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Review article

The role of rapid onset fentanyl products in the management of breakthrough pain in cancer patients

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ABSTRACT

Breakthrough pain is defined as transient aggravation of pain that arises, despite well controlled or stable baseline pain. It may be preceded by known factors or occur spontaneously. Its prevalence is high and it considerably affects patients' quality of life. Therefore, proper clinical evaluation and treatment is required. Fentanyl transmucosal formulations have become the treatment of choice for spontaneous (idiopathic) episodes because of their rapid onset of action, brief period of analgesia, and easy administration *via* transmucosal routes. All rapid onset fentanyl formulations show better efficacy than placebo or immediate-release opioids administered *via* the oral route, with an onset of analgesia within 15 min. Furthermore, most patients show considerable tolerance of these fentanyl formulations, and severe side effects that can potentially be induced by opioids are rarely observed. However, the treatment of breakthrough pain should be adjusted to suit specific patient requirements. Nevertheless, particularly in predictable bursts of pain and also in spontaneous episodes of breakthrough pain with slowly intensifying pain, immediate-release formulations of opioids may play an important role.

Contents

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Definition, prevalence and classification

Portenoy and Hagen were the first to define breakthrough pain in cancer patients (BTCP). Their definition has evolved into the commonly used and is as follows: transient aggravation of pain that arises, despite well controlled or stable baseline pain. Breakthrough pain may be preceded by known factors, or may occur spontaneously [1]. Thus, end–of–dose pain exacerbations and those that occur during titration of opioids used for the treatment of background pain, can be easily distinguished from BTCP. Flares of pain in cancer patients with an absence of background pain or its poor control, regardless of opioid treatment, have been recently defined as episodic pain [2]. More specifically, BTCP is an episode of pain with an intensity score of over 5 on the Numerical Rating Scale (NRS), generally characterized by a rapid onset (within a few minutes). Its duration is normally limited to within 60 min (mostly 15–30 min). Although approximately 30% of patients diagnosed with BTCP experience more than four episodes a day, it usually occurs between one and four times a day [2,3].

A distinct cause, swift onset, high intensity, and repetitive episodes, distinguish BTCP from other alterations in background pain [4]. The prevalence of BTCP ranges from 33% to 95% and varies in different studies [2,3]. Disparities in the clinical, diagnostic criteria applied, and study settings may affect the reported prevalence [3,5]. Nevertheless, BTCP is a common phenomenon that negatively affects patients' well–being and quality of life (QoL), especially the performance status, physical and psychological functioning. Moreover, treatment of patients diagnosed with BTCP requires increased cost for health care systems.

Two main types of BTCP have been distinguished – spontaneous and incidental. The former is also referred to as idiopathic. It is unpredictable and arises without any known causes. Thus, treatment is only possible when the pain occurs. The incidental episodes can be separated into volitional (which is the result of a voluntary act such as walking) and nonvolitional episodes. Nonvolitional episodes are the result of involuntary acts, such as cough or bowel peristalsis. Another type of BTCP is procedural pain. It is usually caused by therapeutic interventions, such as dressing changes, radiotherapy, and diagnostic procedures, such as lying on an X–ray table.

Almost half of all BTCP episodes comprise the most frequent subtype [6]. To make treatment more effective and individualized, it is essential to distinguish transient pain exacerbations in cancer patients due to differences in pathophysiology, for example bone pain (induced typically by bone metastases), neuropathic pain, and visceral pain [2]. Incident voluntary and procedural pain are usually predictable and may be prevented by treatment. Similar to spontaneous episodes of pain, involuntary incident pain is unpredictable, and can thus be treated when the pain is exacerbated.

Clinical assessment

Effective treatment requires accurate diagnosis, which can only be achieved by thorough examination of the characteristics of an individual's pain, such as the time of onset, duration, intensity, association with background pain, location, type, evoking factors, and impact on patient activity and QoL. Similar to background pain, BTCP can be categorized by pathophysiology as nociceptive, neuropathic, or mixed. Furthermore, the etiopathology of BTCP might be a consequence of oncological treatment and accompanying diseases. Careful pain assessment should also include factors such as former experience of pain, social challenges, cognitive aspects, and psychological disorders. Psychological distress has been strongly associated with the severity of cancer-related pain [6].

