

Expert Opinion

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Fentanyl buccal tablets

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Fentanyl buccal tablets (FBT) are designed to manage the breakthrough pain associated with chronic pain with an enhanced rate and extent of fentanyl absorption through the buccal mucosa. The formulation incorporates an effervescent reaction to produce large shifts in pH that enhance absorption. Results from studies of safety and tolerability have shown FBT to be effective and well tolerated in opioid-tolerant chronic pain patients. Adverse events were similar to those seen with other opioids and included nausea and somnolence. Adverse events were common but mild or moderate in most cases and did not cause a high drop-out rate. In addition to the treatment of breakthrough pain, FBT could be clinically efficacious for the treatment of brief, anticipated painful events. The abuse liability of FBT is unknown and caution should be used in prescribing FBT to patients with histories of substance abuse.

Keywords: breakthrough pain, chronic non-malignant pain, chronic pain, effervescent, fentanyl buccal tablets

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1. Introduction

Breakthrough pain (BTP) is defined as a sudden, temporary flare that occurs against a background of otherwise controlled pain [1]. Many patients with chronic cancer and noncancer pain experience several episodes of BTP daily. BTP episodes can be as brief as 10 min, although the median duration is 30 – 60 min; regardless, these episodes can be excruciating [1-3]. A high percentage of patients with pain experience BTP. In a recent survey of 228 patients with diverse types of chronic noncancer pain [3], 74% experienced severe to excruciating BTP.

BTP is of three varieties. Spontaneous pain is marked by a sudden (often disabling) crescendo and comes on without warning. Common in neuropathic pain conditions, an example is the sharp, lancinating pain suffered during attacks of acute shingles or post-herpetic neuralgia. Incident pain is associated with an identifiable cause, either predictable (as in anticipated pain caused by movement) or unpredictable (as in a bladder spasm). End-of-dose failure is the pain that results when the dose of the drug has dropped below the analgesic level.

Presently, only oral transmucosal fentanyl citrate (OTFC®) is available as a rapid-onset, non-intravenous medication for BTP. A new formulation of a fentanyl buccal tablet (FBT) has been developed by Cephalon, Inc. and approved by the FDA. It is differentiated from OTFC by a novel delivery system featuring an effervescent reaction, which facilitates the rate and extent of absorption by increasing the pH of the mucosal surface [4]. FBT is placed between the cheek and gum adjacent to an upper molar and allowed to dissolve passively for 10 – 15 min.

2. Pharmacology and comparable medications

OTFC has been shown to be a fast, effective medication for BTP, delivering analgesia at 15 min and other subsequent time points; for example, 2 randomised, controlled studies found that patients achieved significantly better analgesia with OTFC versus placebo ($p < 0.0001$) at 15, 30, 45 and 60 min [5] and that patients achieved

significantly better analgesia with OTFC versus rescue medications ($p < 0.0001$) at 15, 30 and 60 min [6].

In clinical studies, FBT delivered more fentanyl across the oral mucosa than a comparable dose of OTFC [7]. This greater absorption can be explained by the increased pH associated with FBT effervescence. The delivery route of FBT also avoids the gastrointestinal tract and first-pass liver metabolism. With OTFC, a portion of the medication is swallowed, thus diluting and delaying its absorption beyond the duration of the breakthrough event.

Absorption rates were compared among equivalent doses of OTFC and two formulations of FBT [8]. One formulation of buccal tablets was enhanced with effervescence and the other was not, although both contained the same amount of fentanyl. When blood serum levels for the first 30 min were assessed, the effervescence-enhanced fentanyl formulation showed ~2.5-fold the blood level of the non-effervescent buccal tablet and 5-fold the blood level observed with OTFC.

An open-label, cross-over study of 32 healthy volunteers compared the bioavailability of transmucosal FBT 400 µg; FBT 800 µg p.o.; fentanyl 400 µg i.v.; and OTFC 800 µg [7]. The transmucosal delivery of FBT had a higher absolute bioavailability (0.65) than OTFC (0.47) or oral FBT (0.31; Table 1). The time to maximum concentration (T_{max}) was earlier following transmucosal FBT (47 min) than with either OTFC (91 min) or oral FBT (90 min). In addition, a larger proportion of FBT was absorbed transmucosally (48%) compared with OTFC (22%). As reported by Darwish *et al.* [7] based on values normalised to the equivalent maximum serum concentration (C_{max}), early systemic exposure (area under the curve from 0 to T_{max} [$AUC_{0-T_{max}}$]) and total systemic exposure ($AUC_{0-\infty}$) were greater after FBT than after OTFC.

