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Basics of managing breakthrough cancer pain

Andrew Dickman gives an overview of breakthrough pain experienced by patients with cancer and how this should be managed

Pain is a common symptom of cancer. It has a prevalence of up to 90 per cent in patients with advanced disease.1 It is also probably the most feared of all cancer symptoms, with patients believing it is a sign that their condition has deteriorated. Background pain (also referred to as baseline or persistent pain) can, in most cases, be treated successfully with the use of long-acting opioid formulations and adjuvant drugs such as gabapentin, pregabalin or amitriptyline (see PJ, 9 and 23 June 2007, pp679–82 and pp745–8). However, despite well controlled background pain, cancer patients can experience pain of fast onset and short duration that can occur either predictably or spontaneously. This is referred to as breakthrough pain.

Definitions and characteristics

There is no universally accepted definition of breakthrough pain, which is illustrated by the fact that studies have found between 19 and 95 per cent of patients with background pain experience breakthrough pain.2 Several definitions have been used over the past 20 years. The lack of consensus over a definition has undoubtedly resulted in inadequate assessment and suboptimal treatment, impacting on the patient’s quality of life.

Of the commonly accepted definitions, there is an assumption that the background pain is controlled and stable. The term “breakthrough cancer pain” (BCP) has been introduced to describe a transient exacerbation of pain that occurs on top of otherwise stable pain in cancer patients receiving long-term opioid therapy.

This year, a task group from the Association for Palliative Medicine of Great Britain and Ireland (APM) defined BCP as, “a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, experienced by patients who have relatively stable and adequately controlled background pain.”3 There are essentially two subtypes of BCP using this definition:

- **Incident pain** Incident pain is the most common type of BCP and is precipitated by movement or activity. It is further divided into voluntary (ie, predictable pain caused by a voluntary event, such as walking), non volitional (ie, unpredictable pain caused by involuntary actions, such as coughing or sneezing) and procedural (ie, caused by a particular therapeutic intervention, such as wound dressing).

- **Spontaneous pain** Spontaneous pain, also referred to as idiopathic pain, generally lasts longer than incident pain and the cause is unknown.

Other definitions include a third subtype, namely end-of-dose pain. This is said to occur because a scheduled dose of background analgesic and generally occurs due to an inadequate dose of analgesic or extended dosing interval. In either case, end-of-dose pain can be interpreted as poorly controlled background pain and falls outside the APM definition.

It is unsurprising that a universal definition of BCP does not exist because clinical features can vary. Some patients only experience one type of pain, while others experience several distinct pains. Furthermore, the clinical features can vary within a patient during the course of the disease.

BCP is usually of moderate to severe intensity and the pathophysiology is often, but not always, the same as background pain. In other words, it can be neuropathic, nociceptive or a combination of both (see Panel 1 p214).

The prevalence of BCP varies widely and is difficult to determine given the lack of an accepted definition. Nonetheless, it is suggested that BCP is experienced by 65 per cent of patients with background pain.4 It also appears to be more frequently experienced by patients with advanced disease.

BCP episodes vary in duration, intensity and cause but the typical episode reaches peak intensity...
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after three to five minutes and has an average duration of 15 to 30 minutes. Patients experience a median of two to four episodes per day. The licensed products available for the treatment of BCP should only be used for up to four episodes daily (see below). More than four episodes a day warrants a reassessment of the background pain.

BCP is a self-limiting condition but, if poorly controlled, it can have a profound impact on quality of life. Consequences include:

- Impairment of daily activities (eg, walking, working)
- Anxiety and depression
- Difficulty sleeping
- Reduced social interaction
- Increased pain severity
- Dissatisfaction with overall pain management
- Impairment of daily activities (eg, walking, working)

In addition, it has been shown that patients with BCP are more likely to use health care resources, have more pain-related hospital admissions and emergency medical interventions, and have greater direct and indirect treatment costs than those without BCP.

