RESEARCH

Breakthrough Cancer Pain: The Current Pharmacological Management

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ABSTRACT

Background: Breakthrough pain (BTP) is a transient increase in pain that occurs on a background of stable pain. It contributes substantially to the suffering experienced by most cancer patients. The pharmacologic options for management of BTP have been expanded considerably in the past decade. Opioids remain the most effective pharmaceuticals used for the BTP case. In this systematic review we attempted to provide the currently available clinical data about pharmacological treatment for breakthrough cancer pain.

Objective: To evaluate the efficacy of pharmacological treatments for Breakthrough pain

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed for the last ten years (from September 2010 to September 2020. Further potentially relevant studies were identified from reference lists of studies marked for inclusion and relevant reviews. Two review authors independently assessed trial quality and extracted data. We screened the search results and included studies if they met the selection criteria.

Result: We screened 205 publications of which 14 met the inclusion criteria. In total, we analysed data from 2129 participants. Overall, participant with BTP were treated with short acting opioid. Literature searching did not find any published evidence of non opioid drug to treat the BTP. Most adverse effects of the investigated drugs seemed to be moderate.

Conclusion: The findings of this review suggest that rapid onset opioids play significant role for BTP. Future studies may be conducted to explore the efficacy and safety profiles each regimen for patients with certain categories of cancer.

Keywords*:* breakthrough pain; episodic pain; cancer pain; chronic pain; pharmacological treatment

INTRODUCTION

Pain is one of the most common and important symptoms in cancer. It is experienced by almost 50% of patients in all stages of the disease and by more than 70% in advanced and terminal stages.[1] Good pain control can be achieved in most patient with cancer pain but a number of problems can arise in the treatment of cancer pain. This includes the experience of breakthrough pain, which is reported by a considerable majority of cancer patients.[2]

Breakthrough pain (BTP) is defined as transitory exacerbation of pain that occurs in addition to otherwise stable persistent pain.[2] However, there is a lack of consistency in the use of the term ''breakthrough pain'' within clinical practice and also within the medical literature.[3] The European Association for Palliative Care (EAPC) has recommended to replace the term "breakthrough pain" with "episodic pain" or "transient pain" in order to increase the relevance in the clinical setting.[4]

Several BTP treatment trials have been published in the last decade. The aim of this systematic review was to provide an overview on the currently available clinical data about the pharmacological management of breakthrough cancer pain.

Breakthrough pain is experienced by 40-80%[4] of the patients with cancer pain and it is a significant cause of morbidity in this group of patients.[5] Breakthrough pain is different from persistent pain. Persistent pain is defined as pain lasting for 12 hours/day or more,[6] but in addition there are other factors that characterize breakthrough pain – such as temporal features, precipitating events and predictability. Breakthrough pain usually has a quick onset (less than 3 minutes), a severe intensity but brief duration (range 1 to 240 minutes; average of 30 minutes), and an average frequency of 4 episodes a day.[2] Pain with severe intensity but short duration is particularly difficult to treat because currently available oral agents administered at the onset of a breakthrough pain episode may require 30 to 45 minutes to produce an analgesic effect.

The etiology of breakthrough pain may vary.[7] Breakthrough pain (BTP) can be caused by somatic, visceral, or neuropathic pathophysiology, and it is most often related to the same mechanism that causes the persistent pain.[2] Studies show that 67-76% pains are caused by the neoplasm itself, 20-33% episodes are due to the treatment received, whereas up to four percent breakthrough pains are of uncertain etiology.[2,8]

There are significant adverse consequences of untreated BTP for individual patients and their caregivers. Breakthrough pain may contribute substantially to the suffering experienced by cancer patients, limit patient mobility, adversely affect his mood, and inhibit social interactions.[9]

