Cancer-related breakthrough pain

Breakthrough pain is a common problem in patients with cancer, and is associated with significant morbidity among this group of patients. This review examines the different types of breakthrough pain, and the various options for the management of breakthrough pain.

Patients with cancer may experience two distinct types of pain: background pain – a continuous type of pain; and breakthrough pain (BTP) – an exacerbation of the background pain. This article will highlight the different types of BTP, and the various options for management of BTP. In particular, the article will discuss the role of oral transmucosal fentanyl citrate (OTFC), which is currently the only opioid preparation with a marketing authorization for the treatment of cancer-related BTP in the UK.

Definition

BTP has been defined as 'a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain' (Portenoy et al, 2004). It should be noted that a variety of other terms have been used to describe this phenomenon, including 'episodic pain' and 'transient pain' (Mercadante et al, 2002).

Epidemiology

The prevalence of BTP has been reported to vary from 40–80% among oncology patients (Mercadante et al, 2002). The reasons for this disparity include differences in the populations studied and/or differences in the diagnostic criteria utilized.

Classification

BTP is not a single entity, but a spectrum of very different entities (Twycross, 1978); BTP can be classified according to its relationship to specific events, or to analgesic dosing (Simmonds, 1999):

- Spontaneous pain – this type of pain occurs unexpectedly
- Incident pain – this type of pain is related to specific events, and can be sub-classified into three groups:
  1. Volitional – pain is precipitated by a voluntary act (e.g. walking)
  2. Non-volitional – pain is precipitated by an involuntary act (e.g. coughing)
  3. Procedural – pain is related to a therapeutic intervention (e.g. wound dressing).
- End of dose failure – this type of pain is related to analgesic dosing, i.e. declining analgesic levels.

Dr Andrew N Davies *is Consultant in Palliative Medicine, Royal Marsden Hospital, Sutton, Surrey SM2 5PT*

Clinical features

The clinical features of BTP, like the clinical features of background pain, vary from individual to individual (Portenoy et al, 2004). Nevertheless, BTP is often frequent in occurrence, acute in onset, short in duration, and moderate-to-severe in intensity (Portenoy and Hagen, 1990; Zeppetella et al, 2000). For example, Zeppetella et al (2000) reported a mean number of four episodes per day (range 1–14 episodes per day) among hospice inpatients. Similarly, Portenoy and Hagen (1990) reported a median duration of 30 minutes (range 1–240 minutes) among hospital inpatients. Not surprisingly, the presence of BTP is associated with a negative impact on overall pain control and overall quality of life (Simmonds, 1999). Furthermore, the presence of BTP is associated with increased use of health-care resources (outpatient consultations, inpatient admissions) (Fortner et al, 2002).

Management

Management steps for BTP include:

1. Assessment
2. Treatment
3. Reassessment and follow up.

Assessment is the key to successful management; inadequate assessment often leads to inappropriate treatment. The assessment of BTP is essentially the same as the assessment of background pain. It is particularly important to ascertain the temporal pattern of pain, any precipitating or exacerbating factors, any relieving factors, the response to opioid analgesics, and the response to other therapeutic manoeuvres.

Treatment options include:

- Management of underlying cause of pain
- Pharmacological methods:
  1. Modification of the regular analgesic regimen (Mercadante et al, 2004a)
  2. Use of short-acting opioids (Mercadante et al, 2002)
  3. Use of other short-acting agents (e.g. nitrous oxide, midazolam) (Benitez del Rosaria et al, 2001; Parlow et al, 2005)
- Non-pharmacological methods (e.g. relaxation training) (Sloman et al, 1994).

The optimal treatment is management of the underlying disease (e.g. radiotherapy) or the underlying pathological process (e.g. bisphosphonates). Similarly, in some cases of incident pain, the optimal treatment is management

of relevant precipitating or exacerbating factors (Davies and O'Donnell, 1997).

Modification of the regular analgesic regimen is the treatment of choice for end of dose failure, i.e. increasing the dosage or frequency of dosage of the regular analgesic. Modification of the regular analgesic regimen may also be an option in some patients with paroxysmal pain (e.g. addition of an adjuvant analgesic), and some patients with incident pain (e.g. increase of the background analgesic) (Mercadante et al, 2004a).

Short-acting opioids are the mainstay of the pharmacological treatment of BTP. However, opioid preparations will only be effective if the BTP is an opioid-responsive pain. Furthermore, individual opioid preparations will only be effective if the pharmacokinetic profile of the preparation (i.e. onset of action) mirrors the temporal pattern of the pain (i.e. duration of episode). It should be noted that response (efficacy, tolerability) to individual opioid preparations varies from person to person, and may vary over time within the same person.

