Novel formulations and routes of administration for opioids in the treatment of breakthrough pain

The interest for assessment and treatment of breakthrough pain (BTP) has been increasing, probably due to a growing attentiveness towards the problems associated with BTP, but also encouraged by the development of novel pharmaceutical formulations specially intended for the treatment of BTP. BTP can be described as ‘an episodic increase in pain intensity over a stable and adequately managed baseline pain’. BTP is a heterogeneous condition, and the most optimal treatment is influenced by a number of different pain-related factors, including the etiology of the pain (cancer or noncancer pain), the pathophysiology of the pain (nociceptive or neuropathic), the characteristics of the pain (type, frequency, and duration). Furthermore, it will depend on various patient-related conditions, such as stage of disease, performance status, compliance and the acceptability of different interventions. Treatment of BTP should be individualized to fit the special needs of the single individual patient. The optimal opioid formulation for the treatment of BTP possesses a pharmacological profile that closely mirrors the intensity–time profile of the BTP episode. Thus, a short onset of action (to relieve pain as quickly as possible) and a relatively short duration of action (to prevent side effects) are preferable. Factors that influence the pharmacological profile of a drug are the physicochemical, pharmaco-kinetic and -dynamic properties of the drug substance, the pharmaceutical formulation and the route of administration. To date, only few formulations specially designed and intended for the treatment of BTP are available. However, many are currently under development and clinical assessment, and some of these are very close to reaching the market.

KEYWORDS: administration routes breakthrough pain opioids pharmaceutical formulations

During the past 10 years, the interest in the phenomenon of breakthrough pain (BTP) has been increasing, probably due to a growing attentiveness towards the problems associated with BTP, but also encouraged by the development of novel pharmaceutical formulations specially intended for the treatment of BTP. The term ‘breakthrough pain’ is the more commonly used, but other terms such as ‘episodic pain’, ‘pain flare’, ‘transitory pain’ or ‘transient pain’ are also used in the literature [1].

Definition
Breakthrough pain can be described as ‘an episodic increase in pain intensity over a stable and adequately managed baseline pain’ [2]. Recently, the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland (APM) has suggested the following definition: “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].

As can be perceived by this definition of BTP, its diagnosis relies on the co-existence of an adequately controlled background or baseline pain [4].

Classification, etiology & pathophysiology
Breakthrough pain can be classified according to the causes of the pain. Spontaneous pain occurs unexpectedly, and with no known trigger factor, which renders it to be unpredictable, and thus difficult for the patient to deal with.

Incident pain can be related to a physiological function or to a special event. Incident pain is subclassified into a further three types: volitional pain, which is initiated by a voluntary action; nonvolitional pain, which is initiated by an involuntary action; and procedural pain, which is caused by a therapeutic intervention.

End-of-dose failure is due to a declining analgesia at the end of a dosing interval. End-of-dose failure is not regarded as BTP by some, but merely as an insufficiently treated background...
Breakthrough pain is a heterogeneous condition, and the most optimal treatment is influenced by a number of different pain-related factors, including the etiology of the pain (cancer or noncancer pain), the pathophysiology of the pain (nociceptive or neuropathic) and the characteristics of the pain (type, frequency and duration). Furthermore, it will depend on various patient-related conditions such as stage of disease, performance status, compliance and the acceptability of different interventions. Treatment of BTP should be individualized to fit the special needs of the single individual patient.

The ‘end-of-dose failure’ episodes can be treated by means of dose adjustment of the sustained-release formulation for basal pain treatment.

The core treatment of the spontaneous pain and incident pain is the use of ‘rescue’ medication. Rescue medication is taken as needed, rather than on a regular basis.

When treating incident pain of the volitional type and the procedural pain, the ‘rescue’ medication can be taken before the relevant precipitant of the pain; when treating the spontaneous and the nonvolitional types of BTP, rescue medication should be taken at the onset of the BTP episode. The latter are inherently difficult to treat sufficiently, because the immediate-release oral opioid analogs, which are the most commonly used, have a delayed onset of action [15]. Alternative routes of administration might be more suitable in this situation: subcutaneous administration of opioids can be used in hospitalized patients and if a noninvasive route is preferred; a few oral transmucosal fentanyl products are available; and further oral transmucosal (buccal and sublingual), intranasal, intrapulmonary and subcutaneous products are in development, some of which will soon reach the market.

