Managing Cancer-Related Breakthrough Pain With FENTORA

PERRY G. FINE, MD
Professor of Anesthesiology
Pain Research Center
University of Utah School of Medicine
Salt Lake City

Introduction

Breakthrough pain (BTP) in patients with cancer is a common, distressing, and costly problem. It interferes with functional capacities and virtually all quality-of-life measures, and adds appreciably to physical and psychological morbidity.

Epidemiology, Characteristics, and Impact of BTP

BTP is a transitory exacerbation, or flare, of moderate to severe pain that occurs in patients with otherwise stable, persistent pain.1 The prevalence of BTP in patients with persistent cancer-related pain syndromes varies widely, from 51% to 89%.2-6 BTP appears to become more prevalent with advancing disease. In one survey, up to 86% of hospice patients capable of responding experienced BTP.7 BTP has been categorized by pathophysiology (neuropathic, nociceptive and mixed) and subtype (incident, spontaneous and end-of-dose failure).8,9 (Table). Patients with cancer-related BTP appear to have more intense pain, more substantial functional impairment and greater psychological distress than patients with cancer pain but without BTP.10 Similarly, in one study, cancer patients with BTP had fivefold higher costs for pain-related hospitalizations, emergency room visits and physician office visits than did those without BTP.9

Appropriate pain assessment considers pathophysiology, source, intensity, location, radiating/referred pain patterns, severity and temporal patterns. Successful treatment is important because BTP can have an impact on the patient’s quality of life and the costs of healthcare. Effective management of BTP requires a clear understanding of each patient’s pain in terms of its cause(s), predictability, duration, relationship to the dosing of routinely scheduled analgesic medications, and, most importantly, its onset of action.

Treatment of BTP: Match Drug Delivery With Pain Characteristics

The goal of BTP treatment is to manage an episode effectively with nonpharmacologic and pharmacologic means. The most commonly used nonparenteral treatment strategy for patients with cancer-related BTP has been oral short-acting opioids (often referred to as “immediate release”).10 These have been prescribed as supplemental medication and are taken on an as-needed basis, along with an around-the-clock opioid regimen to control baseline pain.10 However, traditional short-acting, immediate-release oral agents often fail to provide adequate pain relief because of a mismatch between the temporal characteristics of a typical BTP episode and the onset of analgesia of orally administered supplemental opioids.11,12

Optimally, the pharmacokinetic and resultant pharmacodynamic qualities of an analgesic agent should match the

Table. Subtypes, Characteristics, and Impact of BTP

<table>
<thead>
<tr>
<th>Subtype of BTP</th>
<th>Characteristics</th>
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<tr>
<td>Incident</td>
<td>Predictable: consistent temporal relationship with a precipitating factor. Although predictable, the onset and severity cannot always be foreseen.</td>
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<tr>
<td>Spontaneous (idiopathic) BTP</td>
<td>Unpredictable: inconsistent temporal relationship, but usually occurring with some type of a precipitating factor.</td>
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<td>End-of-dose failure</td>
<td>Occurs prior to a scheduled dose of an around-the-clock analgesic; most easily identified through use of pain diaries that include pain episode(s) timing, intensity, duration and time of all medication dosing.</td>
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Impact of BTP4

Patients may:
• Be less satisfied with their opioid therapy
• Demonstrate decreased levels of function
• Have increased levels of anxiety and depression
• Incur higher healthcare-related costs

BTP, breakthrough pain
FENTORA may be an appropriate treatment choice for some patients with chronic cancer pain who experience BTP. Patient-reported outcomes have been evaluated only in an open-label study with FENTORA.

Case 1

Recognition and Treatment of Breakthrough Pain

A 55-year-old woman was recently diagnosed with metastatic lung cancer, after several months of intractable cough and more recent onset of persistent, severe pain in her chest and upper extremities. Motivated by a desire to “get as much time as I can,” she took disability leave from her full-time job to pursue aggressive chemotherapy. Her pain has been both nociceptive and neuropathic, determined to be caused by bone metastases, pleuritic infiltration by tumor and brachial plexopathy from tumor encroachment. Baseline pain was well controlled after a course of dexamethasone and daily use of nonsteroidal anti-inflammatory drugs (NSAIDs). Celecoxib (Celebrex, Pfizer) twice daily was chosen for its “platelet-sparing” properties—especially important while undergoing chemotherapy—along with maximum titration of gabapentin (Neurontin, Pfizer) to tolerability (800 mg three times per day) and controlled-release oxycodone (OxyContin, Purdue Pharma 40 mg three times daily, as twice-daily dosing resulted in end-of-dose failure and higher twice-daily doses caused excessive sedation). Prior use of morphine was discontinued because it made her feel “spaced out.” On this analgesic regimen, the patient continued to have a few episodes of spontaneous and incident pain each day. Spontaneous pain was predominantly neuropathic, affecting her right upper extremity, occurring rapidly and becoming “excruciating” within minutes. Incident pain in her chest wall region was highly predictable, occurring after standing and walking for more than a few minutes. The pain interfered greatly with her quality of life. She had been taking supplemental doses of hydrocodone/APAP and oxycodone, but these took too long to relieve her pain—especially when spontaneous and lasted too long, calling her to be drowsy much of the day if she took more than a single dose.