Researchers concluded that the rate and extent of absorption and, therefore, the absolute bioavailability of fentanyl is greater following transmucosal administration of FBT compared with OTFC. On the basis of comparisons conducted between FBT 400 µg and OTFC 800 µg, a smaller dose of FBT would achieve systemic exposure of fentanyl comparable with that following administration of OTFC [7].

3. Clinical efficacy

A randomised, double-blind, placebo-controlled study [9] was conducted to test the efficacy and tolerability of FBT in opioid-tolerant cancer patients. Patients first identified an effective dose of FBT for BTP in an open-label titration period before being randomised to 1 of 18 dose sequences of 10 tablets (3 placebo and 7 FBT) at the previously identified effective dose. A total of 123 patients were included in the overall study, including safety and tolerability results; 77 patients were included in the double-blind phase of the study with efficacy data evaluable for 72 patients. Clinically significant ($\geq 33\%$) decreases in pain intensity occurred with FBT in 13% of episodes by 15 min and in 48% of

episodes by 30 min. At all of the time points (15, 30, 45 and 60 min), the decrease was significantly greater for FBT than for placebo ($p < 0.05$). At 30 min post dose, pain intensity decreased by $\geq 50\%$ with FBT in 24% of episodes and with placebo in 16% of episodes ($p < 0.05$). The analgesic effect of FBT was apparent at 15 min and the effect was found to last 60 min. FBT exceeded placebo analgesia on all measures including responder analysis and global medication performance ratings. Patients were twice as likely to need supplemental opioids after receiving placebo as after receiving FBT.

Pooled data from the open-label titration phases of 3 studies evaluating FBT suggest that a satisfactory dose with sufficient analgesia and control of adverse events (AEs) was reached in 66.5% of opioid-tolerant patients with cancer-related BTP [10]. Patients were administered a test dose (100 µg) that – if well tolerated – was followed by individual titration to an effective dose of FBT. An effective dose was defined as a single tablet of the dose (100, 200, 400, 600 or 800 µg) that provided satisfactory relief of BTP within 30 min (without unacceptable AEs) for 2 consecutive BTP episodes. No correlation was found between the effective dose of FBT and the baseline around the clock opioids. The researchers suggested studies of higher doses to address the third of patients who did not find an effective dose.

In an interim result from an ongoing, open-label, multi-centre study [11] in opioid-tolerant patients with chronic pain, most of the 85 patients (73%) expressed a preference for FBT versus their previous supplemental opioids after 1 month of use in an open-label phase.

The treatment of BTP would be the primary indication for FBT. It is specifically indicated in the treatment of BTP in patients with cancer who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain. Additional potential uses for FBT are addressed in Section 6.

4. Safety and tolerability profile

In a study of 123 patients with cancer, of which 72 were evaluated for efficacy [9], the most common AEs were nausea (22%), dizziness (22%) and headache (15%). There were two patients who dropped out of the study because of oral tolerability issues. Researchers commented that the AEs observed are typical with opioids.

AEs were identified in an interim analysis of a long-term, open-label multi-centre study in cancer patients [12]. AEs were mild to moderate in 67% of patients and common to patients with cancer, including nausea (35%), vomiting (20%), dizziness (20%), fatigue (15%), headache (12%) and anaemia (11%).

Other researchers reported a similar incidence and type of AEs, all of which were mild to moderate in severity. No report of any serious AEs from respiratory depression or chest-wall rigidity has been found in the literature so far.

Table 1. Pharmacokinetic properties of comparable medications.

Fentanyl delivery	Bioavailability	T _{max}	C _{max} (ng/ml)*	AUC _{0-∞} (ngh/ml)*	AUC _{0-Tmax} (ngh/ml)*
Transmucosal FBTs 400 µg	0.65	47 min	1.02 ± 0.42	6.48 ± 2.98	0.40 ± 0.18
Oral FBT 800 µg	0.31	90 min			
Intravenous fentanyl 400 µg [‡]	§	§			
OTFC® 800 µg	0.47	91 min	0.63 ± 0.21	4.79 ± 1.96	0.14 ± 0.05

n = 32.