The optimal opioid formulation for the treatment of BTP possesses a pharmacological profile that closely mirrors the intensity–time profile of the BTP episode. Thus, a short onset of action (to relieve pain as quickly as possible) and a relatively short duration of action (to prevent side effects) are preferable. However, a number of other factors, such as convenience, acceptability, tolerability and minimization of side effects should be taken in account when choosing the ideal formulation for the individual patient.

**Administration routes**

Time to onset of action is determined by how rapidly the opioid reaches the site of action within the brain, and the duration of action is determined by how rapidly the opioid disappears from the brain. The physicochemical properties of the opioids will influence the absorption rate. Thus, lipophilic opioids such as fentanyl and buprenorphine, which are more rapidly absorbed and cross the blood–brain barrier more readily than
hydrophilic opioids (morphine and oxycodone) are the most attractive for the treatment of BTP, since they provide a fast onset of action. With respect to reduced the duration of action, opioids with short half-lives such as fentanyl and morphine are more attractive than opioids with long half-lives such as buprenorphine and methadone.

The route of administration also influences absorption rate, and thus how rapidly the opioid reaches the brain. Opioids given by the intravenous route bypass the absorption phase, and thus reach the brain most rapidly, followed by opioids given by the subcutaneous, pulmonary, nasal, oral transmucosal (sublingual and buccal), oral, rectal and transdermal routes. Thus, of the noninvasive routes, the pulmonary and nasal routes are considered to be the ones leading to the fastest onset of action. Only the routes that are actually used or considered to have potential for opioids for BTP pain will be discussed in further detail.

### Subcutaneous

The subcutaneous route is commonly used in palliative care [16]. The route is associated with a high and predictable bioavailability and a rapid onset of action—within 10 min depending on the actual opioid. Subcutaneous rescue medication requires special equipment, for example, patient-controlled analgesia devices, and is mostly used in hospitals, hospices and in palliative homecare settings.

A ‘pain pen’, which can be handled by the patients themselves like the injection pens for insulin, for subcutaneous administration of opioids (morphine, hydromorphone and sufentanil) has been tested in 58 cancer patients with BTP. The efficacy was rated as good in 49 patients, moderate in eight patients, and not noticeable in one patient [17].

Results from an acceptability study have shown that the subcutaneous route has an acceptability of 52% when the pain is mild-to-moderate in intensity, and 87% when the pain is severe. The main objection to the subcutaneous route was dislike of injections [18].

### Transdermal

At present, no delivery systems for the transdermal route are available for treatment of BTP. After application of a conventional patch, the absorption through the skin proceeds as a passive diffusion process, which is far too slow to be attractive for the treatment of BTP. However, a new transdermal delivery system using iontophoretic technology has been developed for the treatment of postoperative pain. Fentanyl is delivered rapidly from the reservoir in the patch through the skin by means of a direct electrical current. The system delivers a fixed 40 µg bolus dose over a period of 10 min, when activated by the patient, and has a lock-out period of 10 min [19]. To be useful for the treatment of BTP, the system should be further developed and be able to deliver different doses. The system has been compared with morphine administered by conventional patient-controlled analgesia in a postoperative setting. Results from the study suggest that the system is effective in the population studied, and support a consistent safety and efficacy profile of fentanyl [20]. The pharmaceutical and pharmacokinetic aspects and clinical applications of the system have recently been reviewed [21]. However, the system was withdrawn from the market in September 2008.

### Oral

The oral route has numerous advantages—it is convenient to patients and a large variety of both opioids and formulations (tablet, capsules and solutions) are available. The disadvantages, such as slow onset of action and relative long duration of action, make the route less attractive for treatment of spontaneous and the nonvolitional type of incident pain; since the clinical/pharmacokinetic profile does not match the temporal profile of these BTP types.

In the case of procedural pain or volitional incident pain, oral opioids can be given in advance of the precipitating pain. If treating spontaneous and the nonvolitional type of incident pain with oral opioids, formulations from which the opioids are rapidly released should be preferred. Using an oral solution, the opioid is already dissolved when reaching the gastro-intestinal (GI) tract, and thus instantly available for absorption. Recently, tablets with an intended rapid disintegration have been developed; however, so far these types of tablets are only available containing paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drug substances.

