Breakthrough cancer pain: Assessment and management challenges

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HOT SPOT

Introduction

Cancer pain is a common phenomenon in oncology practice with more than 70% of patients with advanced cancer having moderate to severe pain. Many of these patients, 40% to 80%, will have what is called breakthrough pain. Breakthrough pain (BTP) is a transient exacerbation of pain experienced by a patient who had relatively stable and adequately controlled baseline pain. This phenomenon of BTP has been discussed for many years, but the pathophysiology and neurophysiology of this type of pain has yet to be determined and the management has been very empirical. Recent attention has been focused on BTP and newer approaches to management have an evidence base that was lacking in the past. In this article, the classification of BTP, its components and a best practices approach to management will be discussed.

Classification and characteristics of BTP

There is no consensus on the classification of BTP. As interest in BTP has increased, new terminologies have been proposed including intermittent or episodic pain. There are components, though, which are common in all terminologies or classifications:

a) Any baseline pain should be under stable and "good" control.
b) End-of-dose failure, which is pain that consistently occurs before the scheduled around-the-clock dose, usually indicates an inadequate analgesic dose. This is not seen as BTP by most authors.
c) Incident pain is intermittent but predictable pain related to a specific precipitant, which may be voluntary (e.g., after movement, as with bone metastases) or involuntary (e.g., with cough or sneeze). Incident pain may occur with or, more infrequently, without a background of continuous pain or prescribed around-the-clock analgesics. Incident pain typically is quick in onset.
d) Spontaneous BTP may occur without any precipitating factor with any type of cancer pain. It may be inflammatory, visceral or neuropathic in origin and there is no clear evidence why this type of pain occurs in the face of stable, normally well controlled pain. Spontaneous pain may be rapid in onset, but often builds slowly to a crescendo.
e) Generally, BTP is short in duration lasting a few seconds (e.g., lancinating neuropathic pain) to minutes (e.g., bone pain on movement), but some spontaneous pains may last for hours.

Impact of BTP

BTP has been associated with:

- Poor overall pain control with higher levels of baseline pain and peak pain
- Decreased satisfaction with overall pain management (e.g., 78% of patients with chronic pain satisfied with treatment versus 25% of patients with BTP)
- Multiple physical (e.g., insomnia), psychological (e.g., anxiety, depression) and social (e.g., isolation) complications
- Significant functional impairment
- A significant negative effect on quality of life
- Increased health care costs.

Therefore effective assessment and management of BTP can be very important to patients and their families.

Assessment of BTP

Assessment of BTP depends on careful questioning of the patient. There are a number of clinical assessment tools that have been developed that assist in asking questions to determine the type of BTP. When considering BTP, the following questions should be asked of the patient:

1) How well is the baseline pain controlled? Poorly controlled pain is not BTP.
2) Is there a specific time in the taking of around the clock analgesics when pain appears "spontaneously? This question may indicate end-of-dose failure.
3) Is the pain related to any voluntary or involuntary (e.g., coughing) movement?
4) What is the temporal nature of the pain: how quickly does it come on, how quickly does it resolve, how many times in an hour/day/week.
5) What is the severity of the pain?
6) What do you do to relieve the pain? How many extra doses of analgesics are you taking? Are you missing doses of analgesics and why?
7) Are there any other symptoms such as nausea that are associated with the intermittent pain?
8) How does the BTP impact your function and your quality of life?

A physical examination is important, as usual, to find bony tender points, changes in palpable masses or new problems such as evidence of bowel obstruction.
A review of imaging or ordering of new imaging may be required.

Management of BTP

The evidence base for the management of BTP in cancer is increasing, but there are still some basic principles that must be considered in managing this type of pain:

a) Educate the patient and family and other care providers about the nature of BTP and its treatment.
b) Ensure that baseline pain is correctly managed.
c) Involve the patient and family in monitoring the outcomes of the treatment of BTP.
d) Always consider adjuvant modalities to aid in the management of BTP.
e) Consult cancer pain or palliative care specialists as necessary.

Non-pharmacological approaches

a) Chemotherapy and radiotherapy
There is no clear evidence that chemotherapy can produce immediate help for BTP. Analgesics should be used while awaiting the response to chemotherapy. Radiotherapy, on the other hand, may be the most effective treatment for baseline pain and associated incident BTP from bone metastases.

b) Physical and occupational therapy
Seeking the advice of physical and occupational therapists may be helpful to help control incident pain. Specific splints and braces and mobility aids may help these patients. As well, these therapists can instruct patients and families on the best ways to move to avoid precipitating BTP. Techniques such as TENS, massage, and visualization may also be helpful in some patients as adjuvant techniques.

c) Surgery
Orthopedic surgeons should be consulted, as necessary, for the possible surgical management of incident bone pain. Bowel or duct obstruction causing BTP may require the intervention of surgical oncologists.

d) Interventional anesthesia and neurosurgical approaches
Anesthetic approaches (e.g., nerve block, chemical neurolysis, intrathecal infusions) and surgical interventions (e.g., cordotomy) are generally considered after all other approaches have failed.

