

Effentora: fentanyl buccal tablet for breakthrough cancer pain

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KEY POINTS

- Effentora is a fentanyl buccal tablet (FBT) for breakthrough pain in opioid therapy for chronic cancer pain
- it is available in strengths of 100, 200, 400, 600 and 800µg; 4 tablets cost £20.56 (all strengths)
- the tablet is placed above a molar tooth between the upper cheek and gum and allowed to dissolve for 10-15 minutes
- fentanyl is rapidly absorbed through the buccal mucosa; median time to maximum concentration (T_{max}) is 52 minutes for single doses
- FBT is more readily absorbed transmucosally than oral transmucosal fentanyl citrate (48 vs 22 per cent) and the T_{max} occurs earlier (47 vs 91 minutes)
- in a pivotal study, the primary efficacy measure, the sum of pain intensity differences at 60 minutes (SPID₆₀), significantly favoured FBT over placebo
- the most commonly reported adverse effects were those associated with opioid use, including nausea, dizziness, fatigue, headache, vomiting and constipation



Effentora is a new non-parenteral fentanyl for breakthrough cancer pain that is placed between the upper cheek and gum and is rapidly absorbed through the buccal mucosa. Here, the author discusses the clinical data relating to its efficacy and adverse effects and describes its place in treatment.

The term breakthrough pain – also described as episodic pain, incidental pain, transient pain, exacerbation of pain and pain flare¹ – has been used to describe a phenomenon whereby pain intensity suddenly increases to ‘break through’ the background pain that is otherwise controlled by a fixed-schedule ‘around-the-clock’ (ATC) opioid regimen.

A typical breakthrough pain episode is characterised by a fast onset, is often very severe, usually reaches peak intensity within a few minutes, and can last an average duration of approximately 30 minutes.²⁻⁴

Breakthrough pain is a distinct clinical problem that requires independent assessment and targeted

treatment. It should be distinguished from end-of-dose pain, which consistently occurs just prior to the next scheduled dose of ATC analgesia, usually because of an inadequate analgesic dose or the interval between administrations being too long.

Two types of breakthrough pain exist: incident pain, which can be precipitated by predictable volitional factors such as movement or unpredictable nonvolitional factors such as bladder spasm; and spontaneous pain, which occurs in the absence of a specific trigger and can be unpredictable and occur at random.

Despite the self-limiting nature of breakthrough pain it can place significant physical, psychological

and economic burdens on both patients and their carers. Patients with breakthrough pain are often less satisfied with their analgesic therapy,^{3,5} they have decreased functioning because of their pain, and may also experience social and psychosocial consequences, such as increased levels of anxiety and depression.⁵

Current pharmacological symptomatic management

There is currently no ‘gold standard’ for the pharmacological symptomatic treatment of breakthrough pain. It is important to individualise management and three principles have been proposed:⁶