*Dose-normalised parameter.

[‡]The absolute bioavailability of fentanyl for intravenous fentanyl 400 µg was assumed to be 100% and was used to calculate the absolute bioavailability of fentanyl for transmucosal FBT 400 µg, oral FBT 800 µg and OTFC 800 µg.

[§]Data not reported.

Adapted from DARWISH M, KIRBY M, ROBERTSON P, TRACEWELL W, JIANG JG: Comparative bioavailability of the novel fentanyl effervescent buccal tablet formulation: an open-label crossover study. *J. Pain* (2006) 7(4 Suppl. 4):S35 (Abstract).

AUC: Area under the curve; C_{max}: Maximum serum concentration; FBT: Fentanyl buccal tablet; OTFC: Oral transmucosal fentanyl citrate; T_{max}: Time to maximum concentration.

The author was a principal investigator in a recent 4-month interim analysis of safety and tolerability results from an ongoing, open-label, multi-centre study in opioid-tolerant patients with chronic pain [13]. Data were analysed for 94 opioid-tolerant patients with chronic noncancer pain who experienced 1 – 4 episodes of BTP/day and were receiving around the clock opioids.

Patients were titrated to an effective dose, and safety and tolerability were assessed by evaluating vital signs (heart rate, respiration, and systolic and diastolic blood pressures), weight and AEs. Effective doses were identified as ≤ 600 µg for 48% of patients and 800 µg for 41% of patients; 9% of the patients did not find an effective FBT dose (Figure 1) [13].

A total of 22 patients experienced treatment-related AEs, the most common of which were nausea (7%) and dizziness (5%). One patient experienced serious AEs: vomiting, dehydration and lower abdominal pain. A total of five patients experienced application-site pain with irritation, ulceration or vesicles and three patients discontinued because of AEs (rash, application site-related vesicles, nausea, vomiting, dizziness and headache) [13].

5. Conclusion

In summary, FBT is a new rapid-onset opioid analgesic for BTP that has been shown to be effective for both cancer and noncancer pain. Rapid mucosal absorption of fentanyl allows for early onset of analgesia and the duration of effectiveness encompasses a typical episode of BTP. Over time, clinical use will determine the appropriate place for FBT in the armamentarium of pain therapy.

6. Expert opinion

The special characteristics of BTP call for medications with unique pharmacological properties. The list of desired qualities in an ideal medication include rapid onset, a short

duration of action and quick elimination with no active metabolites left behind to cause AEs. Because medication to treat BTP is taken after the pain event has already started, it should be readily available and simple to use. The drug should also be easy to titrate to an analgesic level that matches the degree of pain experienced, whether neuropathic or nociceptive.

Compared with other medications, fentanyl delivered via the oral mucosa route is particularly well suited to treat BTP and FBT appears to meet several of the desired specifications for a BTP medication; for example, fentanyl is highly lipophilic, rapidly crosses the blood–brain barrier following intravenous or oral transmucosal administration and is eliminated quickly. An advantage of FBT appears to be the medication's ability to deliver targeted pain relief only for the duration of the pain event, then to dissipate quickly without leaving active metabolites. In contrast, oxycodone and other short-acting opioids are not optimal for treating BTP because their peak blood levels usually occur when the pain has already begun to wane. Evidence shows that (on average) FBT delivers an onset of analgesic action of ≤ 15 min compared with ~ 45 min for hydrocodone or oxycodone.

FBT delivered more medication across the oral mucosa during the initial absorption period in a pharmacokinetics study [7] in healthy volunteers than the equivalent doses of OTFC, another fentanyl medication currently available to treat BTP. An additional feature is the lack of stigma offered by the discreet dosing method as no stick betrays the presence of the medication as with the OTFC lozenge.

