

Breakthrough pain is defined as the transient exacerbation of pain occurring in a patient with otherwise stable, persistent pain. It is estimated to affect over 50% of patients, particularly those with moderate to severe background pain. Breakthrough pain is one of the most difficult pain syndromes to treat. There are several types of breakthrough cancer pain: incidental type involves flares of pain associated with movement or activity; idiopathic type is transitory pain unrelated to a specific activity; and in end-of-dose failure pain occurs when blood levels of medications fall below an analgesic threshold at the end of a dosing interval. Persistent and breakthrough pain are distinct components of cancer pain and require separate management. Successful management of breakthrough pain may require a combination of pharmacological and non-pharmacological treatment strategies. Supplemental analgesia, known as rescue medication, is a common pharmacological treatment option. Breakthrough pain is treated with supplemental short-acting opioid use, as needed, e.g. short-acting morphine, intranasal fentanyl and buccal tablets of fentanyl.

Key words: cancer pain, breakthrough pain, breakthrough pain management, neuropathic pain.

Management of breakthrough pain due to cancer

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Introduction

It is estimated that approximately 75% of patients with advanced cancer suffer from pain [1]. This symptom constitutes a cause of great concern, because effective analgesia is the basis of correct management. Available treatments make it possible to relieve pain in most of the patients. In order for the treatment to be effective, insightful analysis of reported symptoms, knowledge of management methods and recognition of the occurrence of breakthrough pain episodes are needed. The incidence of the latter is difficult to estimate, but it is assumed that they occur in approximately 40–60% of patients treated for pain [1].

Breakthrough pain – definition and characteristics

Breakthrough pain (BTP) is a pain flare of a rapidly increasing intensity, which usually lasts from several to tens of minutes. Breakthrough pain is usually superimposed on continuous pain, is usually located in the same place as the persistent pain, is paroxysmal in nature (several to a dozen or so episodes per day), and is characterized by a rapid onset (several minutes), short duration (approximately 30 minutes), and high intensity (at least 7 points on a 10-point VAS scale) [1].

The term ‘breakthrough pain’ appeared for the first time in medical literature in the monograph entitled “Cancer Pain”, published in 1984 by the Canadian Ministry of Health [2]. It was defined therein as a transient exacerbation of pain that occurs either spontaneously or in relation to a specific trigger.

Breakthrough pain is a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain [3].

Breakthrough pain, like background pain, may be of a nociceptive or neuropathic nature (somatic, visceral and pain in a nerve pathway) [4].

The following types of breakthrough pain have been distinguished:

- 1) incidental pain – usually triggered by movement, coughing, swallowing, voiding, defecation, etc.;
- 2) spontaneous or idiopathic pain that is not associated with a specific activity of patients, pain flares are unpredictable, surprising to patients, such as muscle spasm of the gastrointestinal tract, bile ducts, etc.; and
- 3) end-of-dose failure, or pain that occurs at the end of the expected duration of action of the opioid; according to many persons, pain of this type should not be included within BTP, since it gives evidence of using an under-dose of primary opioid [5].

When an increase of the dose of opioids results in intolerable side effects, the problem might be resolved by recommending patients to take medication more often, while maintaining the existing daily dose. For example, instead of 2 × 90 mg of modified-release morphine it is recommended to use the dosage of 3 × 60 mg [4, 5].

In the treatment of cancer pain a strategy of background pain treatment should be established as well. It is also essential to be aware of the prevalence of breakthrough pain and recognize it in our patient. It requires separate treatment. This is very important because BTP episodes occur in at least half of the treated patients and lower the patients' mood and confidence in the effective treatment of pain, thus significantly reducing the quality of life [6].

The data presented in the chart below, obtained by means of IMS (2012), illustrates how underestimated this problem is in Poland.

One must keep in mind that the incidence of breakthrough pain episodes is estimated at more than 50% of patients. Taking into account the given values of sales, more than 30% of Polish patients do not receive short-acting drugs; therefore their breakthrough pain episodes remain a problem that is not given enough consideration.

Treatment of breakthrough pain

Studies published recently in Europe show that cancer pain is inadequately treated in more than half of the patients.