Management

Patients must be assessed in order to differentiate between exacerbations of uncontrolled background pain and BCP because treatment modalities are different. A simple algorithm (see Figure 1) can aid with the diagnosis. BCP should be considered separately from background pain and its treatment must be individualised.

The aim is to reduce the impact of pain episodes on the patient’s quality of life, although complete pain relief is usually an unrealistic expectation. Presently, there is no treatment that can be considered to be ideal, which is understandable given the heterogeneous nature of BCP. Opioids are considered the drugs of choice for the treatment of BCP.

The approach to treatment of BCP must be methodical. Successful management of BCP includes the following:

- Assessment of the characteristics of both the pain and patient (eg, disease, preferences). There is no validated tool for the clinical assessment of BCP but it is usually characterised by cause, location, severity and temporal profile.
- Treatment of the underlying cause (eg, radiotherapy, chemotherapy, surgery).
- Management or avoidance of precipitating factors. For example, if coughing is known to precipitate BCP, antitussive could be used and, if constipation is a known precipitant, laxative treatment can be reviewed. In addition, physical, behavioural and psychological approaches to pain reduction or avoidance could be considered and the patient may need educating about limitations and the need to change behaviours and levels of activity.
- Adjustment of background analgesia (ie, optimising opioid analgesia and adding adjuvant analgesics). Optimisation of background analgesia using the analgesic ladder as described by the World Health Organization is essential. Appropriate opioid titration, ensuring a satisfactory balance between analgesia and undesirable effects, coupled with judicious use of adjuvant analgesics will help to alleviate episodes of BCP.
- Symptomatic management (employing both pharmacological and non-pharmacological modalities).
- Reassessment

It should be noted that opioids are unlikely to control all types of BCP and alternative strategies may need to be adopted. Despite a lack of evidence, consideration should be given to non-pharmacological interventions, such as massage, application of heat or cold, distraction and relaxation techniques, which some patients describe as effective.

Arguably, pharmacological treatment forms the critical aspect of BCP management. Non-opioid analgesics (eg, paracetamol and non-steroidal anti-inflammatory drugs) are used to treat BCP but there is presently no robust evidence to support their use.

Traditional management of BCP involves the administration of fixed doses of normal-release oral opioid preparations of morphine, oxycodone or hydromorphone, the dose typically being one sixth of

Panel 1: Common terms for pain

- **Nociceptive, somatic** Pain produced by activation of peripheral nociceptors found in skin, bone, joints and muscles. Typically described as aching or throbbing, the pain is generally localised and constant and is increased by movement.
- **Nociceptive, visceral** Pain produced by stimulation of nociceptors within internal organs or the lining of body cavities. Often poorly localised and described as constant, sharp or cramping.
- **Neuropathic** Pain caused by damage to or changes in the central or peripheral nervous system. Described in a variety of terms, depending on the nerve affected (eg, burning, sharp, shooting, stabbing and itching).
- **Mixed** A combination of both nociceptive and neuropathic pain.

Figure 1: Simple algorithm for the assessment of BCP

Does the patient have background pain? (Persistent pain for at least 12 hours per day during the previous week)

- Yes
- No

Is the background pain adequately controlled? (No pain or mild pain for at least 12 hours per day during the previous week)

- Yes
- No

Are there exacerbations of pain?

- Yes
- No

Patient has breakthrough pain

Author Andrew Dickman will be available to answer questions online on the topic of this CPD article until 5 September 2009

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the daily background opioid dose. However, this is based on anecdotal evidence only. Such a strategy for BCP is based on the approach used for titration of the background opioid dose (see Panel 2) and is generally not appropriate. An analgesic effect would not be seen for at least 30 minutes and could last for up to four hours. This is illustrated in Figure 2, where a patient with BCP is prescribed an oral normal-release opioid preparation, such as morphine.

