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# The use of rapid onset opioids for breakthrough cancer pain: The challenge of its dosing

Sebastiano Mercadante [a,b,*]

[a] *Anesthesia and Intensive Care Unit and Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Palermo, Italy*
[b] *Department of Anesthesia, Intensive Care & Emergencies, University of Palermo, Italy*

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## Abstract

Breakthrough cancer pain (BTcP) has been defined as a transitory increase in pain intensity on a baseline pain of moderate intensity in patients on analgesic treatment regularly administered. This review provides updated information about the use of opioids for the treatment of BTcP, with special emphasis on the use of new rapid onset opioids (ROOs).

Due to its slow onset to effect oral opioids cannot be considered an efficacious treatment for BTcP. Parenteral opioids may provide rapid onset of analgesia, but not always available particularly at home. Different technologies have been developed to provide fast pain relief with potent opioid drugs such fentanyl, delivered by non-invasive routes. Transmucosal administration of lipophilic substances has gained a growing popularity in the last years, due to the rapid effect clinically observable 10–15 min after drug administration, obtainable in non-invasive forms. Fentanyl is a potent and strongly lipophilic drug, which matches the characteristics to favour the passage through the mucosa and then across the blood–brain barrier to provide fast analgesia. Transmucosal, buccal, sublingual, and intranasal fentanyl showed their efficacy in comparison with oral morphine or placebo and are available for clinical use in most countries. All the studies performed with ROOs have recommended that these drugs should be administered to opioid-tolerant patients receiving doses of oral morphine equivalents of at least 60 mg. The choice of the dose of ROO to be prescribed as needed remains controversial. The need of titrating opioid doses for BTcP has been commonly recommended in all the controlled studies, but has never been substantiated in appropriate studies.


*Keywords:* Cancer pain; Breakthrough pain; Fentanyl; Opioids

* Corresponding author at: Anesthesia and Intensive Care Unit & Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Via san Lorenzo 312, 90145 Palermo, Italy. Tel.: +39 091 6806521; fax: +39 091 6806110.
*E-mail addresses:* 03sebelle@gmail.com, terapiadeldolore@lamaddalenanet.it.

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## 1. Introduction

Patients with cancer pain often present with fluctuations in pain intensity. Breakthrough cancer pain (BTcP) has been defined as a transitory increase in pain intensity on a baseline pain of moderate intensity in patients on analgesic treatment regularly administered [1]. Patients are often receiving basal medication for their pain which is otherwise considered acceptable. Although highly variable, BTcP is typically rapid in onset, moderate to severe in intensity, and relatively short in duration [2]. Three principal categories of BTcP have been identified: (a) spontaneous pain with no evident precipitating event; (b) incident pain, with an evident precipitating cause or event, for example due to activity; (c) end of dose failure, associated with therapeutic holes due to a reduction in blood analgesic levels of medications provided at regular intervals. The latter group does not exactly corresponds to the definition of BTcP, expressing a status of inappropriate analgesia, although from a clinical perspective it still represents a clinical problem to be addressed as BTcP. Another way to classify BTcP could be based on the presence of volitional or precipitant factors, which have been identified in more than 50% of patients. Therefore, for each category different subtypes can be also identified.

Previous surveys have found that this phenomenon, is highly prevalent among patients with cancer pain and predicts more severe pain, pain-related distress and functional impairment, and relatively poor quality of life [2]. In different surveys 50–90% of cancer patients with pain have been reported to experience intermittent flares of their pain, although using different definitions and methodology [1–5]. These figures have been confirmed in a large international survey assessing the prevalence of BTcP, showing a prevalence of about 65% [6].

Pharmacological treatment regimes are based on implementation of primary therapies, optimization of scheduled analgesia [7], and specific treatment of BTcP [2,3]. The aim of this review is to provide updated information about the use of opioids for the treatment of BTcP, with special emphasis on the use of new rapid onset opioids (ROOs).

## 2. Oral opioids

The availability of supplemental doses of oral opioids in addition to the continuous analgesic medication is the main treatment suggested to manage pain flares. Current dosing recommendations for BTcP generally suggest that the effective dose of BTcP medication must be a percentage of a patient's total daily opioid dose [8]. These recommendations, which are based entirely on anecdotal experience, favour the selection of an oral short-acting opioid at a dose proportionate to the total daily dose. However, an oral dose form can take a longer time to relieve pain, with peak concentrations achieved within 30–45 min. Hydromorphone, and oxycodone, all undergo extentive first pass effect, and are hydrophyilic in nature, showing a late onset of analgesia of 30–60 min. Although the use of the same opioid to treat BTcP as to treat baseline pain is common place, it has been shown that the peak effect of orally administered opioids is about 60 min [9]. Due to its slow onset to effect oral opioids cannot be considered an efficacious treatment for BTcP. In a study of 50 oncology patients, equal numbers of individuals used morphine, oxycodone, hydromorphone, methadone or oral transmucosal fentanyl the average time to meaningful pain relief following their administration was about 30 min, whereas the average duration of BTcP was 35 min (range 15–60).

Non-adherence with oral opioids, including morphine, may not be surprising. The temporal characteristics of most BTcP events suggest the use of drugs with a faster onset of action [10]. Thus, more recent recommendations have underlined that orally administered opioids are unsuitable for pains with a short onset and duration [11,12]. Rather, they appear effective when given timely before pain occurs or in well characterized BTcP events with a gradual onset [13]. For example, the slow analgesic peaks achieved with oral opioids could be useful when administered 15–30 min before starting physical activity in patients with predictable incident pain, or during opioid titration phase.

Effervescent morphine resulted in faster relief of BTcP compared to immediate release morphine. The solution rapidly passes through the stomach and could result in a faster transit into the small intestine where the active ingredient is absorbed [14].

## 3. Parenteral opioids

As pain relief is usually required urgently, routes of administration designed to delivery drugs rapidly are often chosen. A shorter onset of effect is commonly obtainable only with parenteral administration of opioid analgesics. Intravenous morphine (IV-MO) has been found to be highly effective and safe, as only a low intensity of opioid-induced adverse effects was observed, even when administering large doses [15]. A recent confirmatory study of a large sample of patients confirmed that IV-MO administered for the management of BTcP in doses proportional to the basal opioid regimen, even given in older patients or relatively large doses, did not result in life-threatening adverse effects while being effective by patients in most cases [16]. While IV-MO is feasible in acute units, in most other centres is not favourite, and at home injections are not easily manageable. Subcutaneous route is commonly preferred in an hospice setting, although the onset of action may be not fast enough. Hydromorphone has been delivered subcutaneously using a "pain pen" [17].

## 4. ROOs

Different technologies have been developed to provide fast pain relief with potent opioid drugs such fentanyl, deliv-