Inadequate management of breakthrough pain may significantly affect the patient's quality of life, interfere with daily activities, interrupt disease-related treatment schedules, and even make it more difficult to treat persistent pain.[10] Treatment costs for cancer patients with breakthrough pain are five times higher than for those without breakthrough pain. This suggests that additional costs associated with optimal assessment and management of breakthrough pain may be offset by cost savings for more

expensive interventions such as physicians' consultations or hospital admissions. Thus effective treatment of breakthrough pain not only is good medical practice, but also cost-effective.[11]

Cancer pain intensity may change significantly throughout the course of the disease. In consequence, the treatment should be dynamic, optimized to the changing needs of an individual and to the effectiveness, and involve ongoing monitoring.[12] More than half of the cancer patients described the analgesic efficacy of breakthrough pain treatment to be inadequate.[13] Several factors such as cultural barriers, educational deficits and health resource utilization contribute to the underassessment and undertreatment of breakthrough pain.[14] Detailed pain diagnosis and assessment play key roles for optimal management of breakthrough pain in cancer.[12] Categorizing pain according to etiology (cancer-related or treatment-related) and type (neuropathic or nociceptive) might be necessary to optimize the treatment.[3] The goal of breakthrough pain treatment is to decrease frequency and intensity with on-demand medications and non-pharmacologic treatment modalities.[15]

The EAPC has developed a new set of guidelines on the management of cancer-related pain in 2012, including statements focussing on the management of breakthrough pain.[16] The EAPC strongly recommended that uncontrolled background pain should be treated with additional doses of immediate-release oral opioid and around-the-clock opioid therapy must be appropriately titrated before potent on-demand opioid analgesics are considered.[12] Oral, immediate-release opioids or application forms with buccal or intranasal fentanyl are recommended to treat breakthrough pain optimally.[16]

METHODS

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed for the last ten years (from September 2010 to September 2020) using the search terms 'breakthrough pain' [Mesh] OR 'episodic pain' [Mesh] AND 'cancer' [Mesh]. Studies were included if they included cancer patients with breakthrough pain. Only publications on randomized or prospective studies were included. Additional articles were identified by searching the reference lists of included papers.

Publications were excluded if they reported on animals, children, non-cancer patients, as well as phamacokinetics studies, ongoing trials, and publications in other languages than English. A spreadsheet was designed for data collection from each included trial. Information on study design, study size by means of patient number, medicines, outcome measures, and adverse reactions were entered (Table 1).

Table 1. Trial with opioids

First Author, Year	Tittle	Design	Patients	Drugs	Outcome result	Adverse effects
Ashburn, M., *et al.* (2011)[23]	The Efficacy and Safety of Fentanyl Buccal Tablet Compared with Immediate-Release Oxycodone for the Management of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Pain	Randomized, open label, cross over	180	FBT or oxycodone	PID_{15} was significantly greater after FBT vs. oxycodone (mean [SD], 0.82 [1.12] vs. 0.60 [0.88]; 95% confidence interval [CI = 0.18, 0.29; P < 0.0001). $SPID_{30}$ and $SPID_{60}$ were greater with FBT than with oxycodone (P < 0.0001 for both measures)	Adverse events with both study drugs were generally typical of opioids
Davies, A., *et al.* (2011)[29]	Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain	Multicenter, randomized, double blind, crossover	106	FPNS or IRMS	FPNS consistently provided relief from pain more rapidly than IRMS; by 10 minutes, there were statistically significant differences in PID scores (P < 0.05)	Only 4.7% of patients withdrew from titration because of adverse effects
Davies, A., *et al.* (2015)[25]	Improved patient functioning after treatment of breakthrough cancer pain: an open-label study of fentanyl buccal tablet in patients with cancer pain	Open label, randomized	330	FBT	Mean (SD) global modified BPI-7S score improved from 39.7 (15.9) at baseline to 31.6 (16.8) for a mean change of −8.6 (95 % confidence interval CI −10.5, −6.7; P<0.0001)	Erythema, swelling, vertigo
Fallon, M., *et al.* (2011)[30]	Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study	Randomized, controlled, double blind, multicenter	110	FPNS or IRMS	Compared with IRMS, FPNS significantly improved mean PID_{15} scores. 57.5% of FPNS-treated episodes significantly demonstrated onset of PI improvement by 5 minutes and 95.7% by 30 minutes.	Vomiting, somnolence, dehydration, nausea, constipation, dizzines, asthenia
Kleeberg, U. R., *et al.* (2015)[26]	Pan-European, open-label dose titration study of fentanyl buccal tablet in patients with breakthrough cancer pain	Open label	442	FBT	Most common effective doses of FBT were 200 µg (39.6%) and 400 µg (26.9%)	Nausea, vomiting, somnolence, dizzines, vertigo, headache, fatigue, dysgeusia, dry mouth

