Fentanyl for breakthrough cancer pain (BTCP)

HOT SPOT

Carlo De Angelis, PharmD, Clinical Pharmacy Coordinator – Oncology, Department of Pharmacy, Odette Cancer Centre, Sunnybrook Health Sciences Centre

Breakthrough cancer pain

Breakthrough pain is a cause of significant morbidity in cancer patients and is associated with decreased satisfaction in overall pain control and reduced quality of life.

Patients who experience BTCP have higher pain scores, overall and functional impairment.

BTCP has a significant impact on the quality of life, including detrimental effects on activities of daily living, sleep, social relationships and enjoyment of life.

Patients with poorly controlled BTCP are more likely to seek medical attention.

The Association for Palliative Medicine of Great Britain and Ireland Task Force define breakthrough pain as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain."

The key elements of this definition are:

- The increase in pain is transient and is either spontaneous or associated with a trigger.
- Background pain is adequately controlled, thus pain that occurs during the titration phase of pain management would not be considered breakthrough pain.
- The occurrence of an end of dosing interval increase in pain is not considered breakthrough pain, since this phenomenon suggests that the patient requires additional adjustment to their around-the-clock analgesic medication requirements to improve control of their background pain.

Breakthrough cancer pain can be categorized as either:

- spontaneous—where it is unpredictable with no identifiable trigger or
- incident—with a clear trigger that can be either the result of a voluntary or non-voluntary act or procedure.

Clinically, breakthrough cancer pain is characterized as being sudden in onset, moderate to severe in intensity and short in duration.

- Onset of BTCP occurs rapidly, within three minutes.
- Occurs one to four times a day.
- Each episode may last for mere seconds or hours. The average duration of a BTP episode is approximately 30 minutes.

Traditionally, breakthrough cancer pain is managed by the use of supplemental doses of opioid medication without regard to its nature or cause.

The ideal agent for managing breakthrough cancer pain would:

- Address the pathophysiology of the breakthrough pain
- Have a rapid onset of action (several minutes)
- Have a short duration of action (less than 30 minutes)
- Be available in a formulation that is easy and convenient to administer
- Have minimal side effects.

Currently there is no "ideal" agent to manage BTCP, but recent development of new formulations of fentanyl address some of these issues.

Fentanyl

Fentanyl, a synthetic opioid, possesses many of these qualities making it highly suitable for the management of BTCP.

Fentanyl is a μ-opioid receptor agonist with an analgesic potency 80 to 100 times that of morphine.

Fentanyl has poor oral bioavailability as a result of extensive first-pass metabolism, resulting in only approximately one third of the swallowed dose being systematically available.

The high lipophilicity of fentanyl allows it to be rapidly absorbed through cellular layers and to cross the blood brain barrier to quickly exert its action on the μ-opioid receptor to alleviate pain.

These characteristics make fentanyl suitable for transmucosal delivery.

Intranasal and oral transmucosal formulations of fentanyl have been developed for the management of BTCP.

The formulations available or soon to be available in Canada are reviewed on the reverse of this insert.

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Fentanyl Preparations							
Brand name	**Dosage form**	**Indication**	**Pharmacokinetic and related issues**	**Onset duration**	**Side effects**	**Contraindications and caution**	**Dosing/Convenience**
ORAL TRANSMUCOSAL							
Abstral®	**Sublingual Tablet** Strengths: 100, 200,300, 400, 600, 800 mcg Non-PH dependent rapidly disintegrating sublingual tablet	Breakthrough cancer pain for opioid tolerant patients	Absorption occurs across the oral mucosa and avoids first-pass metabolism BA: 54% Time to first detectable plasma levels: 8–11 minutes Elimination Half-life: 5.4–6.1hr Dose proportionality tested across dose range of 100 to 800 µg. Dose after single and multiple dosing	**Onset:** After a 400mcg dose there was significant improvement in pain intensity after 10 minutes. Duration: at least 60mins	Well Tolerated No formulation specific SE found Typical opioid side effects • N/V • dizziness • somnolence Side effects are not dose related	Opioid non-tolerant patients e.g. use in acute or post-operative pain, treating headache or migraine pain, dental pain Severe respiratory depression or severe obstructive lung conditions	SL tablet (do not swallow, suck or chew) Tablet disintegrates within 30 seconds 100mcg: repeat dose if inadequate pain relief within 15–30min If 2 × 100mcg is inadequate—consider increase to 200mcg for next episode with supplemental second tablet after 15–30min Continue dose escalation until adequate analgesia Maximum 4 tablets per episode Each dose must be separated by at least 2 hours
Onsolis®	**Film** Fentanyl Buccal Soluble Film (FBSF) PVP film delivers fentanyl across mucosa in pH dependent manner Dose: 200, 400, 600, 800, 1200 mcg buccal strip	Breakthrough pain for cancer patients • only for opioid tolerant patients	BA: 71% (51% from buccal mucosa, 49% from slow GI absorption) Time to first detectable plasma levels: 9.0 ± 4.8 (SD) minutes Elimination half-life: 14 hours Median Time to maximum plasma concentration (for 800 mcg dose): 60 minutes (range: 45–240) Dose proportionality demonstrated after single dose across dose range of 200 to 1200 mcg	**Onset:** 15 minutes	Well Tolerated No formulation specific SE found No evidence that mucositis is worsened Typical opioid side effects • N/V • dizziness • somnolence	Opioid non-tolerant patients e.g. use in acute or post-operative pain, treating headache or migraine pain, dental pain Severe respiratory depression or severe obstructive lung conditions	Buccal and transmucosal products are not bioequivalent—do not substitute mcg per mcg basis—always initiate treatment with recommended start dose for the product and titrate **Titration:** Start 200mcg buccally × 1 Titrate dose by 200mcg/episode prn Each dose must be separated by at least 4 hours Max: 1 dose/episode **Maintenance:** Use single film once dose established Max: 1200mcg/dose 4 doses/day Film dissolves within 15–30 min
INTRANASAL							
*Instanyl®	50, 100 and 200 micrograms/dose nasal spray	management of breakthrough cancer pain in patients on maintenance opioid therapy for cancer pain e.g. those taking: ≥ 60 mg of oral morphine daily ≥ 8 mg of oral hydromorphone daily ≥ 30 mg oxycodone daily ≥ 25 micrograms/ hour transdermal fentanyl patch Patients must be on opioid for a week or longer	single doses of 50 to 200 micrograms fentanyl per dose produces a C_{max} of 0.35 to 1.2 ng/ml. with a median T_{max} of 12–15 minutes	**Onset:** Significant pain intensity difference within 10 minutes of administration Duration of benefit up to 60 minutes	No formulation specific side effects no reports of nasal mucosa irritation	previous facial radiotherapy, recurrent nosebleeds	Each patient requires individual titration Start with 50 mcg/dose strength Administer dose in one nostril only An additional dose for a given BTCP episode may be used if no pain relief in 10 minutes Wait at least 4 hours prior to treating another BTCP episode Maximum daily dose: treat up to four breakthrough pain episodes, no more than two doses per episode

* European Union Product information
Abstral – Health Canada Notice of Compliance given, product available through access program
Onsalis – Health Canada Notice of Compliance given, product availability pending
Instanyl – Health Canada Notice of Compliance pending