Pharmaceutical Management of Cancer Breakthrough Pain

a report by
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Cancer patients on around-the-clock opioids often experience temporary flares of pain against a background of otherwise controlled pain. Breakthrough pain (BTP) can reach peak intensity in three minutes and typically lasts for 30–60 minutes.[1–2] An estimated 64% of cancer patients treated for persistent pain also experience BTP, sometimes several episodes a day.[1] Although brief, these episodes can be excruciating.

The special characteristics of BTP call for medications with unique pharmacologic properties. The list of desired qualities in an ideal medication includes rapid onset, a short duration of action, and quick elimination with no active metabolites left behind to cause adverse side effects. Because medication to treat BTP is taken after the pain event has already started, the drug should be readily available and simple to use. It should also be easy to titrate to an analgesic level that matches the degree of pain experienced.

Hydrophilic compounds, such as oral or sublingual morphine and oxycodone, are absorbed too slowly to address most BTP, having a T_{max} of about 45 minutes, when the pain has already begun to wane. In addition, hydrophilic compounds pass easily into the gastrointestinal (GI) tract where they are likely to cause constipation and also leave behind active metabolites produced in the liver. Cancer patients often are unable to tolerate oral medications due to nausea or impaired GI function. Even oral liquid morphine is primarily absorbed through the GI tract after it is swallowed rather than absorbed sublingually as is commonly believed. Methadone is less hydrophilic, but its long half-life can lead to toxicity with repeated as-needed dosing; therefore, it should not be used to treat BTP.

In contrast, fentanyl delivered via the oral transmucosal route appears particularly well suited to treat BTP. Fentanyl is highly lipophilic. It rapidly crosses the blood–brain barrier with a T_{max} of approximately 20 minutes following oral transmucosal administration and is eliminated quickly. Onset of action with transmucosal fentanyl is comparable to intravenous (IV) morphine.[3]

At present, two rapid-onset, oral-delivery fentanyl products are US Food and Drug Administration (FDA)-approved to treat BTP: oral transmucosal fentanyl citrate and fentanyl buccal tablets. Both are specifically indicated for treatment of BTP in cancer patients who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain. Patients are considered opioid tolerant if they are taking at least 60 mg of oral morphine per day, at least 25μg of transdermal fentanyl per hour, at least 30mg of oxycodone daily, at least 8mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.[4]

Two additional delivery systems of fentanyl are in development but are not yet available. One is designed to deliver the drug across mucous membranes using water-soluble, bioerodable delivery discs that are composed of an adhesive layer and a non-adhesive backing layer.[5] Upon application, the disc adheres to the mucosal surface. The second is a tablet that rapidly disintegrates into ordered units of carriers that adhere to the sublingual mucosa, allowing the active compound to dissolve.[6] The aim is to enhance quicker absorption than offered by drugs that are absorbed from the GI tract.

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4. *"Cephalon announces positive result for FENTORA™ (fentanyl buccal tablet) for breakthrough pain in patients with chronic low back pain",* Medical News Today *(12 Oct 2006). Available from URL: http://www.medicalnewstoday.com/medicalnews.php?newsid=53920*
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Oral Transmucosal Fentanyl Citrate

Oral transmucosal fentanyl citrate (OTFC) is a fast, effective medication for BTP with an average delivery of analgesia of approximately 15 minutes. The fentanyl in OTFC is embedded in a hardened polymer in the form of a lozenge that is dissolved in the mouth. Two randomized, controlled studies involving ambulatory cancer patients found patients achieved significantly better analgesia with OTFC than with placebo ($p<0.0001$) at 15, 30, 45, and 60 minutes.[7-8] In one clinical study, 74% of patients were successfully titrated to an analgesic dose.[8] In addition, patients achieved significantly better analgesia versus rescue medications ($p<0.0001$) at 15, 30, and 60 minutes. Adverse effects were mostly mild or moderate and were typical of opioid-related side effects, including nausea and dizziness. Very few adverse events have been reported as severe or serious.

Fentanyl Buccal Tablets

Fentanyl buccal tablets (FBT) are differentiated from OTFC by a novel delivery system featuring an effervescent reaction that facilitates absorption through transient shifts in the pH balance. FBT is placed between the cheek and gum adjacent to an upper molar and allowed to dissolve for 10–15 minutes. In clinical studies, FBT delivered more fentanyl across the oral mucosa than did a comparable dose of OTFC, a result researchers concluded was due to increased pH associated with FBT effervescence. A randomized, double-blind, placebo-controlled study was conducted to test the efficacy and tolerability of FBT in opioid-tolerant cancer patients.[9] Clinically significant (≥33%) decreases in pain intensity occurred with FBT in 13% of BTP episodes by 15 minutes and in 48% of episodes by 30 minutes. At all time points (15, 30, 45, and 60 minutes), the decrease was significantly greater for FBT than for placebo ($p < 0.05$). At 30 minutes post dose, pain intensity decreased by ≥50% with FBT in 24% of episodes and with placebo in 16% of episodes ($p < 0.05$). The analgesic effect of FBT was found to last 60 minutes. Patients were twice as likely to need supplemental opioids after receiving placebo as after receiving FBT.

FBT has been reported to be well-tolerated with adverse events typical of opioid administration, including nausea, vomiting, application site abnormalities, fatigue, anemia, dizziness, constipation, edema, asthenia, dehydration, and headache. Adverse events are generally mild to moderate in severity.

Dosing and Safety Considerations

The common guideline of administering a rescue medication at the equivalent of 5–15% of the total daily opioid dose does not apply to oral transmucosal fentanyl. Clinical trials established no relationship between the dose needed to treat BTP and the daily dose of opioids. Starting doses are based on the intensity of the BTP, not the intensity of the persistent pain. Conversion tables for equianalgesic doses are not very useful in determining the appropriate starting dose of transmucosal fentanyl. The suggested guideline is to initiate a low dose and titrate until an effective dose is found. A common starting dose is 400μg for OTFC and 100 or 200μg for FBT. Interestingly, once the effective dose is found, it tends to remain effective with continued use; most patients do not experience the dose creep common with short-acting opioids.

As with any opioid, the most serious adverse event to guard against is respiratory depression. No data showed increased risk for respiratory depression when compared with other short-acting opioids, although it is intuitive that greater risk could exist with faster absorption. Patients should be monitored for symptoms. Mouth irritation is a potential side effect from FBT. Also, as with any potent opioid, fentanyl carries the disadvantage of being liable to abuse. Because fentanyl is highly lipophilic, it is prone to deliver the 'binge' effect often sought by abusers. However, misuse of opioids is rare in the cancer population, and the fear of perpetuating abuse should not prevent clinicians from treating cancer BTP with rapid-acting agents.

Conclusion

Most cancer patients experience BTP, and some of them suffer several episodes of moderate-to-severe pain daily. Fentanyl delivered oral transmucosally is a rapid-onset analgesic shown to be effective for cancer BTP. Rapid transmucosal absorption of fentanyl allows for early onset of analgesia, and the duration of effectiveness lasts throughout a typical episode of BTP. ■

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