The sensation of pain and powers of reasoning can be affected by cognitive skill. Therefore, proper pain assessment should consist of thorough medical history and careful physical examination. According to Davis et al. [1], the use of standard pain questions to assess the clinical nature of BTCP is advisable (Fig. 1). A few tools have been created to assess BTCP, including Breakthrough Pain Questionnaire (BPQ), developed by Portenoy and Hagen [7]; and the Alberta Breakthrough Pain Assessment Tool (ABAT) developed by Hagen et al. [8], which is used mostly for research purposes, owing to its detailed nature and length of 22 pages. Recently, the Breakthrough Pain Assessment Tool (BAT) was successfully validated among cancer patients, and seems to be a promising means for clinicians to assess breakthrough pain [9].

Onset of pain?
Frequency of pain?
Site of pain?
Radiation of pain?
Quality (character) of pain?
Intensity (severity) of pain?
Duration of pain?
Exacerbating factors?
Relieving factors?
Response to analgesics?
Response to other interventions?
Associated symptoms?
Interference with activities of daily living?

Fig. 1. Breakthrough pain questions [1].

Treatment of breakthrough pain

Immediate–release opioid formulations

The role of immediate-release (IR) oral formulations of opioids is limited in the treatment of spontaneous breakthrough pain episodes, mostly because of a time lag between the onset of action and peak analgesic effect. Furthermore, their duration of analgesic effect is often longer than needed [10]. Nevertheless, IR morphine and other short acting opioids, such as oxycodone, hydromorphone, buprenorphine, and methadone can be used in the management of volitional and procedural pain episodes. There is a weak recommendation for use of IR oral formulations of opioids with short half-lives to manage foreseeable episodes of breakthrough pain administered 20–30 min before the causative factor [11]. It is also noteworthy that intravenous or subcutaneous morphine injections provide effective treatment of BTCP episodes, both with a speedy onset of action (quicker *via* the intravenous route); however, this form of therapy is less convenient for patients [12,13]. In a double-blind, randomized, noninferiority trial, subjects expressed a stronger preference for the sublingual route of administration (93%) than the subcutaneous [14]

Fentanyl

Fentanyl is a synthetic opioid analgesic, which exerts its effects mainly on the μ-opioid receptor. It is about 75–100 times more powerful than morphine. Fentanyl is a lipid-soluble drug, with high potency and low molecular weight. Therefore, it is typically well distributed within the tissues. It crosses the blood-brain barrier more quickly than morphine; thus its analgesic effect is strong and mostly central, and side effects related to its peripheral mode of action are less severe. These side-effects are generally evident in the gastrointestinal tract, and include opioid-induced constipation, nausea, and vomiting [15]. Fentanyl blood concentrations between 0.3 and 1.2 ng/ml usually provide sufficient

analgesia, whereas blood levels of 10–20 ng/ml result in anesthesia and deep respiratory depression [16].

Fentanyl is metabolized by cytochrome enzymes into inactive metabolites; therefore, any drug that induces or inhibits cytochrome P-450 can affect its metabolic conversion [17]. Co-administration of fentanyl with other drugs that inhibit CYP3A4 (Table 1) could increase fentanyl concentrations, potentiate analgesia and pose an increased risk of side effects, potentially leading to sedation and respiratory depression. Conversely, concurrent administration of fentanyl with drugs that induce CYP3A4 (Table 1) may reduce the levels of fentanyl in the blood and attenuate analgesic effects. Withdrawal of drugs that induce CYP3A4 may have similar effects (increased fentanyl concentrations) as co-administration of CYP3A4 inhibitors. If possible, the concurrent use of moderate or strong CYP3A4 inhibitors and inducers should be avoided. Otherwise, close monitoring of the patient and potential dose adjustments may be required when concurrent use of drugs affecting CYP3A4, especially the inhibitors, is unavoidable [18].

