Palliative Medicine Doctors’ Meeting

Any Breakthrough for Breakthrough Pain?

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ABSTRACT

Breakthrough pain is commonly encountered in daily practice and could be difficult to control. A number of studies have been carried out to compare the effectiveness of various opioids in different preparations and dosages for the management of breakthrough pain. Oral transmucosal fentanyl citrate (OTFC) is specifically developed for this purpose and evidence supports the greater analgesic effect. The relative efficacies of other opioids and non-opioids for breakthrough pain await further studies.

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Introduction

Breakthrough pain has been defined as a transitory increase in pain intensity on a baseline pain of moderate intensity, in patients on analgesic treatment being regularly administered. Other terminologies used to describe breakthrough pain include “episodic pain”, “transient pain” and “pain flare”. It is a distinct and common component of cancer pain which was reported by 64-90% of palliative care patients. The origins of breakthrough pain are somatic (33%), neuropathic (27%), visceral (20%) and mixed organ (20%). Of those, deep somatic pain from bone metastasis is commonly encountered in our daily practice.

Some people propose different subtypes of breakthrough pain. Firstly, incident pain is pain precipitated by certain events such as movement and defaecation. Another type is spontaneous pain which occurs without identifiable precipitating event. Lastly, there is pain resulting from end-of-dose failure, inadequate analgesic dose or too long interval between administrations.

Why is breakthrough pain difficult to be treated? It is likely due to its changing frequency, unpredictability and high pain severity. Even worse, doses required to control incident pain may produce unacceptable adverse effects when the patient is at rest or pain spontaneously stops. Therefore, ideal medications are those of rapid onset, early peak effect, and duration of action of no more than 1-2 hours.

Pharmacological treatment - opioids

The commonly used medications for breakthrough pain are opioids in different forms:

Oral short-onset opioids on as needed basis

These include morphine, oxycodone and hydromorphone. However, optimal dose for breakthrough pain is controversial due to variability in presentation of pain flare.

Normal release oral morphine (NRM)

The Expert Working Group of the European Association for Palliative Care (EAPC) recommended the use of NRM as early as 1996. For initiation and titration, the dosage is modified every 4 hours according to patient’s need, with the NRM rescue dose being one-sixth (17%) of the total daily dose, every 2-4 hours as needed. In a consecutive sample of 159 morphine-naive patients, 50% and 75% of patients achieved pain reduction of at least 50% with respect to baseline pain score, within 8 and 24 hours after initiation of NRM.

NRM is also said to be immediate release morphine (IRM). Is its immediate effect really achieved pain control immediately? When administrated through the oral route, onset of effect is 30-45 minutes and time to peak effect is one hour. While typical pain flare could last to the median time of 30 minutes, it may have subsided by the time IRM begins to work. Therefore, parenteral routes such as subcutaneous and intravenous routes are alternatives.
Parenteral routes of opioid administration

Standard injection pen

In two separate pilot studies, 58 patients used standard injection pen for self-administered subcutaneous rescue morphine involving hydromorphone (43 patients), morphine (11 patients) and sufentanil (4 patients). The median dose per injection was equianalgesic to 25 micrograms of subcutaneous morphine. Efficacy was rated “good” in 49 patients (84%), “moderate” in 8 patients (14%) and not noticeable in 1 patient (2%) 5.

Patient controlled analgesia (PCA)

Another subcutaneous measure is patient controlled analgesia (PCA) which involves continuous infusion with an initial bolus dose at 25% of the hourly dose and a lock-out interval of two hours. It allows treatment for fluctuating pain with its rapid adjustment of analgesic level to the degree of pain. However, drawbacks are invasiveness, limited mobility, technical demand and high cost 1.

Intravenous opioid

Apart from subcutaneous route, intravenous route has been proven to be safe and effective for breakthrough pain. The morphine IV dose was one-fifth of the oral daily dose, converted using an equi-analgesic ratio of 1/3 (IV/oral). In 496 events of breakthrough pain, a decrease in pain intensity of more than 33% and 50% was observed in 287 (61.2%) and 115 (24.5%) events. No life-threatening event in most cases was reported 6.