Kongsgaard U.E., *et al.* (2014)[32]	The use of Instanyl® in the treatment of breakthrough pain in cancer patients: a 3-month observational, prospective, cohort study	Prospective, observational, cohort	309	INFS	BPI-SF total score improve significantly at Week 4 (-1 ± 2.1 vs. -10.2 ± 57.9, $P < 0.001$)	No unexpected adverse drug reactions occurred
Kosugi, T., *et al.* (2014)[27]	A randomized, double-blind, placebo-controlled study of fentanyl buccal tablets for breakthrough pain: efficacy and safety in Japanese cancer patients	Randomized, double blind, placebo controlled	101	FBT	The PID% and PR of FBT showed significant improvements compared with that of placebo at 15, 30, and 60 minutes	No serious medical side effects were reported
Mercadante, S., *et al.* (2009)[31]	A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial	Open label, randomized, cross over	139	INFS or OTFC	PID was statistically significantly greater for INFS than OTFC from 5 min post-dose	No serious adverse effects were reported
Mercadante, S., *et al.* (2015)[21]	Fentanyl Buccal Tablet vs. Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Randomized, Crossover, Comparison Study	Randomized, crossover, comparison	81	FBT or OM	Pain intensity significantly changed with both drugs ($P = 0.0005$). A statistical difference between the two groups was observed at T_{15} and T_{30} ($P < 0.0005$). There was a pain decrease of ≥33% in a higher number of episodes treated with FBT in comparison with OM after 15 and 30 minutes ($P < 0.0005$)	No severe adverse effects after study drug administration were observed
Mercadante, S., *et al.* (2016)[22]	Fentanyl Pectin Nasal Spray Versus Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Comparative Study	Randomized, crossover, open label	53	FPNS or OM	Pain intensity significantly changed with both drugs ($P < 0.0005$). Pain significantly decrease ≥33% with FPNS in comparison with OM after 15 and 30 minutes (76.5% vs. 32.8%, and 89% vs. 54.9%, respectively) ($P < 0.0005$)	Nausea-vomiting, drowsiness, confusion
Portenoy, R., *et al.* (2010)[35]	A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain	Multicenter, placebo controlled, double blind, multiple crossover	83	FPNS	Compared with placebo, FPNS significantly improved mean SPID from 10 min ($P < 0.05$) until 60 min ($P < 0.0001$). FPNS significantly improved PI scores as early as 5 min ($P < 0.05$); PID from 10 min ($P < 0.01$); and PR scores from 10 min ($P < 0.001$)	Only 5.3% of patients withdrew from treatment due to adverse effects