However, it should be noted that FBT is not a perfect solution for brief pain events. Of course, respiratory depression is the number one risk to be managed, as with any opioid. No data showed increased risk for respiratory depression, although it is intuitive that greater risk could exist with faster absorption. The risk that patients will chew the medication is similar to the risk seen with OTFC, although chewing the medication does not increase risk for toxicity

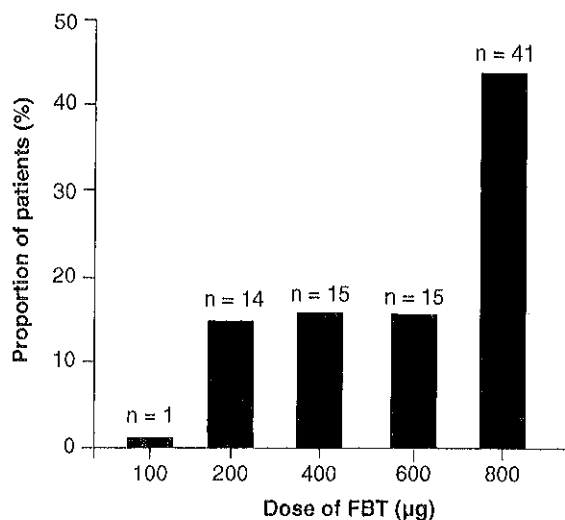


Figure 1. Safety and tolerability of FBTs. Proportion of patients at each dose of FBT for the effective doses of FBT. The effective dose of FBT is defined as the single-dose strength of FBT used consistently for episodes of BTP during the titration period. The n value represents the number of patients at each dose of FBT. Proportions of patients do not total 100% because 9% of patients were unable to find an effective dose of FBT.

Source: HALE ME, WEBSTER LR, PEPPIN JF, MESSINA J: Open-label study of fentanyl effervescent buccal tablets in patients with chronic pain and breakthrough pain: interim safety and tolerability results. *Programme and Abstracts of the Annual Meeting of the American Academy of Pain Medicine*, San Diego, USA (22 – 25 February 2006) (Abstract 120).
BTP: Breakthrough pain; FBT: Fentanyl buccal tablet.

because gastrointestinal absorption is delayed. Mouth irritation is a potential side effect. In the efficacy trial, 2 (2%) patients had application-site ulcers on the oral mucosa that the investigator considered to be definitely or probably related to FBT administration during the dose-titration period; these AEs led to withdrawal of these 2 patients from the study [9]. It is suggested that future research should focus more on the risk for respiratory depression and the potential for site ulcers along with the possible effects on absorption conferred by food intake, inter- and intra-individual variability, smoking and age.

As with any potent opioid, fentanyl carries the disadvantage of being liable to abuse. Some clinicians consider the introduction of rapid-onset analgesics somewhat risky outside the cancer population, which traditionally has low rates of abuse. FBT is highly lipophilic and thus is prone to delivering the 'binge' effect sought by abusers under certain conditions. In addition, as with any opioid

delivered outside a hospital setting, it has a potential for diversion to black-market sales. The risk for the abuse of fentanyl delivered through the oral mucosa is not yet known and no risk-management studies have been performed with FBT. There have been some news reports in Philadelphia, USA regarding the abuse of the OTFC lozenge [101,102].

The faster action of FBT compared with OTFC could be clinically useful for patients who experience sudden, excruciating episodes of BTP when every minute counts. Clinicians must determine case by case whether faster analgesia is a benefit to warrant switching medications. Some may even question whether a quicker onset with greater bio-availability could trigger euphoria in patients vulnerable to substance abuse; however, in general, the rapid, unpredictable nature of BTP events would make faster, targeted analgesia desirable.

Until more is known, care should be observed in prescribing any rapid-onset, lipophilic opioid (including FBT) to people with serious current or lifetime substance use or mental disorders. One could go further and say that FBT should be prescribed only to patients who have proven themselves to be compliant and reliable. A growing view exists among experts that drug properties contribute less to the development of drug abuse and addiction than the individual's genetics and environmental influences.

The label for FBT states that the drug is indicated for the treatment of BTP in patients who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain. Off-label applications (which could occur with FBT) are similar to those now practiced with OTFC. A patient who is nonambulatory following knee surgery but who is planning to move to participate in a social event could take FBT 5 min before the anticipated painful move. FBT could be administered as the sole medication for isolated pain incidents of brief duration (such as biopsies) and would be less invasive than an intravenous medication. FBT could deliver 'abortive therapy' for severe pain events (such as migraines) that are recalcitrant to other treatments. To target the incident pain in a patient who is not opioid tolerant, including an individual about to undergo a painful procedure, would constitute an off-label use. One would need to choose a single dose carefully and understand the risk of respiratory depression. However, this should not be a clinical problem because the available dosages (FBT 100, 200, 400, 600 and 800 µg) are easy to titrate and a low starting dose can be introduced.

Disclosure

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