Considering the etiology and temporal patterns of this patient’s cancer-related pain, it was determined that FENTORA would provide the flexibility required to meet her needs. Her physician discussed its use, benefits and risks, and initiated therapy with the lowest dose, 100 mcg. The patient then met with the supportive care nurse to review proper use of FENTORA, including an instruction sheet that had been prepared (Figure). They spoke briefly by phone each day to determine the optimum dose and timing of the BTP medication. After a few days, most spontaneous pain episodes could be well controlled with a single, 100-mcg dose of FENTORA. For incident pain, the patient took a dose a few minutes before initiating activity, and she would carry a second dose in the sealed blister pack if she took a walk, went shopping, attended medical appointments, etc., for additional use if needed. The result was that her pain was sufficiently well managed.
The macodynamics of this drug make it well-tolerated and effective for patients experiencing severe pain. The absorption characteristics, onset of action and duration of effect vary among the available opioid compounds based mostly on lipophilicity and clearance. Oral transmucosal fentanyl citrate (OTFC, Actiq®, Cephalon, Inc.), a relatively lipophilic compound, was the first agent approved specifically for BTP in cancer patients.13,14

Building on this noninvasive oral transmucosal approach, a novel formulation that enhances buccal absorption by raising local pH, called the fentanyl buccal tablet (FENTORA™, Cephalon, Inc.), was recently approved for the treatment of BTP in opioid-tolerant cancer patients. The absorption kinetics and related pharmacodynamics of this drug make it well suited for BTP.15 Once in the bloodstream, fentanyl enters the central nervous system quickly because of its lipophilicity. In clinical trials of opioid-tolerant patients with chronic cancer pain, BTP episodes treated with FENTORA have shown clinically and statistically significant improvement as measured by pain index scores as in as early as 10 minutes.16

In addition to its favorable kinetic profile, FENTORA represents an important advance for patients who require an alternative to OTFC. The buccal tablet formulation uses OraVescent® (CIMA Labs Inc.) drug delivery technology to produce a reaction that enhances the rate and extent of fentanyl absorption.17 FENTORA is placed above a rear molar tooth and between the gum and cheek. When the tablet comes in contact with saliva, a reaction takes place resulting in transient changes in pH. On initial contact, as the pH decreases, dissolution is facilitated. As carbon dioxide is released, the pH rises, enhancing the absorption of fentanyl through the mucosa by altering the ionic charge and making it more lipophilic.17 The median time to reach maximum serum concentrations (T_{max}) was found to be consistent irrespective of dose.18 Individual dose–response seems to be unrelated to baseline (around-the-clock) opioid dose.19,20 The dose of FENTORA therefore should be titrated to effectiveness for each patient, starting with the lowest dose (100 mcg), rather than calculated or predicted as a percentage of an existing opioid regimen. If the patient has been using OTFC, then a dosing conversion has been recommended when the patient is switched from OTFC to FENTORA. (Please refer to prescribing information, dosing section.) The doses shown in the prescribing information are conservative recommended starting doses, not equianalgesic doses.) From the initial dose, titrate to effect.

FENTORA has consistently demonstrated a greater decrease in pain intensity compared to placebo. In the initial trial, a clinically significant decrease in pain intensity was demonstrated at 15 minutes (the first time point measured), and in a subsequent trial onset of relief was shown at 10 minutes.21,22 In addition to an early onset of effect, patients also experienced analgesic effects with FENTORA that were sustained throughout the 2-hour study period.22 FENTORA is well tolerated, with most adverse effects mildly to moderately severe, which is typical of opioid use.22,23 Serious adverse events associated with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. The most common adverse events observed in all FENTORA clinical trials were nausea, dizziness, vomiting, fatigue, headache, constipation, somnolence, anemia, dehydration, and application site abnormalities.

Conclusions

Breakthrough pain is highly prevalent among cancer patients with pain conditions from multiple etiologies, and timely treatment is important to prevent pain-related morbidity and optimize therapeutic outcomes. In appropriately selected patients, BTP can often be successfully treated through the use of FENTORA, which has an onset and duration that closely matches the majority of BTP flares. When used properly, FENTORA is safe and well tolerated in most opioid tolerant patients. As with all opioid therapies, regularly scheduled patients, BTP can often be successfully treated through the use of FENTORA, which has an onset and duration that closely matches the majority of BTP flares. When used properly, FENTORA is safe and well tolerated in most opioid tolerant patients. As with all opioid therapies, regularly scheduled patients, BTP can often be successfully treated through the use of FENTORA, which has an onset and duration that closely matches the majority of BTP flares. When used properly, FENTORA is safe and well tolerated in most opioid tolerant patients. As with all opioid therapies, regularly scheduled patients, BTP can often be successfully treated through the use of FENTORA, which has an onset and duration that closely matches the majority of BTP flares. When used properly, FENTORA is safe and well tolerated in most opioid tolerant patients. As with all opioid therapies, regularly scheduled patients, BTP can often be successfully treated through the use of FENTORA, which has an onset and duration that closely matches the majority of BTP flares. When used properly, FENTORA is safe and well tolerated in most opioid tolerant patients. As with all opioid therapies, regularly scheduled patients, BTP can often be successfully treated through the use of FENTORA, which has an onset and duration that closely matches the majority of BTP flares. When used properly, FENTORA is safe and well tolerated in most opioid tolerant patients. As with all opioid therapies, regularly scheduled patients, BTP can often be successfully treated through the use of FENTORA, which has an onset and duration that closely matches the majority of BTP flares. When used properly, FENTORA is safe and well tolerated in most opioid tolerant patients. As with all opioid therapies, regularly scheduled patients, BTP can often be successfully treated through the use of fentanyl, then a dosing conversion has been recommended when the patient is switched from OTFC to FENTORA. (Please refer to prescribing information, dosing section.) The doses shown in the prescribing information are conservative recommended starting doses, not equianalgesic doses.) From the initial dose, titrate to effect. 

FENTORA sites

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References