Pharmacological approaches

a) Adjuvant analgesics
For lancinating neuropathic BTP, the usual neuropathic adjuvants such as the antidepressant and anticonvulsant adjuvants should be prescribed. NSAIDs may be helpful on occasion in managing bone pain, but there is little evidence for efficacy in managing incident pain. Bisphosphonates have no proven efficacy in managing BTP.

b) Immediate release opioids
The mainstay of treatment of BTP until recently has been the immediate release opioids such as morphine, oxycodone and hydromorphone. The main drawback to oral IR opioids is the 30 to 60 minutes it takes for onset of the analgesic effects. For patients with spontaneous BTP, if they can take these IR opioids as the pain is beginning to get stronger, they may be able to reduce the BTP considerably. For voluntary incident pain, IR opioids can be taken prophylactically before movement, although this is often impractical and is not very effective. Using intravenous or subcutaneous IR opioids like morphine or hydromorphone may be more effective, but increases the complexity and costs of treatment.

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c) Transmucosal fentanyl
In Canada, we will see, in the near future, the introduction of several different formulations of oral and nasal transmucosal fentanyl for the management of BTP. These preparations make use of the excellent potency and lipophylic properties of fentanyl that enable it to cross mucous membranes unlike other opioids. In Canada, palliative care specialists have been using the parenteral form of fentanyl applied to oral membranes, but this method presents difficulties with administration and dose titration. These new formulations are generally easier to administer and titrate.

All the formulations share common characteristics:
1) Rapid onset, usually within 10 to 15 minutes to effective pain control and a $T_{½}$ of three to six hours.
2) All avoid first pass metabolism of fentanyl.
3) Easy administration and preference by patients over the oral IR opioid route.
4) Similar adverse effects as all opioids.
5) Not to be used in opioid naïve patients.
6) Metabolism through the cytochrome P450 process and, therefore, the possibility of interaction with drugs using the same route of metabolism.
7) All have the possibility of abuse and diversion like all opioids.
8) All should be used by prescribers experienced in prescribing opioids. They all require careful titration and monitoring.

Formulations of Transmucosal Fentanyl
Oral transmucosal fentanyl citrate lozenge
Sublingual fentanyl tablet
Fentanyl buccal tablet
Bioerodible mucoadhesive buccal film
Intranasal fentanyl

i) Oral transmucosal fentanyl lozenges (OTFC) have been available in the U.S. and in Europe for some time for BTP. OTFC produced greater analgesic effect, increased global satisfaction and more rapid onset of action than usual rescue medication or placebo. It has been proved safe and effective for long-term use. There is evidence that OTFC can significantly reduce visits to emergency and rates of hospital admission. However, this preparation is not likely to be introduced in Canada because of Health Canada's concerns about safety of this lollipop-like formulation.

ii) Fentanyl buccal tablets (FBT)
FBTs are of two types. One utilizes effervescent reaction that is accompanied by transient change in pH to facilitate tablet dissolving and enhanced absorption of un-ionized fentanyl across buccal mucosa and with increased early systemic uptake of fentanyl.

Doses should be reduced by 30% compared with dose of OTFC. Another type of tablet adheres to the oral mucosa where it slowly releases fentanyl. Both of these are currently under review by Health Canada.

iii) Bioerodible mucoadhesive buccal film (FBSF)
This film is applied to the oral mucosa where it slowly dissolves releasing fentanyl through the mucosa. This is the only formulation currently approved in Canada. It has greater bioavailability than OTFC and a higher C_{max}. Time to first detectable plasma concentration eight to 11 min with T_{max} in the range of 40 minutes to 57 minutes. Experience so far is limited, but studies have shown efficacy and good patient acceptance.

iv) Intranasal fentanyl (INF)
INF can only be given in small volumes of <200 mcL at a time, as a nasal spray, in order to avoid runoff into the pharynx because of the relatively small surface area of the nasal mucosa. It is rapidly absorbed into systemic circulation from highly vascularized and extensively perfused nasal mucosa, avoiding first-pass metabolism. INF has been shown to be safe, effective and well tolerated in regulatory studies. It is under review by Health Canada.

Summary

BTP is an important source of suffering for cancer patients who have pain with considerable impact on quality of life. Effective assessment and a multimodal approach can be effective. The new transmucosal fentanyl products may represent an important step in managing BTP effectively.