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

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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

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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 correspond 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 precipitating 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 some 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 extensive first pass effect, and are hydrophilic 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 favoured, 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-
ered 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. Not all drugs are suitable for transmucosal administration. 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. 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.

4.1. Oral transmucosal fentanyl citrate (OTFC)

OTFC is a fentanyl-impregnated lozenge, available in six dosage strengths (200, 400, 600, 800, 1200, and 1600 μg). The oral mucosal route of delivery offers several advantages. The oral mucosa is highly permeable and is highly vascularized, and has a large surface area and a relatively uniform temperature. The lozenge is gently rubbed against the buccal mucosa until it has completely dissolved (which should take no longer than 15 min, if appropriately used). An active participation is required to correctly use the lozenge. Fentanyl is absorbed in about 15 min through the oral mucosa. Absorption rate and total bioavailability for fentanyl was greater and occurred sooner after OTFC administration than after oral administration. Serum fentanyl levels achieved with OTFC are proportional to the dose administered [18]. Mucositis, and local infection, and dry mouth may limit the use or reduce the absorption of the drug. Absolute availability is about 50%. However, the percentage absorbed by mouth and immediately available for treating BTcP is about 25% [18].

Several trials have shown that OTFC in doses ranging from 200 μg to 1600 μg is an effective analgesic for BTcP in patients already receiving maintenance opioid therapy for chronic cancer pain. This approach produces a faster onset of relief and a greater degree of pain relief than the placebo or oral morphine, at 15, 30, and 60 min [9,19–21]. The adverse effects associated with OTFC in studies of patients with chronic cancer pain were typical opioid side effects. Mucositis, and other side effects may have been attributable to patients’ underlying disease or to other analgesics or medications patients were using at the time of the study, other than opioids used for background analgesia [18]. A lack of relationship between the effective OTFC dose and fixed schedule opioid regimen, regardless of the opioid used, was observed suggesting the need to titrate the dose of OTFC.

4.2. Fentanyl buccal tablets (FBT)

FBT is a formulation of transmucosal fentanyl designed to provide a rapid penetration of fentanyl through the buccal mucosa by using effervescence to cause pH shifts that enhance the rate and extent of fentanyl absorption. A reasonable level of salivation is needed to allow dissolution. The tablet is placed between the upper gum and cheek, above a rear molar tooth, and patients are instructed to gently rub outside of the cheek until all material is dissolved. Fentanyl is rapidly absorbed from FBT with a mean peak plasma concentration reached in 35–90 min. The absolute bioavailability of fentanyl from FBT was greater that from OTFC. FBT is absorbed in approximately equal proportions through the buccal mucosa and the gastrointestinal tract whereas, with OTFC, the proportion absorbed through the buccal mucosa was lower (22%) than that absorbed gastrointestinally (78%) [22]. Thus the drug immediately available to treat BTcP is about the double of OTFC (48% versus 22%) [23,24]. Sublingual placement of FBT resulted in similar values of pharmacokinetic parameters [25]. Patients with cancer, particularly those undergoing chemotherapy or radiotherapy, may develop oral mucositis. In patients with mild mucositis the absorption of fentanyl with FBT was not different from that of patients without mucositis [26].

Controlled studies have reported the efficacy and safety of FBT in opioid-tolerant cancer patients with BTcP even after 10 min, after performing a titration phase to determine the effective dose. There seemed to be no relationship between effective FBT dose and the dose of baseline opioid regimen [27,28].

4.3. Intranasal nasal fentanyl (INFS)

The intranasal administration route is an alternative with several benefits, including fast systemic penetration and the potential for self-administration, as well as being acceptable to patients with reduced salivary flow. INFS has been associated with minimal local irritation in the nasal cavity. In a pharmacokinetic study in cancer patients, fentanyl was quickly absorbed through the nasal mucosa, attaining peak plasma concentrations within 12–15 min for all the dosage strengths examined (50–200 μg) [29]. After a titration phase to determine the effective dose, the use of INFS at doses of 50–200 μg was associated with an onset of activity at 10 min and a more effective treatment of BTcP compared with placebo [30]. The only existing study comparing two different ROOs showed a decrease in pain intensity which was significantly greater with INFS than OTFC from 5 min post dosing. More patients attained significantly faster meaningful pain relief with INFS than OTFC, and more patients preferred INFS to OTFC [31].