continued on page 32

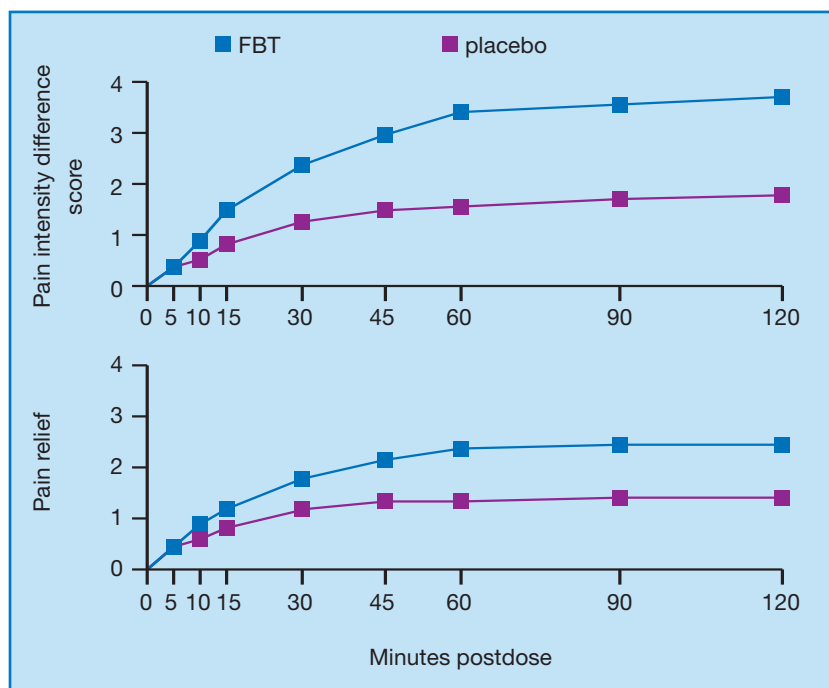


Figure 1. Effect of fentanyl buccal tablet (FBT) and placebo on pain intensity difference score and pain relief; significant differences versus placebo were seen at 10 minutes and all subsequent time points¹¹

- implementation of primary therapies, *eg* radiotherapy, chemotherapy or surgery
- optimisation of scheduled analgesia
- specific analgesia for breakthrough pain (rescue medication).

Given the heterogeneous nature of breakthrough pain, a combination of the above may be required. However, the commonest treatment strategy is the use of rescue medication.

Rescue medication

Opioids are the most commonly used rescue medication and a number of factors should be taken into account when selecting the appropriate drug, including the class of drug, the route of administration, the dosage, the patient setting and the breakthrough pain subtype.⁷ The ideal rescue medication should be efficacious and patient friendly, with a rapid onset of action a relatively short duration of action, and minimal adverse effects and can be

used either prophylactically for predictable pains or as soon as pain starts when unpredictable.

The effectiveness of oral opioids has not been adequately evaluated; indeed there is evidence to suggest that they do not prevent the adverse consequences of breakthrough pain in most patients.⁵ The commonest method of providing rescue medication is with normal-release formulations of morphine, hydromorphone (Palladone) or oxycodone (OxyNorm). In most cases, oral opioids can take 30–40 minutes to produce an analgesic effect, reach a peak at one hour and last for four hours.⁷

Breakthrough pain with a slow onset and lasting for more than one hour is therefore likely to respond best to oral opioids, whereas breakthrough pain of short duration may not.

The potential usefulness of a nonparenteral drug for breakthrough pain with a faster onset of effect was the rationale for the

development of oral transmucosal fentanyl citrate (OTFC; Actiq), a fentanyl-impregnated sweetened lozenge, as a treatment for breakthrough pain. Controlled studies showed that this formulation could provide analgesia at 15 minutes.⁸

Efforts are currently underway to develop other nonparenteral opioid formulations that could provide more rapid, and possibly more effective, relief of breakthrough pain. One such development is the fentanyl buccal tablet (FBT; Effentora).

Fentanyl buccal tablet

Pharmacology

Fentanyl is a synthetic opioid first synthesised more than 40 years ago.⁹ Related to the phenylpiperidines, fentanyl is primarily a μ agonist and is estimated to be 100 times more potent than morphine. Fentanyl is a highly lipophilic compound that is freely soluble in organic solvents and sparingly soluble in water (1:40). When placed in saliva under normal conditions of the mouth, fentanyl is 80 per cent nonionised; at lower pH fentanyl becomes ionised and readily soluble in aqueous solution.

Drugs best suited to oral transmucosal administration are those that are potent, lipophilic and are ionised at physiological pH – fentanyl is therefore a strong candidate for such a delivery system.

OTFC was the first transmucosal formulation of fentanyl developed specifically for the management of breakthrough pain. More recently the FBT has been introduced into clinical practice; it disperses quickly in the mouth without chewing or the need for water, thus making it easier for patients to take.