Results from an acceptability study showed that 97% of patients stated that the oral route is acceptable when the pain is mild-to-moderate in intensity, whilst 88% stated that the route is acceptable when the pain is severe. The only objection to the oral route was the slow time to onset of action (30 min) [18].
Oral transmucosal

The oral transmucosal route comprises buccal and sublingual administration, and offers some advantages over the oral route. For example, it is suitable for patients with dysphagia, nausea and vomiting; first-pass metabolism is avoided; and with lipophilic opioids such as fentanyl, which readily crosses the epithelial lining of the oral mucosa, a fast absorption and, hence, a fast onset of action can be achieved. Despite these advantages, only a few formulations have so far reached the market, most likely due to the pharmaceutical challenges needed to develop suitable formulations.

The area available for absorption (200 cm²) is small compared with the area available in the GI tract (350,000 cm²) and furthermore, the oral mucosa consist of multiple layer epithelial cells, whereas in the GI tract the epithelial cells consist of only one layer. Thus, if a sufficient amount of drug is to be absorbed, only highly potent and lipophilic drug substances are potential candidates. However, drug substances should also possess a certain hydrophilicity in order to dissolve in saliva; a prerequisite for later being absorbed. Hence, a balance must be found between good dissolution (implying a large ionized fraction of drug) and a large unionized fraction of drug (implying high lipophilicity and good absorption).

The thickness of the mucosa varies in different parts of the oral cavity – the buccal mucosa is approximately three-times as thick (500–600 µm) as the sublingual mucosa (100–200 µm), which means that the lag time for permeation of the epithelial cells in the sublingual area is shorter than in the buccal area. Thus, the sublingual route will theoretically give rise to a faster absorption than the buccal route. However, in the context of bioavailability, the buccal route might be more reliable than the sublingual route, since the salivation rate and, hence, risk of swallowing, is less likely to influence the absorption.

Formulations used for sublingual and buccal administration should be able to disintegrate and release the opioid in the oral cavity, which in this context represents a special problem, since one of the main side effects of opioids is dryness of the mouth. Saliva is an important factor, as it is maintaining the pH value in the oral cavity, which affects the ionized proportion of the opioid and, therefore, its overall lipophilicity. In addition, saliva is needed both for the disintegration of the formulation and for dissolving the opioid. On the other hand, excess of saliva will cause a higher fraction of the dissolved opioid to be swallowed and exposed to first-pass metabolism, which will lead to both a high intra- and inter-individual variation in the bioavailability.

Thus, formulations which only need an extremely small quantity of liquid to disintegrate and which do not promote salivation, are advantageous in order to achieve a fast and consistent absorption.

Currently, two opioid products are licensed for transmucosal administration: fentanyl for buccal administration and buprenorphine for sublingual administration. The fentanyl buccal lozenges is licensed for treatment of BTP, and the onset of action has been reported to be 5–10 min, with a peak effect occurring within 20–30 min. It will be discussed in further detail later on. The buprenorphine sublingual tablet is licensed for treatment of moderate-to-severe pain in general, and mainly used for management of background pain, but is also used for BTP in patients prescribed a buprenorphine transdermal patch for background pain, although no studies on the efficacy in BTP pain have been published. The time to onset of action is 15–30 min, peak effect occurs after 60–120 min, and the duration of action is 8 h.

New oral transmucosal preparations of fentanyl for the treatment of BTP, including effervescent tablets for buccal administration and a muco-adhesive tablet for sublingual use, are under development. These will be discussed in detail later on.

Results from an acceptability study showed that the sublingual route is accepted by 63% of patients who stated that the oral route is acceptable when the pain is mild-to-moderate in intensity, whilst 75% stated that the route is acceptable when the pain is severe. Slow action and fear of bad taste and nausea were the main objections to the sublingual route. The transmucosal route is accepted by 44% of patients who stated that the oral route is acceptable when the pain is mild-to-moderate in intensity, whilst 63% stated that the route is acceptable when the pain is severe. Localized pain, fear of bad taste/nausea and being regarded as ‘child-like’ were mentioned as objections to the transmucosal route.