4.4. Sublingual fentanyl (SLF)

The sublingual mucosa is well suited for the delivery of ROO. The high vascularity and good permeability of the sublingual mucosa offer the potential for a rapid absorption of lipophilic opioids such as fentanyl [32]. In addition, this is a convenient and popular method for patients to self-administer effective pain relief medication that matches the temporal characteristics of BTcP. A novel rapidly absorbed sublingual form following the administration of single doses of 100,
200, and 400 μg provided plasma concentration increasing linearly with dosage [33].

Two studies assessed the clinical efficacy of SLF. In a clinical study, SLF was administered in opioid-tolerant cancer patients. Placebo, and doses of 100, 200, and 400 μg were administered in random order at four pain episodes. Pain intensity significantly decreased with SLF 400 in comparison with placebo at 15 min, while doses of 100 and 200 showed only a trend towards improved pain relief. The incidence or severity of adverse effects did not increase with increasing SLF dose [34]. In a placebo-controlled conducted in opioid-tolerant cancer patients, SLF, administered for BtCP, provided significant improvements in pain intensity compared to placebo, from 10 min post-administration and throughout the 60 min post-dose assessment period [35].

5. The problem of dosing ROOs for the treatment of BtCP

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 with OTFC and FBT. The reasons for these findings are not clearly explained, considering that the presence of tolerance should suggest a dose proportional to those used for background analgesia. An expected tolerance to adverse effects in patients chronically exposed to opioids has been found, despite serum fentanyl levels as high as 6–8 ng/mL [18]. Dose titration may make the practical use of ROOs difficult in the daily activity, particularly at home or in outpatients. Moreover, using different pieces or spray of ROOs for treating each episode may be time consuming exceeding the spontaneous duration for BtCP which can spontaneously subside, as evidenced by successful placebo-treated patients. Most patients may be reluctant to try the dose and avoid to use these drugs, preferring, at the end, traditional oral dosing of morphine [13].

More information is necessary. For instance, OTFC, given in doses proportional to the basal opioid regimen, has been found quite effective and, above all, safe, avoiding to titrate the dose, which is considered boring for patients, reducing their compliance with the treatment, suggesting that opioids given as needed could be safety used at proportional doses, regardless of the modality of administration. Preliminary and confirmatory surveys have shown the safety of this approach in a large number of patients with no life-threatening adverse effects occurring even in older patients [16,36]. Respiratory depression, which is the most feared adverse effect, has never occurred, and no emergency call was needed [37]. Finally, in a recent survey reproducing a real clinical scenario, patients receiving a mean oral morphine dose of 132 mg, required 800 μg of OTFC after dose titration [10], suggesting that titration process may provide even higher doses that those expected by using proportional doses to basal opioid regimen.

These observations contrast with almost all studies of OTFC. Some data need accurate interpretation. For example, in successful patients the regular rescue dose was a moderate predictor of the effective OTFC dose. In one of the controlled studies of OTFC, a relationship between the OTFC dose and the fixed scheduled opioid had been already found, and regular rescue dose was a moderate predictor of the effective OTFC dose. However, only 19% of the variability of the final dose of OTFC was explained by basal doses of opioids, according to the low-R-square vale of the model used [20]. Finally, recent observations from data pooled from trials of OTFC showed a statistically significant relationship between the breakthrough dose and around-the-clock dose, despite a relevant interindividual variability in patients’ dose requirements for BP [38]. The need to titrate has never been determined on the basis of a real comparison between titration strategy and no titration strategy [39].

It is likely that patients receiving high doses of opioids as basal analgesic regimen will not be candidates for titration with minimal initial doses of ROOs, as they are opioid-tolerant, and the process would be time consuming. Thus, a reliable compromise between the different opinions could be to start with relatively higher doses of ROO in highly-tolerant patients, until more information will be available to settle the question. Future studies should settle this controversial issue.

Conflict of interest statement

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