The World Health Organization guidelines promote the use of the oral route in the management of cancer pain (WHO, 1996). However, although the oral route is generally effective in managing background pain, it is generally less effective in managing BTP. Thus, the oral route is associated with a delayed onset of action (e.g. morphine sulphate: 20–30 minutes) (Twycross et al 1998), and a delayed peak effect (e.g. morphine sulphate: 60 minutes) (Mercadante et al, 2002).

In an attempt to overcome this problem, a variety of alternative routes have been employed, including the intravenous (Mercadante et al, 2004b), subcutaneous (Enting et al, 2005), intranasal (Pavis et al, 2002), intrapulmonary (Zeppetella, 2000), and oral transmucosal routes (Gardner-Nix, 2001). Unfortunately, although these routes are generally very effective, the widespread use of these routes is limited by practical issues, such as the availability of trained personnel, suitable drug preparations, and suitable drug delivery systems.

Oral transmucosal fentanyl citrate

OTFC (Actiq, Cephalon UK Ltd, Guildford) is unique in being the only opioid preparation licensed for the treatment of BTP in cancer (*Figure 1*). OTFC consists of a lozenge impregnated with fentanyl citrate, which is a semi-synthetic, potent, highly lipid-soluble, highly selective μ opioid receptor agonist. OTFC is available in a number of different dose strengths (i.e. 200 μg, 400 μg, 600 μg, 800 μg, 1200 μg, 1600 μg).

OTFC is rubbed against the inside of the cheek, which permits the lozenge to be dissolved by saliva, and the fentanyl citrate to be absorbed through the buccal mucosa. It takes approximately 15 minutes for the lozenge to completely dissolve. However, a patient with a dry mouth may take longer to dissolve the lozenge, or may even be incapable of dissolving the lozenge.

OTFC has a relatively rapid onset of action (5–10 minutes), a relatively rapid peak effect (30 minutes) and a relatively short duration of action (2 hours) (Hanks, 2001). The bioavailability of OTFC is 50%: 25% is absorbed through the buccal mucosa, while 25% is absorbed through the gastrointestinal mucosa as a result of swallowing the drug (Hanks, 2001). The rapid onset of action is dependent on the absorption through the buccal mucosa. Indeed, patients who suck the lozenge, rather than rub the lozenge against the inside of the cheek, will experience a delayed or reduced effect.

Several randomized controlled studies have confirmed the efficacy and tolerability of OTFC (Christie et al, 1998; Farrar et al, 1998; Portenoy et al, 1999; Coluzzi et al, 2001). Indeed, the European Association for Palliative Care has specifically endorsed its use in the management of BTP (Hanks et al, 2001). Its main advantage is the speed of onset of analgesia, rather than the degree of analgesia. Thus, OTFC can significantly shorten the duration of pain episodes as compared with the short-acting oral opioids (see above). It should be noted that OTFC will only be effective if the BTP is an opioid-responsive pain, and is only suitable for patients already receiving maintenance opioid therapy for chronic cancer pain.

Randomized controlled studies have demonstrated that there is no correlation between the dose of opioid needed to control the background pain and the dose of OTFC needed to control the BTP, i.e. the dose of OTFC requires individual titration (Christie et al, 1998; Portenoy et al, 1999; Coluzzi et al, 2001). The recommended starting dose is 200 μg, although many patients require larger doses (Hanks et al, 2004).

The side effects of OTFC are typical of other opioid preparations, and include somnolence, nausea, vomiting and dizziness (Christie et al, 1998; Portenoy et al, 1999; Coluzzi et al, 2001; Hanks et al, 2001, 2004). However, OTFC is not a panacea for BTP. Thus, it is not indicated for patients who do not respond to fentanyl, who do not tolerate fentanyl, who have contraindications to the use of fentanyl, who are severely disabled (and so cannot use the preparation), who are severely fatigued (and so cannot use the preparation), who have ongoing oral dryness (and so cannot dissolve the preparation), and who have ongoing oral pathology (that may affect absorption of the preparation).

Conclusions

BTP represents a diverse group of conditions, and the management of BTP requires an individualized

Figure 1. Oral transmucosal fentanyl citrate (Actiq) lozenge.

approach. Oral opioids are frequently used to treat BTP, but their pharmacokinetic profile is not suited for the treatment of BTP. OTFC is a novel preparation which has been shown to be effective in the management of cancer-related BTP and well tolerated by patients already receiving opioid drugs. Moreover, OTFC is capable of providing significantly quicker analgesia than oral opioids. However, OTFC is not a panacea for BTP, and certain patients may not be able to use this preparation. BJHM

Conflict of interest: The author has received honoraria for lecturing, and grants for research projects, from Cephalon UK Ltd.

