in the dose-proportionality study. Reproduced with permission from Cephalon Inc. (2003)

| Pharmacokinetic parameter | 200 μ g | 400 μ g | 800 μ g | 1600 μ g |
|---|-------------|-------------|-------------|--------------|
| T_{max} , minute median (range) | 40 (20–120) | 25 (20–240) | 25 (20–120) | 20 (20–480) |
| C_{max} , ng/mL mean (% CV) | 0.39 (23) | 0.75 (33) | 1.55 (30) | 2.51 (23) |
| AUC_{0-1440} , ng/mL minute mean (% CV) | 102 (65) | 243 (67) | 573 (64) | 1026 (67) |
| $t_{1/2}$, minute mean (% CV) | 193 (48) | 386 (115) | 381 (55) | 358 (45) |

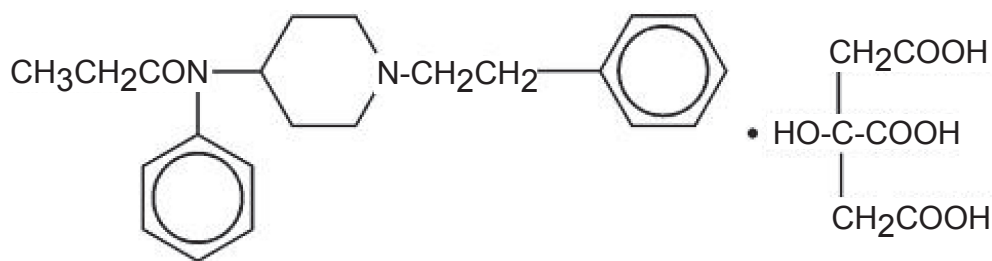


Figure 2 The structural formula of fentanyl citrate.

vomiting (5%). Six patients (4%) discontinued therapy due to an OTFC-related adverse event. There were no reports of abuse and no concerns about the safety of the drug raised by patients or families. OTFC was used safely and effectively during long-term treatment of breakthrough pain in cancer patients at home.

Finally, a recent study evaluated the efficacy of OTFC in the outpatient management of severe cancer patient crises (Burton et al 2004). 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.

Conclusions

The integration of nanotechnology into cancer therapeutics, including the management of breakthrough pain in cancer patients, is a rapidly developing field which will dramatically change medical practice in future years. Numerous data accentuate the great potential of nanosized transmucosal delivery systems and their promising future in the clinical setting. Oral transmucosal drug delivery of fentanyl citrate for the management of breakthrough pain, as an application of nanotechnology, is an alternative method of systemic drug delivery, offering convenience in administration, improved absorption and pharmacokinetics (rapid onset of action bypassing gastrointestinal tract, and first-pass metabolism in the liver), and thus better patient compliance and overall efficacy.

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