Rauck, R., *et al.* (2010)[34]	Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study	Multicenter, randomized, double blind, placebo controlled, multiple crossover	80	FBSF	The leastsquares mean (LSM ± SEM) of the SPID30 was significantly greater for FBSF-treated episodes of breakthrough pain than for placebo-treated episodes (47.9 ± 3.9 versus 38.1 ± 4.3; P = 0.004)	There were no unexpected adverse events or clinically significant safety findings
Takigawa, C., *et al.* (2015)[28]	Breakthrough pain management using fentanyl buccal tablet (FBT) in combination with around-the-clock (ATC) opioids based on the efficacy and safety of FBT, and its relationship with ATC opioids: results from an open-label, multi-center study in Japanese cancer patients with detailed evaluation	Open label, multi center	75	FBT	FBT improve significanty mean PID_{30}, (2.74 ± 1.84 vs. 2.94 ± 1.68; P = 0.02) and $GMPA_{30}$ (1.55 ± 0.78 vs. 1.73 ± 0.07; P = -0.01)	Somnolence, nause, vomiting
Velazquez Rivera, I., *et al.* (2014)[33]	Efficacy of sublingual fentanyl vs. oral morphine for cancer-related breakthrough pain	Prospective, longitudinal, controlled	40	SLF or OM	The mean pain intensity levels were significantly lower with SLF than OM at 3 days (6.0 vs. 6.95; p = 0,001), 7 days (4.15 vs. 6.25, P < 0.001), 15 days (3.45 vs. 5.35, P < 0.001), and 30 days (3.05 vs. 4.45, P < 0.001)	Vomiting, somnolence. One patient discontinued treatment due to side effects.

RESULT

We screened 205 publications of which 14 met the inclusion criteria. In total, we analysed data from 2129 participants. There were some sources of potential bias in the included studies, such as: a lack of description of the methods of blinding and allocation concealment and the small size of the study populations. There was insufficient comparable data for a meta-analysis to be undertaken.

The intermittent use of nonopioid analgesics, such as acetaminophen or nonsteroidal anti-inflammatory medicines (NSAIDs)/cyclooxygenase (COX)-2 inhibitors, may be effective in treating breakthrough pain because of their nociceptive mechanisms. These medicines are also useful for improvement of baseline analgesia, and thus preventing or reducing the occurrence of BTP.[17] However, the use of these agents is complicated by dose-limiting toxicities, an onset of 30 minutes or more, duration of action of several hours, and concerns about renal and cardiovascular morbidity.[18] In addition, our literature search did not find published evidence to support their use in rapid-onset breakthrough pain.

Opioids, particularly oral morphine, have been the mainstay approach in doses proportional to around the clock opioid medication used for baseline analgesia. Normal-release formulations of morphine are the most common on-demand medication.[19] Nonetheless, there are limitations of treating breakthrough pain with oral immediate-release opioid administration forms, such as morphine, oxycodone and hydromorphone, due to the pharmacokinetic characteristics of these opioids. It takes 20 to 30 minutes until therapeutic levels are reached in the bloodstream and 60 minutes until maximum effect is achieved.[20] This does not seem to fit the characteristics of breakthrough pain for the majority of patients.[19]

The literature search identified two randomized trials on oral morphine compared with fentanyl buccal tablets (FBT)[21] or fentanyl pectin nasal spray (FPNS).[22] Both studies demonstrated that oral morphine were significantly inferior (Table 1). One randomized study of oxycodone compared with fentanyl buccal tablets included 180 cancer patients with BTP.[23] Improvement assessed with the Pain Intensity Difference (PID) was superior with fentanyl buccal tablet compared to oxycodone.

Rapid onset opioids (ROO_s) highly lipid-soluble, pure μ-opioid agonists with the onset 5 to 15 minutes.[24] It's pharmacokinetics profile makes ROO_s particularly suitable for the treatment of BTP, with rapid onset, short duration of effect, non-invasive application and easy usage.[18] Our literature search identified 14 trials ROO_s using a range of application forms for transmucosal fentanyl.

Fentany buccal tablets were used in six studies with a total of 1209 participants with BTP. Studies reported heterogenous outcomes, with a tendency towards improved outcomes with FBT in different pain assessment instruments.[21,23,25–28] Two studies compared FBT with oral morphine or oxycodone, with FBT showing significantly superior.[21,23]

In a multicenter, placebo controlled, double blind study with 83 cancer patients, Portenoy *et al.* compared fentanyl pectin nasal spray (FPNS) with placebo using Sum of Pain Intensity Difference (SPID), Pain Relief (PR), and