Intranasal

Like the oral transmucosal route, the intranasal route is noninvasive and offers some advantages over the oral route: it is suitable for patients with dysphagia, nausea and vomiting; and first-pass metabolism is avoided. The epithelial cells lining the nasal cavity are, in contrast to the cells in the oral cavity, highly permeable, resulting in...
a fast absorption and also allowing more hydrophilic opioids to traverse. The area available for absorption is approximately 150 cm². The nasal cavity can accommodate volumes of 150–200 µl in each nostril, and excess will be drained to the esophagus. The turnover of the nasal mucus layer occurs rather quickly, leaving only 15 min for absorption [25].

The intranasal route seems easy; however, patients might require initial instructions on how to handle the delivery device in order for the drug to reach the absorptive area of the nasal cavity. Opioids can be delivered by conventional spray bottles, or by delivery devices that increase the deposition of the spray into the deeper parts of the nasal cavity. In order to improve safety, the spray devices might be equipped with a lock-out facility.

Disadvantages of the intranasal route relate to local side effects such as irritation and inappropriateness in patients with local disease of the nose. Since only small volumes can be accommodated in the nasal cavity, the opioids used need to be highly soluble in water.

Results from pharmacokinetic studies of intranasally administered fentanyl in volunteers [26–28] have shown that fentanyl is rapidly and almost completely absorbed from the nasal cavity. In a study where fentanyl was administered in solution with different pH values, it was found that fentanyl was rapidly absorbed through the nasal mucosa, with $T_{\text{max}}$ values of 5–40 (mean) and 4–11 (median) min [26]. In a study using a fentanyl formulation specifically designed for intranasal administration with an appropriate (100 µl) volume, fentanyl doses of 75, 100, 150 and 200 µg administered either intranasally using an intranasal fentanyl spray or intravenously displayed linear dose relationships, bioavailability was close to 100% and the time to maximal plasma concentration was estimated to be 12.8 min [27].

Whereas two of these studies analyzed venous blood samples [26,27], one study [28] analyzed both arterial and venous blood samples, and a significant arterio-venous difference was seen. This study reported a $T_{\text{max}}$ of 11.6 min estimated from venous blood samples – the arterial $T_{\text{max}}$ was found to be 5 min shorter than the venous.

Intranasal administration of fentanyl has been associated with minimal local irritation in the nasal cavity [25], and has been used for premedication and acute pain in children [29,30] postoperative pain [31–37] and procedural wound care pain [38–40].

Results from explorative studies of nasal administration of different opioids for the treatment of BTP have been reported. In most studies time to onset of action was 5–10 min [41–44].

Preparations for nasal administration of fentanyl are currently undergoing clinical trials and might soon be licensed. These will be discussed in more detail later on.

Results from an acceptability study showed that the intranasal route is accepted by 50% of patients who stated that the oral route is acceptable when the pain is mild-to-moderate in intensity, whilst 68% stated that the route is acceptable when the pain is severe. Localized pain, fear of bad taste, difficulties in administration, and catching in back of the throat were mentioned as objections to the intranasal route [18].

### Intrapulmonary

The lungs have a very large surface area available for absorption and, in addition, the epithelial cells are highly permeable and the blood perfusion is very high. These three factors all favor a rapid absorption of drugs. Thus, the route might be attractive for the treatment of BTP because it offers the potential of a very fast absorption rate.

The route requires use of special delivery devices. There are two possible mechanisms for delivery of drugs to the lungs, either via an aerosol or by direct instillation. The aerosol is the most commonly used and consists of finely divided liquid droplets or solid particles in a gaseous suspension. The main types of devices used at present to produce aerosols are nebulizers, metered-dose inhalers and dry powder inhalers, although development of the technology is causing the distinction between these devices to become blurred.

Like the intranasal route, the intrapulmonary route is noninvasive; however, it might seem difficult for the patients, since they require initial instructions on the inhalation technique and handling of the device in order to assure that the drugs reaches the distal parts of the lungs.

Nebulized opioids have been used for treatment of apnea [44], but only few papers have described its use for the treatment of BTP.

A case report on two patients who received intrapulmonary fentanyl and experienced good pain relief within 15 min has been reported [45].