Since the pharmacokinetic parameters of morphine do not match the temporal profile of the BCP, the analgesia provided occurs after the BCP has spontaneously subsided. For patients with several episodes of BCP, there is a cumulative increase in the peak intensity of BCP, which may be treated with multiple doses of the normal-release morphine, with the undesirable result that the peak intensity of BCP is never effectively treated, but undesirable effects of the drug (ie, fatigue, sedation, confusion) become problematic. This approach is, therefore, not the most appropriate treatment for pain of quick onset and short duration (ie, most BCP episodes) but it may be suitable for BCP of slower onset and duration of an hour or more (eg, patients with predictable incident pain could be given a rescue dose of oral morphine 30 minutes before physical activity).

Although non-opioid and adjuvant analgesics are still used in practice to manage BCP, the ideal treatment for most BCP episodes is a rescue dose of strong opioid with pharmacokinetic properties that closely match the temporal characteristics of the BCP. This should be simple to administer with minimal risk of undesirable effects.

Panel 2: Opioid titration for background pain

Oral normal-release opioid formulations remain the most suitable choice of treatment for background pain. The following points illustrate an example of opioid titration:

- For opioid naive patients, give 5mg oral morphine regularly every four hours, with a 5mg rescue dose that can be taken as necessary.
- The following day, add the dose of morphine taken as rescue doses (if any) to the total daily background dose. This figure becomes the new total daily background dose. For example, if four rescue doses were taken, the new total daily background dose would be (5mg x 6) + (5mg x 4) = 50mg. The patient would then be prescribed 7.5mg every four hours, with 7.5mg rescue doses to be taken as necessary.
- Once a stable background dose has been achieved, this can be converted to a modified-release formulation. For example, if the patient is stabilised on a background dose of morphine 10mg every four hours, this can be replaced by 30mg of twice daily. The need for 10mg rescue doses of oral morphine should now cease because the patient has well controlled background pain.

Panel 3: Licensed products for BCP

Abstral The sublingual tablets are available in strengths of 100, 200, 300, 400, 600 and 800µg. NHS cost: £4.99 per tablet (all strengths).

Actiq The lozenges are available in strengths of 200, 400, 600, 800, 1,200 and 1,600µg. NHS cost: £6.19 per lozenge (all strengths).

Effentora The buccal tablets are available in strengths of 100, 200, 400, 600 and 800µg. NHS cost: £5.14 per tablet (all strengths).

The typical episode of BCP reaches peak intensity after three to five minutes and has an average duration of 15 to 30 minutes.

For typical episodes of BCP, the use of a short-acting opioid with quick onset and short duration of action is the most appropriate treatment. Fentanyl is a lipophilic opioid that is rapidly absorbed across mucosal membranes, with the promise of a rapid onset and shorter effect that more closely matches the profile of the ideal rescue treatment (see Figure 3). The administration of this drug via the buccal, sublingual or nasal routes provides more rapid drug absorption and onset of action compared with the oral route, and with oral morphine.

Products Three products are licensed for the treatment of BCP, all of which contain fentanyl: Actiq lozenges, Abstral sublingual tablets and Effentora buccal tablets (see Panel 3 for further details).

These are all licensed for use by patients taking at least 60mg of oral morphine, or equivalent, per day, for at least a week. With all three products, the rescue dose that successfully treats BCP cannot be predicted from the background opioid dose — there is no correlation. Titration to an effective dose is necessary, starting at the lowest available dose. Each product has its own dosing schedule. In addition, the products are not interchangeable and use of the brand name when prescribing is advised.

Oral transmucosal fentanyl marketed as Actiq lozenges was the first product developed specifically for the treatment of BCP. The patient is required to place the lozenge in the mouth and rub it against his or her cheek, without sucking or chewing it. Each lozenge should be consumed within 15 minutes. If the patient has a dry mouth, a small amount

Figure 2: Traditional treatment of BCP

Figure 3: Treatment of BCP using a preparation with a quick onset and short duration
of water can be used to moisten the buccal mucosa. Several trials have confirmed the safety, efficacy and tolerability of oral transmucosal fentanyl. In addition, they have confirmed a lack of relationship between a successful dose and the background opioid dose. A significant improvement in pain is seen within 15 minutes of medication. However, it is likely that two newer products (discussed below) will eventually supersede Actiq.