Pain Intensity Difference (PID) as outcome measure. FPNS significantly improved mean SPID from 10 min until 60 min and PID from 10 min; and PR scores from 10 min. Two studies with a total of 226 patients tested FPNS compared with immediate-release morphine sulfate.[29,30] FPNS significantly relieved pain intensity in both intervention arms, but with significant superior effect with FPNS. FPNS appeared to be superior to oral morphin in another study with 53 participants as measured with a Pain Intensity (PI) scale.[22]

Mercadante *et al.* compared intranasal fentanyl spray (INFS) with oral transmucosal fentanyl citrate (OTFC) in a randomized, opel label study (139 participants).[31] The INFS group demonstrated significant superior analgesia compared to OTFC . A recent prospective cohort study compared INFS with placebo, with INFS showing superior effect.[32]

Our literature search included one prospective study with 40 cancer patient.[33] The study was performed to compare sublingual fentanyl (SLF) with oral morphine over 30 days. Mean pain intensity levels were significantly lower with SLF compared to morphine. In the group treated with SLF no patient reported dissatisfaction with treatment for BTP, but more than a third of the patients treated with oral morphine reported being dissatisfied (31.25%) or very dissatisfied (6.25%).

Fentanyl buccal soluble film (FBSF) was compared to placebo in a randomized study with 80 participants.[34] The leastsquares mean (LSM ± SEM) of the $SPID_{30}$ was significantly greater for FBSF-treated episodes of breakthrough pain compared to placebo-treated episodes.

Overall, most adverse effects of the investigated drugs seemed to be fairly moderate. Adverse events were generally typical for opioids such as nausea, vomiting, somnolence or constipation. Only one patient with sublingual fentanyl discontinued treatment due to side effects.[33]

DISCUSSION

Using a systematic search strategy, a number of studies on the use of pharmacological management of BTP were found in two major literature databases. However, only 14 studies fulfilled the inclusion criteria and were part of this review. The search terms were formulated to cover relevant studies. There was considerable heterogeneity between trials. The trial designs ranged from experimental to observational study. The number of participants varied across studies, including six studies with less than hundred patients well. Half of them investigated intervention comparing with other substances and the rest provided information on effects of single ingredients. Outcome measures across all studies included pain intensity or pain relief.

Regarding to WHO pain ladder, non opioid regiments such as $NSAID_s$ or acetaminophen play a role to treat cancer patient. However, these WHO step 1 analgesics did not seem to play a role in the alleviation of BTP. Our literature search identified not a single study using non opioids for the trearment of BTP in last decade.

Oral opioids such as oxycodone or morphine have traditionally been the mainstay of both chronic pain and BTP

management. Nevertheless, there are limitations using these preparations as the pharmacokinetic and pharmacodynamic profiles do not seem to fit the usual characteristics of BTP. Several trials in this review demonstrated that oral opioids were significantly inferior to rapid onset opioids.[21–23]

The need for more rapid pain relief in BTP has led to growing interest in the use of rapid onset opioids (ROOs). Several trials with ROOs in this review demonstrated their efficacy to treat BTP and their superiority to oral opioid application forms. ROOs produced a bigger analgesic effect and a more rapid onset of action than the comparator or placebo. The findings are in line with the EAPC which recommends ROOs as the treatment of choice for BTCP.[24]

In addition, the results of the literature search indicate that recent research focused on fentany buccal tablets (six studies) for treatment of BTP.

The literature search was restricted to publications in English language, to the last decade of research and to two major databases. There may have been other studies published that we did not find, and indeed regulatory approval for the newer transmucosal application forms might have required more controlled trials than those identified in the literature. However, even considering publication and language bias there was a clear indication of superiority of transmucosal application forms with their more rapid time of onset compared to oral medications.

CONCLUSION

In the last decade pharmacologic options for management of BTP have significantly increased. There is a range of different substances and application forms available by now. There is considerable evidence that rapid onset opioids are an effective treatment of breakthrough pain. Further research is needed to identify the efficacy and safety of these pharmacological interventions, in particular in head-to-head comparisons between these transmucosal application forms, to be able to produce clear evidence-based recommendations for optimal management of BTP.

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