Breakthrough Pain in Cancer Patients

Breakthrough pain is a transient flare-up of pain superimposed on an otherwise stable pain pattern in patients treated with opioids. Breakthrough pain, called episodic pain in some countries, is normally severe in intensity, with a rapid onset and variable duration (an average of 30 minutes). Breakthrough pain is considered a negative prognostic factor. A recent survey of 1,095 patients with cancer pain from 24 countries indicates that breakthrough pain is associated with higher pain scores and interferes with physical activity. Patients with untreated breakthrough pain have decreased physical activity, greater levels of anxiety and depression, are less satisfied with their opioid therapy, and have more emergency department visits and more unscheduled office visits. A study looking at the direct and indirect costs associated with pain in cancer patients found that the presence of breakthrough pain predicted higher direct and indirect medical expenses.

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Prevalence

Breakthrough pain is still not routinely recognized, evaluated, and treated. In a recent international survey, clinicians reported breakthrough pain in 65% of cancer patients. This figure is quite close to the 64% prevalence reported by Portenoy and Hagen in the first published survey of breakthrough pain in cancer patients. Other studies indicate that breakthrough pain is more prevalent in hospice patients than in outpatients, i.e., is more common in patients with advanced disease. However, reported prevalence rates for breakthrough pain vary widely from country to country, and a uniform definition of breakthrough pain has been lacking in the published literature. For example, many studies of breakthrough pain do not report whether patients had well-controlled baseline pain and do not specify the baseline drug regimen.

Characteristics

Breakthrough pain results from a predictable activity such as walking, sitting, or coughing; from end-of-dose failure, i.e., soon before the next analgesic dose is due; or, often, from causes that are unclear. Incident pain, triggered by movement and commonly associated with bone metastases or fractures, is a
well-recognized subtype of breakthrough pain. Because this type of breakthrough pain makes it particularly difficult for sufferers to move without pain, it limits functional activity. Incident pain is generally predictable and therefore potentially treatable preemptively.

Pain induced by swallowing or chewing in patients with oral or esophageal mucositis or by touching areas of allodynia in patients with neuropathic pain may precipitate a crisis. Pain or tenesmus (a feeling of fullness of the colon or bladder) may be induced by attempted defecation or micturition in patients with pelvic tumors. Several mechanisms may account for breakthrough pain that appears to occur spontaneously, with no obvious precipitating event. Muscular spasms of hollow organs (including the esophagus, intestine, the gallbladder and its duct, the urinary bladder, and the ureter) commonly result in paroxysmal transient pain exacerbations. Irritant factors or the obstruction of any hollow viscus may generate a typical colicky pain. A potentially reversible type of breakthrough pain often occurs during opioid titration, before a suitable, stable dose is achieved. Breakthrough pain in the absence of an apparent cause may also indicate opioid under-dosing, including dosing that is too infrequent. End-of-dose failure may readily be confirmed by having patients and care-givers keep diaries that document the time of breakthrough pain along with the time of the last prior dose of scheduled medication.

Assessment of breakthrough pain may be difficult, particularly in patients with incident pain who avoid specific movements that might trigger pain. It is important to assess breakthrough pain as a pattern that is distinct from baseline pain. A comprehensive pain assessment should include the frequency and duration of each episode, pain intensity, precipitating factors, and previous and current pain treatments for baseline (persistent) pain and their effectiveness. Pain assessment should also include the inferred pathophysiology and etiology of the pain syndrome. The patient’s involvement in assessment is of paramount importance, as is communication between the patient and the health care team. When patients are educated about cancer pain, learn to use a pain diary, and talk with members of their health care team, they receive better pain relief.