Fentanyl transmucosal formulations

Owing to its fast onset of analgesic action, short duration, and easy dosing through transmucosal routes, fentanyl has now become a treatment of choice for spontaneous BTCP episodes [4]. Rapid onset formulations of fentanyl, such as oral transmucosal fentanyl citrate, fentanyl buccal tablets, sublingual fentanyl, intranasal fentanyl spray, fentanyl–pectin nasal spray, and fentanyl buccal soluble film, have been more effective than a placebo or IR opioids administered via an oral route [19], with an onset of action of 15 min or less [20–23]. Nevertheless, according to The Summary of Product Characteristics, the use of rapid-onset formulations of fentanyl is indicated for patients who are on a daily dose regimen not lower than: 60 mg of oral morphine, 25 μg/h of transdermal fentanyl, 30 mg oxycodone, 8 mg of oral hydromorphone, or an equianalgesic dose of another opioid for at least a week [24]. This regulation limits the wider use of transmucosal formulations of fentanyl.

Rapid-onset formulations of fentanyl may be administrated through the oral or nasal mucosa, which differ slightly from each other. The mucosa on the internal wall of the cheek is five times thicker than the sublingual mucosa; thus, absorption is prolonged. The oral route of administration causes a certain degree of dissolution of the drug in the saliva; thus, some of the drug is ingested. Regarding buccal tablets, 50% of the drug is absorbed by the mucosa and 50% is swallowed. Nevertheless, the bioavailability of orally administered fentanyl accounts for only 15%, owing to the strong hepatic first pass effect – it is mostly modified by CYP3A4-mediated N-dealkylation to norfentanyl. Less than 1% is converted to despropionylfentanyl, hydroxyfentanyl, and hydroxynorfentanyl, which are inactive metabolites [25,26]. Nevertheless, fentanyl formulations are generally designed to prevent swallowing of the drug.

Buccal tablets

Fentanyl buccal tablet uses OraVescent technology that initiates a process in which carbon dioxide is released as the tablet makes contact with saliva. The reaction is associated with temporary pH alterations, which improve solubility and membrane permeation of fentanyl across the buccal mucosa [27]. The bioavailability of fentanyl buccal tablets and fentanyl sublingual tablets has been calculated to be 65% and 54%, respectively.

Table 1
Cytochrome P-450 3A4 (CYP 3A4) inhibitors and inducers.

CYP 3A4 inhibitors	CYP 3A4 inducers
Macrolides	Barbiturates
Azole antifungals	Anti-epileptic drugs
Anti-emetics	Psychotropic drugs
Calcium channel blockers	Particular antiviral drugs
Some protease inhibitors	Some antibiotics – nafcillin, rifampicin, rifabutin
Antidepressants	
Antacids	

Buccal soluble film

Fentanyl buccal soluble film is applied to the inside of the cheek. The drug consists of an active layer, which adheres to the mucosa, and an inactive layer, the role of which is to prevent diffusion the drug into the oral cavity [18].

Oral transmucosal lozenge

In this formulation, fentanyl is embedded within a sweetened matrix on a small stick, which facilitates placement of the drug between the cheek and gums, and enables repeated upward and downward moves to achieve optimal absorption.

Sublingual tablets

Fentanyl sublingual tablets consist of controlled-release drug particles connected to a more resistant carrier constituent. When the drug is dissolved, it is immediately released, leaving the carrier layer adhered to the mucosa [28]. Hypofunction of the salivary gland may reduce the efficacy of sublingual tablets; however, this may be prevented by moistening the oral cavity prior to drug administration [29].

Fentanyl sublingual spray

Fentanyl sublingual spray is applied under the tongue. The volume of a single dose is 0.1 mL. The bioavailability of this formula is relatively high (approximately 76%) [30].