The fentanyl buccal tablet, marketed as Effentora, uses a delivery technology based on an effervescent reaction that enhances the rate and extent of fentanyl absorption across the buccal mucosa. The tablet should be placed in the upper portion of the buccal cavity, above an upper rear molar between the cheek and gum. The tablet should not be sucked, chewed or swallowed, nor should the patient eat or drink anything while the tablet is in the mouth. The tablet usually disintegrates within 14 to 25 minutes. After 30 minutes, the mouth can be rinsed to remove the remnants. Water can be used to moisten the buccal mucosa in patients with a dry mouth. Effentora has been shown to produce an effect within 10 minutes of administration.

The latest product to be licensed for BCP is the fentanyl sublingual tablet, marketed as Abstral. This product uses a delivery system based on the use of ordered units of fine drug particles attached to coarser excipient carrier particles that adhere to the sublingual mucosa, permitting rapid disintegration of the tablet and optimal drug exposure. The sublingual tablets should be administered directly under the tongue, at the deepest part. The patient must not swallow, suck or chew the tablet, nor should the patient eat or drink anything until the tablet has completely dissolved. However, this happens within less than a minute. Again, water can be used to moisten the buccal mucosa in patients with a dry mouth. Although the summary of product characteristics states analgesia occurs within 15 minutes, unpublished data suggest Abstral produces an effect within 10 minutes. (Data on file 2009. Kauck R, Derrick R, Howell J. Efficacy and tolerability of sublingual fentanyl in opioid-tolerant cancer patients with breakthrough pain: interim findings from two long-term, phase III multi-centre studies.)

Within the next 12 months, two additional products for BCP may become available. Instanyl and Nasalfent are preparations of fentanyl for transmucosal or intranasal use. Instanyl uses a delivery system based on the use of ordered units of fine drug particles attached to coarser excipient carrier particles that adhere to the sublingual mucosa, permitting rapid disintegration of the tablet and optimal drug exposure. The sublingual tablets should be administered directly under the tongue, at the deepest part. The patient must not swallow, suck or chew the tablet, nor should the patient eat or drink anything until the tablet has completely dissolved. However, this happens within less than a minute. Again, water can be used to moisten the buccal mucosa in patients with a dry mouth. Although the summary of product characteristics states analgesia occurs within 15 minutes, unpublished data suggest Abstral produces an effect within 10 minutes. (Data on file 2009. Kauck R, Derrick R, Howell J. Efficacy and tolerability of sublingual fentanyl in opioid-tolerant cancer patients with breakthrough pain: interim findings from two long-term, phase III multi-centre studies.)

Within the next 12 months, two additional products for BCP may become available. Instanyl and Nasalfent are preparations of fentanyl for intranasal delivery. Intranasal delivery. These products are expected to produce similar results as the currently available licensed options. Alfenlent spray, for oral transmucosal or intranasal use is currently manufactured by Torbay Hospital (tel: 01803 664707) as an unlicensed special. This product may have a faster onset of effect (although this is unproven) and shorter duration of action so, for example, intranasal alfenlent may be a suitable choice for dressing changes.

Conclusion

BCP is a heterogenous condition that requires comprehensive assessment and an individualised approach to treatment. Both pharmacological and non-pharmaceutical treatment modalities should be considered. The widespread prescribing of a fixed (proportional) dose of an oral normal-release opioid preparation as rescue medication is no longer recommended for most BCP episodes. This traditional approach will not provide the fast onset of analgesia required for most BCP episodes because it occurs after the pain has resolved. The availability of three transmucosal fentanyl preparations and the promise of more will, undoubtedly, have a significant role in the management of BCP. Nonetheless, the use of rescue medication is only one aspect of the management of BCP and other factors, such as treatment or avoidance of the underlying cause of the pain and modification of the background analgesic regimen, should be considered.

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References