Recently, results on the development of a commercial dry powder inhaler containing fentanyl, TAIFUN®, have shown that it is possible to achieve a rapid and reliable absorption of fentanyl ($T_{\text{max}} = 1$ min) after intrapulmonary administration [46]. Results from a Phase II study...
of the same preparation showed the median time to significant pain relief for patients was 5.2 min. This result was statistically significant versus placebo (p = 0.007) [101].

Results from an acceptability study showed that the intrapulmonary route is accepted by 60% of patients who stated that the oral route is acceptable when the pain is mild-to-moderate in intensity, whilst 75% stated that the route is acceptable when the pain is severe. Previous bad experience, localized pain, fear of bad taste/nausea, difficulties in administration, and catching the back of the throat were mentioned as objections to the route [18].

Formulations intended for treatment of BTP
This section will deal with preparations intended for treatment of BTP, and that are currently on the market or very close to reaching the market.

Actiq®
Actiq® (Cephalon Inc., PA, USA) was the first oral transmucosal fentanyl citrate (OTFC) delivery system to be approved for cancer-related BTP in 1998. Generic products of the OTFC are now available.

OTFC is a lozenge attached to a plastic stick (lollipop). The lozenge contains glucose, and thus is not suitable for patients suffering from diabetes. When the lollipop is rubbed against the oral mucous membrane inside the cheek the lozenge is dissolved by the saliva and fentanyl is subsequently released, dissolved in saliva and finally absorbed through the buccal mucosa.

The lozenges normally dissolve within 10–15 min; however, the method requires a considerable degree of psychomotor performance of the patient and the prolonged rub-in phase of the hyperosmolar fentanyl solution may cause mucosal irritation. In addition, many cancer patients suffer from xerostomia, causing a prolonged or even unsuccessful dissolution of the lozenge.

The absolute bioavailability of fentanyl after administration of OTFC is approximately 50%. Approximately 25% is rapidly absorbed through the buccal mucosa, and the remaining 75% is more slowly absorbed from the GI tract after being swallowed, and subsequently first-pass metabolized in the liver [47]. Results from pharmacokinetic studies in volunteers have shown linearity between dose and bioavailability in the therapeutic dose range [48].

Results from controlled clinical studies have confirmed the efficacy, safety and tolerability of oral transmucosal administration of fentanyl, which was shown to provide considerably better and quicker (15–60 min) pain relief than orally administered morphine [2,48–53] but the onset time to analgesia seems longer compared with intravenously administered morphine [54]. When assessed using global rating scales or quality-of-life scores, the OTFC was considerably better than oral opioids in breakthrough episodes in noncancer pain patients [55].

Results from a recent study in hospice inpatients using OTFC, oral morphine, oxycodone, hydromorphone or methadone demonstrated no difference in efficacy between morphine, oxycodone and hydromorphone. However, OTFC showed a more rapid onset of action than the oral BTP opioids, supporting the notion that patients who are able to handle and willing to use the OTFC will achieve a faster onset of analgesia than with conventional oral BTP opioids [55].

The pharmacological and clinical aspects of OTFC have recently been subjected to review [56,57].

Fentora® (Effentora™)
Fentora® (Effentora™ [Cephalon Inc., PA, USA]) is a fentanyl buccal tablet (FBT) and belongs to the second-generation highly soluble fentanyl preparations for oral transmucosal administration. It is formulated using an enhanced effervescent absorption technology (OraVescent© [Cima Labs Inc., MN, USA]) [58]. FBT contains citric acid sodium bicarbonate and sodium carbonate. When placed in the buccal cavity the tablet reacts with saliva, resulting in an effervescent reaction, where citric acid and sodium bicarbonate forms carbonic acid. The reaction causes a decrease in pH, which enhances the dissolution of fentanyl citrate by increasing the proportion of ionized fentanyl. Because of the low pH, the carbonic acid dissociates into carbon dioxide and water and the carbon dioxide is released, resulting in the effervescent. The loss of carbon dioxide results in an increase in pH, which in turn increases the proportion of unionized fentanyl, thus favoring rapid absorption of fentanyl through the buccal mucosa. The pH cycle occurs repeatedly until the tablet is completely disintegrated and the fentanyl dissolved. The release of carbon dioxide may additionally enhance the absorption of fentanyl by reducing the thickness of the hydrophilic mucus layer covering the epithelial cells in the membrane. Results from a pharmacokinetics study in healthy volunteers showed that the absorption of fentanyl in fact
occurred more rapidly after administration of FBT compared with noneffervescent FBT and OTCF [59].