Each FBT contains fentanyl expressed as the amount of fentanyl citrate equivalent to fentanyl free base – 100, 200, 400, 600 and 800 μ g. Patients are instructed to

place the buccal tablet above a molar tooth between the upper cheek and gum and allow it to dissolve for approximately 10-15 minutes.

Fentanyl is rapidly absorbed through the buccal mucosa with a median time to maximum concentration (T_{max}) of 52 minutes for single doses and 50 minutes for multiple doses; the rate and extent of fentanyl absorption does not appear to be affected by the time taken for complete dissolution of the tablet.¹⁰

When compared to OTFC, a larger proportion of FBT is absorbed transmucosally (48 per cent) compared with OTFC (22 per cent) and the T_{max} is achieved earlier (FBT 47 minutes, OTFC 91 minutes); as a consequence, dose adjustments when switching from OTFC to FBT may be required.

Efficacy studies

In a pivotal efficacy study, 129 patients with cancer-related background pain, experiencing one to four breakthrough pain episodes per day and receiving more than the equivalent of oral morphine at 60mg per day were enrolled in a randomised, double-blind, placebo-controlled trial in 30 outpatient treatment centres in the USA.¹¹

The patients first entered a dose-titration phase; those patients who achieved an effective dose of FBT were then randomly assigned to 1 of 18 double-blind dose sequences to treat 10 breakthrough pain episodes.

The primary efficacy measure was the sum of pain intensity differences (PID) for the first 60 minutes (SPID₆₀); secondary efficacy measures included PID and pain relief (PR) measured from five minutes through two hours.

Of 129 patients enrolled, 87 identified a successful dose of FBT and entered the double-blind

| Adverse event | n (%) |
|---------------|---------|
| nausea | 16 (13) |
| dizziness | 14 (11) |
| fatigue | 10 (8) |
| headache | 8 (6) |
| vomiting | 8 (6) |
| constipation | 7 (6) |

Table 1. Adverse events occurring in ≥ 5 per cent of patients; these were typical of opioids

phase; there was no simple linear relationship between effective FBT dose and either the dose of the baseline opioid regimen or the supplemental opioid taken at the start of the study. The main reasons 38 patients discontinued from the titration phase were withdrawal because of adverse effects (14 patients), lack of efficacy at the highest tolerated dose (eight patients), consent withdrawal (eight patients) and protocol violations (three patients).

In the efficacy analysis of patients successfully titrated, SPID₆₀ significantly favoured FBT *vs* placebo (mean 9.7 ± 0.63 *vs* 4.9 ± 0.50 , $p < 0.0001$). Secondary measures also favoured FBT: PIDs and PR showed significant differences versus placebo at 10 minutes (0.9 *vs* 0.5 ; 0.815 *vs* 0.606 , respectively, $p < 0.0001$) and all subsequent time points ($p < 0.0001$; see Figure 1).

Safety and tolerability

Adverse effects were reported by 83 patients and were typical of opioids (see Table 1).¹¹ There were no reported incidents of respiratory depression. Ten per cent of patients had adverse effects involving the application site of FBT, most commonly during the dose-titration phase, and these were of mild intensity and transitory. One patient discontinued the study due to an application-site irritation that was considered mild and related to treatment with the study drug. All deaths

during the study were due to progression of the underlying cancer.

Implications for practice

Breakthrough pain has been shown to occur commonly in patients with cancer and is often of sudden onset, severe or excruciating and short lasting, making management difficult. FBT is an effervescent buccal formulation of the potent opioid analgesic fentanyl, indicated for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant of opioid therapy for their background cancer pain.

The pharmacokinetic, efficacy, tolerability and safety profile of FBT suggest that it has a valuable role to play in the symptomatic pharmacological management of breakthrough pain. The effective dose of FBT cannot be predicted from previous ATC or rescue medication, and titration is required to determine the effective dose according to the needs of the individual patient.

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