There was another open-label study which verified the effectiveness of IV morphine for the treatment of episodic pain in patients receiving transdermal Buprenorphine. In 106 breakthrough pain events involving 29 patients, 98 episodes were successfully treated by pain reduction of more than 33% within 15mins and mean pain intensity was decreased to 2.9. Equivalent oral daily dose was calculated using a ratio of transdermal buprenorphine/oral morphine of 1:75, and morphine IV/oral ratio of 1:3 7.

Transmucosal fentanyl

Compared to morphine, oxycodone and hydromorphone, fentanyl series of drugs have higher lipid solubility, higher potency, shorter duration of action and better therapeutic index. Congeners of fentanyl are Alfentanil (less potent, rapid onset of action), Sufentanil (ten times more potent) and Remifentanil (faster onset and offset of effect).

Oral transmucosal fentanyl citrate (OTFC)

One of the popular options is oral transmucosal fentanyl citrate (OTFC) which is the first analgesic specifically investigated for breakthrough pain. Fentanyl is incorporated into the matrix and rubbed over the oral mucosa. It is administrated through the oral route with 25% fentanyl crosses the buccal mucosa, avoids the first-pass metabolism; remaining one third is swallowed giving bioavailability of 50% 2. Pain relief was similar to intravenous morphine in greater than 80% of 133 post-op non-cancer patients 8.

Truly, when OTFC was evaluated in opioid-tolerant cancer out-patients, it was suggested to be an effective alternative over intravenous morphine 9.

The Cochrane Database of Systemic Review 2009 reported four studies of 393 patients which showed that OTFC was superior to placebo, immediate-release oral morphine and previous rescue medication [2]. One point to note is that effective dose is independent of the basal opioid regime and should be titrated. A new preparation was proposed, it was the Fentanyl effervescent buccal tablets (FEBTs). Efficacy and safety has been evaluated in a double-blind, placebo-controlled study in opioid-tolerant cancer patient 10.

Intranasal analgesia device

Sufentanil is delivered by patient controlled intranasal (IN) analgesia device. It delivers 0.18ml as a fine spray with each depression of the nasal applicator (9 mcg). The side effects are drowsiness, nausea, facial flushing and sweating. It is published in a prospective, open-label, observational study involving 30 patients in three palliative care units in Australia. Significant reduction in pain scores at 15 and 30 minutes was reported. 77% of the study population rated IN sufentanil better than pre-study medication 11.

Weak opioids and Non-opioids

Non-steroidal anti-inflammatory drug (NSAID) has been commonly prescribed in incident pain due to bone metastases and mucositis while intended to avoid opioid use. The use of Tramadol for breakthrough pain was also suggested. Nevertheless, freedom from pain...
during movements is still difficulty to be achieved in patients with bone metastases.

Non-pharmacological treatment

It involves radioisotopes used with single dose samarium-153 (153-Sm) lexidronam intravenous infusion. The mechanism is not fully understood. Reduction of pain on movement, at rest and reduction of analgesic consumed within 4 weeks was shown 12.

Discussion

Breakthrough pain is a common and distinct component of cancer pain that have a negative impact on quality of life. Current approach involves giving an additional dose based on patient’s round-the-clock analgesia. An ideal medication should have a rapid onset and short duration of action.

Although a number of advanced treatment options for breakthrough pain are present in the market, there is limited availability of those new items in our daily practice. It is also said that whenever possible, breakthrough medications should be the same opioid as the round-the-clock opioid the patient is taking. However, there is still no common consensus about the choice for breakthrough pain when patients are taking certain analgesia such as Methadone and Tramadol.

In addition to the use of different treatment options for breakthrough pain, successful management depends on thorough assessment of pain characteristics. It is especially important due to high prevalence of breakthrough pain in the palliative care population. Temporal pattern of pain, which includes breakthrough pain in particular, was ranked as the second most important dimension. Nevertheless, only 16% of the pain assessment tools measure this dimension 13. Therefore, breakthrough pain may be under-detected.

Conclusion

OTFC is the drug specifically developed for management of breakthrough pain. Evidence exists for greater analgesic effect and better global satisfaction than the usual rescue medication. On the other hand, use of opioids such as morphine, hydromorphone and oxycodone still need to be compared. Further recommendations are also required for the use of non-opioids for breakthrough pain.

References