Benitez del Rosaria MA, Martin AS, Ortega JJ, Feria M (2001) Temporary sedation with midazolam for control of severe incident pain. *J Pain Symptom Manage* **21**(5): 439–42

Christie JM, Simmonds M, Patt R et al (1998) Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol* **10:** 3238–45

Coluzzi PH, Schwartzberg L, Conroy JD et al (2001) Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC®) and morphine sulphate immediate release (MSIR®). *Pain* **91:** 123–30

Davies AN, O'Donnell V (1997) Trigeminal neuralgia managed by a change in lifestyle. *J Palliat Care* **13**(2): 50–1

Enting RH , Mucchiano C, Oldenmenger WH et al (2005) The "pain pen" for breakthrough cancer pain: a promising treatment. *J Pain Symptom Manage* **29**(2): 213–17

Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E (1998) Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst* **90**(8): 611–16

Fortner BV, Okon TA, Portenoy RK (2002) A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain* **3**(1): 38–44

Gardner-Nix J (2001) Oral transmucosal fentanyl and sufentanil for incident pain. *J Pain Symptom Manage* **22**(2): 627–30

Hanks G (2001) Oral transmucosal fentanyl citrate for the management of breakthrough pain. *Eur J Palliat Care* **8**(1): 6–9

Hanks GW, De Conno F, Cherny N et al (2001) Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* **84**(5): 587–93

Hanks GW, Nugent M, Higgs CM, Busch MA (2004) Oral transmucosal fentanyl citrate in the management of breakthrough pain in cancer: an open, multicentre, dose-titration and long-term use study. *Palliat Med* **18**(8): 698–704

Mercadante S, Radbruch L, Caraceni A et al (2002) Episodic (breakthrough) pain. Consensus conference of an Expert Working Group of the European Association for Palliative Care. *Cancer* **94:** 832–9

Mercadante S, Villari P, Ferrera P, Casuccio A (2004a) Optimization of opioid therapy for preventing incident pain associated with bone metastases. *J Pain Symptom Manage* **28**(5): 505–10

Mercadante S, Villari P, Ferrera P, Bianchi M, Casuccio A (2004b) Safety and effectiveness of intravenous morphine for episodic (breakthrough) pain using a fixed ratio with the oral daily morphine dose. *J Pain Symptom Manage* **27**(4): 352–9

Parlow JL, Milne B, Tod DA, Stewart GI, Griffiths JM, Dudgeon DJ (2005) Self-administered nitrous oxide for the management of incident pain in terminally ill patients: a blinded case series. *Palliat Med* **19:** 3–8

Pavis H, Wilcock A, Edgecombe J et al (2002) Pilot study of nasal morphine-chitosan for the relief of breakthrough pain in patients with cancer. *J Pain Symptom Manage* **24**(6): 598–602

Portenoy RK, Hagen NA (1990) Breakthrough pain: definition, prevalence and characteristics. *Pain* **41:** 273–81

Portenoy RK , Payne R, Coluzzi P et al (1999) Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain* **79:** 303–12

Portenoy RK, Forbes K, Lussier D, Hanks G (2004) Difficult pain problems: an integrated approach. In: Doyle D, Hanks G, Cherny N, Calman K, eds. *Oxford Textbook of Palliative Medicine.* 3rd edn. Oxford University Press, Oxford: 438–58

Simmonds MA (1999) Management of breakthrough pain due to cancer. *Oncology (Huntingt)* **13:** 1103–8

Sloman R, Brown P, Aldana E, Chee E (1994) The use of relaxation for the promotion of comfort and pain relief in persons with advanced cancer. *Contemp Nurse* **3:** 6–12

Twycross R, Wilcock A, Thorp S (1998) *Palliative Care Formulary.* Radcliffe Medical Press, Abingdon

Twycross RG (1978) Relief of pain. In: Saunders CM, ed. *The Management of Terminal Disease.* Edward Arnold (Publishers) Ltd, London

World Health Organization (1996) *Cancer Pain Relief.* 2nd edn. WHO, Geneva

Zeppetella G, O'Doherty CA, Collins S (2000) Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *J Pain Symptom Manage* **20**(2): 87–92

Zeppetella G (2000) Nebulized and intranasal fentanyl in the management of cancer-related breakthrough pain. *Palliat Med* **14:** 57–8

KEY POINTS

- Breakthrough pain (BTP) is a common problem among cancer patients, with a reported prevalence rate of 40–80%.
- BTP is associated with a negative impact on overall pain control, and overall quality of life.
- Oral transmucosal fentanyl citrate (OTFC) is the only opioid preparation with a marketing authorisation for the treatment of cancer-related BTP in the UK.
- OTFC has been shown to be effective in the management of cancer-related BTP, and well tolerated by patients already receiving opioid drugs.
- OTFC is capable of providing significantly quicker analgesia than oral opioids.