Nasal spray

The volume of the nasal mucosa cavity ranges from 15 to 20 ml, with an area of 150–180 cm^2. Blood flow reaches higher values within the nasal cavity than in the muscle, brain, or liver. Because the nasal cavity is directly connected to the brain, the administration of drugs through the olfactory route can be effectively achieved with relatively lower doses. The bioavailability of fentanyl via the intranasal route reaches approximately 70% [31]. The recommended drug volume is 0.15 ml in one or both nostrils, which prevents diffusion into the oral cavity and subsequent swallowing. Thus, penetration enhancers are necessary to compensate for the volume restrictions, in addition to substances like polymers, gels, polysaccharides, or pectin to improve absorption [32]. The half–life of intranasal fentanyl is shorter than that of transmucosal fentanyl [33]. Two formulas of nasal fentanyl spray are currently available: an aqueous clear, colorless solution of fentanyl citrate, and the PecSys technology – based fentanyl citrate (Pecfent). After administration of the latter, a gel is formed as a result of co-acting calcium ions secreted by the nasal mucosa and pectin. Fentanyl is subsequently released from the gel and absorbed *via* the nasal mucosa [34]. A new formulation of intrapulmonary fentanyl, Taifun, was developed for the treatment of BTCP. A multicenter, randomized, open-label, phase III safety study was completed [31].

General recommendations regarding rapid-onset fentanyl formulations

It must be emphasized that each formulation of rapid-onset fentanyl should be carefully titrated to an optimal dosage that provides satisfactory analgesia and acceptable adverse effects. Moreover, because of the considerable differences in absorption profiles and bioavailability among various products, switching between other fentanyl-containing products cannot be achieved on a mcg-per-mcg basis, and the dose should always be titrated (Table 2) [35]. The titration process should occur whenever

Table 2
Pharmacokinetic data for fentanyl products [35].

Route of administration	Sublingual (Vellofent)	Buccal (Effentora)	Intranasal (Instanyl)	Intranasal (Pecfent)
Bioavailability (%)	70	65	89	60
Time to reach maximum concentration (min)	50–90	47	9–15	15–21
Half–life (h)	12	22	3–4	15–25
Onset of action (min)	6–10	10–15	5–10	5–10

treatment commences, the route of administration is changed, or even if a different fentanyl formulation is administered *via* the same route (for example a water-based nasal spray *vs.* a pectin-based nasal spray). Titration of rapid-onset fentanyl formulations is also necessary in patients who have undergone a significant change in background pain management, such as in the dose, route of administration, or choice of opioid administered.

Adverse effects and misuse

In the vast majority of previous research, rapid-onset fentanyl formulas showed enhanced efficacy and quicker onset of action in comparison to a placebo and morphine [36]. In addition, fentanyl formulas have been generally well tolerated [28,37,38]. However, one 16-week reported that a quarter of the subjects enrolled in the study experienced adverse effects [36]. The most common of these include dizziness, sedation, nausea, and constipation. Nasal discomfort and irritation are the most frequent local effects.

Records on the long-lasting effects of intranasal opioids are limited. However, some reports of the occurrence of sinus congestion, epistaxis, and pharyngitis exist [28]. Regarding the administration of buccal tablets, site reactions have been reported in approximately 10% of the patients evaluated. Among those reactions, paresthesia, ulceration, and bleeding were the most common [39].

Following reports of severe overdoses and deaths associated with the administration of buccal tables, safety warnings have been implemented. Extreme caution should be exercised in the prescription, patient education, storage, and disposal of such drugs [40]. Previous research has highlighted misuse of fentanyl nasal spray. One report revealed that among 272 eligible questionnaire responses, 95% noted misuse [41]. Out of 160 patients with cancer, 94% admitted misuse; 76% conceded one or more instances of misuse associated with an indication/contraindication, and almost 86% used an inadequate dosage of the drug. Furthermore, 21 patients (15 with cancer, and six without) used the drug to achieve psychical contentment [41].

Summary

Breakthrough pain is a common symptom among patients with cancer, which can considerably affect their normal physical and psychological functioning, well-being, and QoL. Therefore, the proper clinical evaluation and management of BTCP is crucial for the well-being of both patients and caregivers. Rapid-onset fentanyl products significantly contribute to the effective management of BTCP, particularly spontaneous and involuntary episodes. Future studies may explore the use of rapid-onset fentanyl products in the treatment of predictable episodes of breakthrough (volitional and procedural) pain, and compare different routes of administration, taking the patients' QoL into account.

Conflict of interest

Authors reports no conflict of interest in this work.

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