The effectiveness of treatment of breakthrough pain depends on:

- 1) awareness of the fact that it might occur in more than half of our patients;
- 2) knowledge of the mechanisms of its development; and
- 3) selection of appropriate methods to control it.

The purpose of breakthrough pain management is to reduce the intensity and impact of any kind of pain. There is no gold standard for breakthrough pain control and, given its diverse nature, effective treatment is best achieved through a thorough assessment, good communication, informing the patient that it is possible to obtain pain relief, and encouraging the patient to cooperate [7].

The treatment methods may be both non-pharmacological and pharmacological [7].

Non-pharmacological methods

1. Lifestyle changes, such as efforts to encourage the patients to gradually reduce the activity that is most likely to result in breakthrough pain episodes, encouraging the patients to accept help from caregivers in carrying out such activities as washing, cooking, etc. [7].
2. Achieving control of reversible causes, e.g., using antitussive drugs, if BTP is caused by coughing, laxatives if pain is caused by constipation, using stabilizing braces in case of metastases to the spine [4, 7].
3. Causal treatment: whenever possible, it is essential to consider the possibility of palliative radiotherapy in cases of bone pain. They represent a significant percentage of incidental pain. In such cases irradiation is normally used once and its efficacy is observed in about three out of four irradiated patients in the form of reduced doses of analgesic medication required and sometimes in total elimination of the need to take such medication. In generalized bone pain, e.g. in the course of prostate cancer, radioisotope therapy should be considered [4, 7].

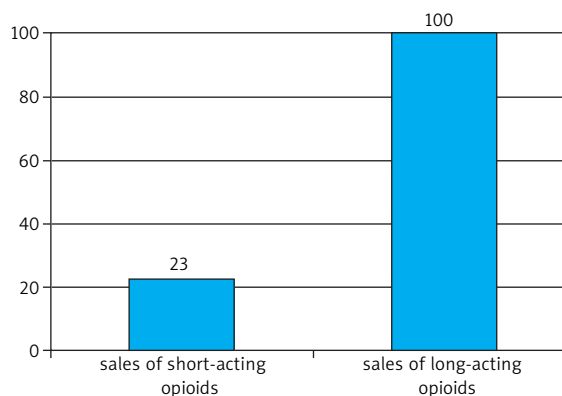


Fig. 1. Relative percentage of sales (6.2011–6.2012)

Another form of using causal treatment in combating breakthrough pain is palliative chemotherapy, for example in metastatic pancreatic cancer and prostate cancer. In pancreatic cancer, in the course of episodes of severe pain, palliative radiotherapy could be performed in the tumor area [4, 7].

In the case of pain resulting from bone metastases, it is a good alternative to use bisphosphonates [8]. These drugs are effective not only in hypercalcemia, reducing skeletal events, but also in the type of clinical situations where they produce an analgesic effect.

Pharmacological methods

Whenever we recommend a long-acting drug to the patient in the treatment of chronic pain, we should prescribe at the same time a short-acting form of the drug to use as a rescue medication. Selecting an appropriate analgesic for breakthrough pain control is pivotal to the effectiveness of cancer pain treatment.

The use of a combination of a daily dose of long-acting opioid and a rescue dose should give better analgesia and cause fewer side effects than increasing the dose of modified-release opioid [4].

The preferred route of administration is the oral route [9].

The main method of relieving acute exacerbations of pain is to use additional doses of oral opioids in addition to the primary treatment. Current recommendations for dosage to relieve breakthrough pain suggest that the effective dose in such a situation should be a certain percentage of the total daily opioid dose [4]. The first drug used in this indication was morphine oral solution. Currently, it is to a large extent replaced by oral morphine in the form of immediate-release tablets, i.e., a preparation called Sevedol.

When administered by the oral route, morphine is relatively quickly absorbed. After a single dose, peak serum concentration is achieved after 10–30 minutes. The analgesic effect generally develops within 30 minutes [2]. The half-life of morphine is 1.5–4.5 h.

Sevedol is approved for use in two dosages, 10 and 20 mg; the latter is refunded in Poland.

In cases of breakthrough pain, it is customary to use a single dose of Sevedol that represents 5–15% of the daily dose

[4]. It is a first-line therapy, especially in incidental pain. An additional advantage of this drug is its antitussive effect (for breakthrough pain provoked by coughing) [11].