**Careful opioid titration may improve baseline analgesia while limiting adverse effects**

**Management of Episodic Pain**

Patients or family caregivers may help manage an episode of breakthrough pain by changing the patient’s position, applying heat or cold, massaging the painful area, and using relaxation techniques while waiting for relief from medication. Beyond these simple nondrug methods, two major medical strategies are recommended for management of episodic pain. First, it is essential to optimize round-the-clock analgesia by using an appropriate opioid titration to obtain the best balance between analgesia and adverse effects. Optimization may involve using different sequences of opioids and supplementing analgesics with adjuvants. Careful opioid titration may improve baseline analgesia while limiting adverse effects. Breakthrough pain due to end-of-dose failure may promptly respond to increasing the dose of basal medication or decreasing the interval between doses. A recent study suggests that optimization of basal opioid therapy—chiefly, dose escalation—benefits patients with bone metastases who present with incident pain upon movement. However, large dosage increases may produce unacceptable toxicity, particularly sedation, between episodes of incident pain. Doubling opioid doses in six days resulted in better pain control in one study of patients with incident pain from bone metastases, although methylphenidate was required to reverse sedation during this opioid titration. Nociceptive pain tends to respond well to opioids and anti-inflammatory drugs, while neuropathic pain will more likely require adjuvant analgesics. Additional research is needed to assess whether bisphosphonates may provide preemptive analgesia. These drugs are effective in reducing bone pain and preventing skeletal events. Thus, their routine, preventive administration in patients with for metastatic bone pain might reduce the development of incident pain and thereby improve quality of life. This hypothesis has not yet been evaluated and should be assessed in studies with appropriate cost-benefit assessment.

**The goal of pain management is to individualize rescue medication according to the underlying mechanisms**

Second, the physician should prescribe a rescue medication alongside the basal medication, teaching the patient when and how to use it. The goal of pain management is to individualize rescue medication according to the mechanisms underlying each person’s pain. The rescue medication used should have an appropriate onset of action and suitable potency, and must be easy to administer (or self-administer whenever possible). Immediate-release oral morphine, oxycodone, and hydrocodone are the mainstay of pharmacotherapy for breakthrough pain. If possible, the rescue dose should be the same opioid as the patient is taking around the clock for baseline pain to facilitate identification of potential adverse effects. Dosing recommendations, based on anecdotal experience, suggest that the initial dose of breakthrough pain medication may be estimated as a fixed fraction of the patient’s total daily opioid dose. In the case of morphine, the European Association for Palliative Care recommends one-sixth (17%) of the daily dose as a starting point, with subsequent increases or decreases according to clinical effect.

For outpatients or patients at home in whom continuous venous access is not practical, the oral route is the most convenient. However, immediate-release oral opioids in tablet or liquid form may take up to 45 minutes to become effective, while the peak intensity of episodic pain can occur in 5 to 15
minutes. Few studies have reported on the use of morphine as a rescue drug. Very little is known about the pharmacokinetics of rescue doses of opioids superimposed on regular doses of opioids or about the consequent increases of plasma concentrations of opioids and their metabolites after the breakthrough pain has resolved.

The fastest onset and shortest duration of action are provided by intravenous administration of a bolus dose, which takes effect in 2 to 5 minutes for methadone and 15 to 30 minutes for morphine and hydromorphone. If available, a patient-controlled analgesia pump can deliver the analgesic “on demand,” allowing patients the rapid relief of brief episodes of intense pain that oral formulations cannot always provide. We have shown that intravenous morphine at a dose equivalent to 20% of the basal daily oral dosage is safe and effective in the majority of patients experiencing pain exacerbations. This treatment is inexpensive and low-risk.7

Administration of opioids via the nasal or oral mucosa provides a non-invasive mechanism for more rapid drug absorption and more rapid onset of pain relief compared with oral dosing. Lipophilic drugs such as fentanyl, sufentanil, and methadone readily cross the blood-brain barrier and are well suited for nasal or oral mucosal delivery. On the other hand, a solution of morphine with chitosan (a natural mucoadherent derived from crustaceans) also proved effective in relieving breakthrough cancer pain when administered nasally.11 The respiratory tract and mouth provide a large mucosal surface for drug absorption, allowing drugs to directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. Oral transmucosal fentanyl citrate (OTFC) has been developed to manage episodic pain in patients who are opioid tolerant, i.e., receiving about 60 mg/day of oral morphine or the equivalent. OTFC has been shown to be effective for breakthrough pain episodes, producing a faster onset of relief and a greater degree of pain relief than oral morphine at 15, 30, and 60 minutes.12-15