The absolute bioavailability of fentanyl after administration of FBT was found to be 65%. Approximately half of the dose administered (48%) is absorbed rapidly from the buccal mucosa; the remaining half (52%) is swallowed and absorbed from the GI tract, and subsequently subjected to first-pass metabolism in the liver [60]. The maximal plasma concentrations were attained at 52 and 50 min after single and multiple dose administration, respectively [61]. Judged from the maximal plasma concentrations of fentanyl seen following single dose (0.88 ng/ml) and multiple dose (1.77 ng/ml), fentanyl accumulates following multiple dosing; however, after reaching steady state (within 5 days), no further accumulation was seen [64].

Results from pharmacokinetic studies in volunteers have shown linearity between dose and bioavailability in the therapeutic dose range [62–64]. Furthermore, the rate and extent of absorption was not affected by dwell time (period from application of FBT and its complete disintegration) [65] or by the application site (buccal vs sublingual) [66]. Results from a pharmacokinetic study in cancer patients showed that mild oral mucositis did not affect the absorption of fentanyl; neither the extent nor the rate [67].

Results from two placebo-controlled clinical studies in cancer patients with BTP have confirmed the therapeutic efficacy and safety of fentanyl after administration of FBT [68,69]. A significant improvement in pain intensity was provided from 15 min and throughout the 1-h assessment period [68]. In the second study, improvements in pain intensity from baseline were achieved after 10 min, and this was maintained during the 2-h assessment period [70].

Results from a long-term open-label safety study in patients with chronic cancer pain showed that FBT was generally well tolerated and had a favorable safety profile similar to that observed in the short-term studies [69].

The efficacy of BTP has also been studied in patients with BTP from noncancer-related chronic pain [71,72]. In both the population of patients with low back pain and the population of patients with neuropathic pain, approximately 80% identified an effective dose of FBT for their BTP, time to onset of action was 10–15 min and pain relief was maintained during the 2-h assessment period.

The pharmacological and clinical aspects of FBT have recently been subjected to reviews [73–76].

Abstral™
Like FBT the Abstral™ sublingual fentanyl (SLF) preparation belongs to the second-generation highly soluble fentanyl preparations for transmucosal administration. The SLF preparation consists of a small tablet containing micronized fentanyl, which is adhered to the surface of water-soluble microspheres (mannitol) and the muco-adhesive agent croscarmellose sodium. Following application of the tablet under the tongue, the tablet rapidly disintegrates and releases fentanyl, which subsequently dissolves in saliva and is absorbed through the sublingual mucosa. The used of micronized (ultra-small particles) fentanyl promotes the dissolution of fentanyl in the saliva, and retention of the fentanyl microspheres on the mucosa, reducing the risk of swallowing the drug, and thus increasing the amount of fentanyl being absorbed through the oral mucosa [77].

Pharmacokinetic data obtained in cancer patients after administration of 100, 200 and 400 µg of fentanyl at different occasions indicate rapid transmucosal absorption, with maximum fentanyl plasma concentration being achieved within 1 h for all three doses. The first measurable value for plasma fentanyl was obtained within approximately 10 min after administration of SLF.

Dose-proportionality of fentanyl, with respect to extent of absorption (AUC and C_{max}) over the dose range 100–400 µg, was observed. Dose-normalized AUC values were similar across the dose range, and C_{max} increased fourfold from 0.24 ng/ml with the 100 µg dose to 0.96 ng/ml with the 400 µg dose, indicating that the total exposure to fentanyl was proportional to the administered dose [78]. Results from a single-dose pharmacokinetic study in Japanese and Caucasian healthy volunteers also showed similar pharmacokinetics, with rapid absorption and dose proportionality and no difference between Japanese and Caucasian subjects [79].