The total dose of rescue medication may enable administration of an increased dose of long-acting opioid. If the number of episodes of breakthrough pain per day exceeds 4, it is recommended to increase the dose of the long-acting opioid.

An alternative way of taking the drug might be considered if the oral route is not available due to vomiting, dysphagia, or if there are side effects when using the drug in this form (nausea, vomiting, dizziness).

In such cases, the alternative is to use short-acting forms of fentanyl. In Poland two fentanyl formulations are refunded: Instanyl, PecFent (in the form of nasal spray) and Effentora (buccal tablets).

Fentanyl in the form of buccal preparations reaches maximum plasma concentration at about 46 minutes, and its statistically significant improvement in pain intensity difference was observed after 10–15 minutes [12, 13].

This quick effect is particularly useful in spontaneous pain.

The practical drawback of using these formulations is the selection of the fentanyl dose that is to be used in treating breakthrough pain in a particular patient. In this case, the total daily dose of long-acting opioid does not affect the size of the dose of fentanyl used for breakthrough pain. Conversion rates do not apply and the amount of effective dose is individually adjusted. Titration of fentanyl in the form of buccal formulation usually starts from the dose of 100 µg at the time of the pain flare occurrence. If the pain persists for more than 30 minutes, the next dose is administered. During another episode of breakthrough pain, not earlier than after 4 hours, the dose depends on the dose used in the treatment of the previous episode [5, 13].

Intranasal fentanyl titration begins with a dose of 50 µg. If no analgesic effect is observed in 10 minutes, another dose of 50 µg should be given. During the next episode of pain another, higher dose is administered [14].

In the study of the pharmacokinetics of nasal fentanyl in patients with cancer, fentanyl is rapidly absorbed through the nasal mucosa, reaching peak plasma concentrations within 12–15 minutes [15].

The main disadvantage of the currently available nasal fentanyl formulation appears to be the relatively small volume of the drug that the nasal cavity is able to accommodate [7]. As for the buccal tablets, their use is limited due to the mucosal lesions present in patients who have undergone chemotherapy, radiotherapy, etc. [7].

In addition to rescue opioids, other successfully used medications are effervescent paracetamol (onset of action after ca. 10 minutes) and metamizole. Both drugs may be administered orally at a dose of 1000 mg [4].

Less frequently used routes of administration of drugs in breakthrough pain are the subcutaneous and the intravenous route.

Another problem is neuropathic pain. If the primary pain and breakthrough pain attacks have the same neuropathic pathogenesis (about 40–50% of breakthrough pain is neu-

ropathic in nature), combating attacks of pain will depend largely on increasing fixed doses of drugs used in neuropathy, rather than using rescue doses. In the first place, one should mention tricyclic antidepressants (amitriptyline), anticonvulsants (carbamazepine and recently gabapentin are reimbursed for this indication) and antiarrhythmic drugs (lidocaine). Appropriate treatment with these drugs can significantly reduce the number of pain flares. The plan of treatment must also take into account the use of corticosteroids [6].

Within the specialized departments and pain clinics it is possible to fight both primary neuropathic pain and breakthrough pain based on such a mechanism by intrathecal administration of various drugs (opioids, clonidine, ketamine), the use of neurolysis (e.g., celiac plexus neurolysis in patients with inoperable pancreatic cancer), blockades and thermolesion of selected sensory nerves [6].

Summary

More than 50% of patients with cancer pain reported episodes of severe pain of high intensity, occurring between administered doses of long-acting medications. The occurrence of breakthrough pain can have a devastating impact on both the patients and their caregivers. It can constitute a difficult problem for the attending physician. First, you need to be aware of the existence of this phenomenon, secondly you need to recognize it, and finally they have to be treated. It is easy to make a clear distinction between the phenomenon of background pain exacerbation and the occurrence of breakthrough pain, in the case of incidental pain. The methods of control of such pain can be effective. In other cases, such as idiopathic pain and neuropathic pain, diagnosis is not easy and treatment is complicated.

From an ethical point of view, every patient has the right to receive effective analgesia using all the means available. Not every patient with cancer can be cured, but the majority of them should benefit from all available methods for the elimination or alleviation of existing pain.

The author declares no conflict of interest.

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Submitted: 10.12.2012

Accepted: 18.12.2012