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Contradicting the anecdotal impression drawn from practical experience that the effective dose is a certain fraction of the opioid daily dose, clinical trials with OTFC have failed to demonstrate a relationship between the effective OTFC dose and baseline opioid requirement, regardless of the opioid used. This negative finding has several potential explanations. Sixty-six percent of the episodes responded to placebo of the same shape and taste as OTFC. This response is attributable to the normally brief, self-limited course of many breakthrough pain episodes, or to a true placebo response. Alternatively, such episodes may have resolved because they represented a low-intensity flare of baseline pain. Differences between fluctuations in baseline pain intensity and peaks of breakthrough pain are not striking. Moreover, the clinical trials of OTFC did not specify the etiology of breakthrough pain, nor whether they were incident or spontaneous in nature.12-15

Sublingual and intranasal mucosa have high permeability and extensive vascularity, qualities that facilitate rapid systemic absorption of lipophilic drugs such as fentanyl. Ketamine has the advantage of efficacy independent of the degree of opioid tolerance. Although the bioavailability of different ketamine formulations is variable, favorable results for this treatment have recently been reported in a placebo-controlled crossover trial in patients with cancer and noncancer pain receiving chronic opioid therapy. Intranasal ketamine, given as a repeated spray of 10 mg at up to five 90-second intervals, provided statistically significant pain relief within 10 minutes, and only one patient out of 20 reported no relief after treatment.16 Ketamine has also been used for treating breakthrough pain in difficult conditions, such as in highly opioid-tolerant patients receiving a combination of intrathecal opioids and local anesthetics.17

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Treatments that employ non-opioid drugs make it possible to overcome the common problem of analgesic tolerance to opioids, although the prospect of tolerance to non-opioid agents during long-term therapy cannot be excluded and should be assessed in future studies. Moreover, ketamine requires careful and skilled titration in light of its well-known, dose-dependent excitatory or dysphoric effects.

Translational Perspectives

Experimental models of bone cancer pain have been developed in the last few years to better explain the mechanisms of incident pain due to bone metastases. Parallel to increased bone destruction, tumor-bearing mice showed signs of ongoing and stimulus-evoked pain behaviors after inoculation of sarcoma cells into the intramedullary space of the femur.19 Ipsilateral spinal cord segments that receive primary input from the cancerous femur display several notable neurochemical changes, including an increase in the prohyperalgesic peptide dynorphin, a massive astrocytic reaction, substance P receptor internalization, and C-fos expression. From a pathophysiological point of view, incident pain could be considered as a peripheral innocuous stimulus able to excite spinal cord neurons to a pathological degree, resembling a form of profound mechanical allodynia. Doses of morphine required to inhibit noxious behaviors seen with experimental bone metastases are in general tenfold greater than those required to alleviate pain behaviors of comparable magnitude generated by inflammatory pain.20 Consistent with this preclinical observation, a recent clinical trial found that incident pain could be controlled by increasing the opioid dose well above that required to control pain at rest.21

Each patient’s cancer pain is a mosaic whose mechanisms, locations, and temporal patterns fit together into an individualized picture.
Approximately 20 years have elapsed since the World Health Organization declared the relief of cancer pain to be a major priority. A simple three-step method for cancer pain relief has been established and disseminated, although it is still evolving. At the same time, increasing attention by clinicians worldwide to the control of cancer pain has generated a multitude of clinical observations on the assessment, etiology, and therapy of cancer pain. It has become clear that each patient’s cancer pain is a mosaic whose mechanisms, locations, and temporal patterns fit together into an individualized picture and impair quality of life. Although preclinical models of cancer pain now permit a deeper understanding of each of these elements—particularly breakthrough pain—the need to address each element and integrate therapies to improve quality of life will challenge front-line clinicians, patients, and their families for some time to come.

References


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