In accordance with the rapid absorption seen in the pharmacokinetics studies, preliminary reports of clinical data indicate fast onset of analgesia and good tolerability. In a double-blind, randomized, placebo-controlled, four-way cross-over study in cancer patients, improvements in pain intensity were seen to occur within 5 min after SFL administration. Clinically effective improvements were seen with SLF 100 and 200 µg doses; however the overall improvement in pain intensity was significantly superior with SLF 400 µg compared with placebo, the effect being evident at all time points assessed and becoming statistically
significant from 15 min after administration [80]. Results from an interim analysis of a double-blind, randomized, placebo-controlled study in cancer patients showed a statistically significant improvement in summed pain intensity difference at 30 min seen with the SLF preparation compared with placebo. With regards to pain intensity difference and pain relief, a statistically significant better performance was seen from 10 min in the SLF group compared with the placebo group. SLF was well-tolerated, with serious adverse events reflecting the underlying disease state and physical condition of the patients, rather than the study medication (SLF) [81].

Instanyl®

Instanyl® (Nycomed, Zurich, Switzerland) intranasal fentanyl spray (INFS) is a simple solution of fentanyl citrate in isotonic phosphate buffer with a pH value of 6.4.

Pharmacokinetic data from a study in 19 cancer patients, who received doses of 50, 100 and 200 µg of fentanyl [Kaasa S, Moksnes K, Nolte T, Liefvendahl A, Kuntz D, Popper L, Kress HG: Pharmacokinetics of intranasal fentanyl spray in patients with cancer and breakthrough pain. Manuscript submitted (2009)], showed a pharmacokinetic profile of fentanyl similar to that obtained in healthy volunteers [27]; fentanyl plasma concentrations increased in a dose-dependent manner. Median T_{max} values were 15, 12 and 15 min for the 50, 100 and 200 µg doses of INFS, respectively.

Six patients (32%) experienced adverse events during the treatment period, the majority being mild in severity. Data from a randomized, double-blind, placebo-controlled, crossover efficacy and tolerability study in 159 cancer patients receiving placebo, 50, 100 and 200 µg of INFS have shown a fast onset of pain relief as early as 10 min after intranasal administration. Pain intensity differences between baseline and 10 min after administration were significantly higher for all three INFS doses than for placebo. Mean pain relief during the 60-min period following administration of INFS was also significantly greater compared with placebo. All doses examined were well-tolerated and effective in treating BTP in cancer patients regardless of level of background opioid dose. Evidence of a dose response to INFS was observed [Nolte T, Oronska A, Kaczmarek Z, Sopata M, Teglkamp K, Kaasa S: Intranasal fentanyl spray for the treatment of breakthrough pain in adult patients with cancer – a randomized, double-blind, placebo-controlled, crossover study. Manuscript submitted (2009)].

These results were confirmed in a randomized, double-blind, placebo-controlled efficacy and tolerability study with an open-label follow-up period in 113 cancer patients. Pain relief was seen 10 min after administration, and pain-intensity differences between baseline and 10 min after administration and mean pain relief 60 min after administration were significantly higher for all three INFS doses than for placebo. Incidence of adverse events was low (19.8%, 22 patients) during the efficacy period, and were most frequently nausea and vertigo, with no serious adverse events considered to be related to the study treatments. In total, 108 patients entered a 10-month open-label extension treatment period, with mean exposure to INFS of 134.9 days. Progression of underlying malignant disease was the most common adverse event during this period [82].

NasalFent®

NasalFent®: Fentanyl Pectin Nasal Spray (Archimedes Pharma, Reading, UK) is based on the PecSys® (PEC Systems Inc., AL, USA) delivery system, which turns from a liquid into a gel when applied to mucosal tissue surfaces. The gel formation has been shown to modify the rate of drug absorption, and thus to attenuate the high peak concentrations seen after nasal administration of simple solutions; however, the time to C_{max} is at the same time prolonged compared with a simple solution.

Results from a pharmacokinetic study in healthy volunteers receiving 100 μg of fentanyl in the PecSys compared with non-PecSys showed that C_{max} was reduced from 0.647 ng/ml to 0.337 ng/ml, and T_{max} was prolonged from 10 to 20 min [83]. Preliminary results from Phase II and III studies in breakthrough cancer pain have shown good tolerability [84–86] and a fast onset of action within 10 min after administration [85–87].

Future perspective

The oral transmucosal administration of fentanyl is currently the most rapid, clinical delivery method for management of BTP. Even though theoretically sublingual administration favors a more rapid absorption than does the buccal route, the results from clinical studies on Effentora (buccal) and Abstral (sublingual) so far reported do allow the time to onset of analgesia between the two products to be distinguished. This might be due to the pharmaceutical formulation strategies used, both aiming at reducing the disadvantages of the two...
administration routes. In Effentora™, a buffer system promoting the absorption of fentanyl has been added to the tablet, and in Abstral a mucos-adhesive substance has been added in order to reduce swallowing of fentanyl dissolved in saliva.

Results from pharmacokinetic and clinical studies on intranasal fentanyl have indicated that the intranasal administration of fentanyl might cause an even more rapid absorption, and hence a more rapid onset of analgesia than oral transmucosal administration.

However, since other factors than rapid onset of action, such as convenience, acceptability, tolerability, and minimization of side effects, should be taken into account when choosing the ideal formulation for the individual patient, both administration routes have their place in the market and represent a significant improvement in patient care compared with conventional opioids such as morphine or methadone given orally or by the subcutaneous route [55].

However, some important issues remain to be resolved. First, while fast-acting formulations of opioids are recommended for BTP episodes in cancer pain and acute pain, it is a matter of debate if they should be used for BTP in chronic noncancer pain [88]. Several studies in chronic noncancer pain patients treated with transmucosal fentanyl have been published with consistently favorable results [51,71,72], but adverse effects such as dependence and abuse in this patient group are not known [89]. Second, opioids are the rescue medication of choice in the management of BTP episodes in cancer patients [3], but nonopioid analgesics and nonpharmacological methods may sometimes be valuable alternatives. However, these aspects have not been systematically addressed. Third, although the individual dose requirements of intranasal and oral transmucosal-delivered fentanyl probably require a titration procedure [90], predictors of the individual requirement have not yet been determined in large-scale studies.

Executive summary

Breakthrough pain
* Breakthrough pain (BTP) can be described as ‘an episodic increase in pain intensity over a stable and adequately managed baseline pain’.
* BTP can be classified according to the causes of the pain:
  - Spontaneous pain which occurs unexpectedly;
  - Incident pain can be related to a physiological function or to a special event. Incident pain is subclassified into a further three types: volitional pain, which is initiated by a voluntary action; nonvolitional pain, which is initiated by an involuntary action; and procedural pain, which is caused by a therapeutic intervention. End-of-dose failure is due to a declining analgesia at the end of a dosing interval.
* The etiology and pathophysiology of the BTP is most frequently the same as that of the background pain.

Treatment strategies
* Treatment of BTP should be individualized to fit the special needs of the single individual patient.
* The optimal opioid formulation for the treatment of BTP possesses a pharmacological profile that closely mirrors the intensity–time profile of the BTP episode. Thus, a short onset of action (to relieve pain as quickly as possible) and a relatively short duration of action (to prevent side effects) are preferable. However, a number of other factors, such as convenience, acceptability, tolerability and minimization of side effects should be taken in account when choosing the ideal formulation for the individual patient.

Opioid characteristics
* The physicochemical properties of the opioids will influence the absorption rate. Thus, lipophilic opioids such as fentanyl and buprenorphine, which are more rapidly absorbed and cross the blood–brain barrier more readily than hydrophilic opioids (morphine and oxycodone), are the most attractive for the treatment of BTP, since they provide a fast onset of action. With respect to a reduced duration of action, opioids with short half-lives such as fentanyl and morphine are more attractive than opioids with long half-lives such as buprenorphine and methadone.

Administration routes
* The route of administration also influences absorption rate, and thus how rapidly the opioid reaches the brain. Opioids given by the intravenous route bypass the absorption phase, and thus reach the brain most rapidly, follow by opioids given by the subcutaneous, pulmonary, nasal, oral transmucosal (sublingual and buccal), oral and transdermal routes. Thus, of the noninvasive routes, the pulmonary and nasal routes are considered to be the ones leading to the fastest onset of action.

Pharmaceutical formulation
* Within the same administration route the pharmaceutical formulation will have an impact on the time to onset of action. The more rapid the opioid is released from the formulation, and thereby available for absorption, the shorter will be the period from application to onset of action.

Formulations intended for BTP
* Five formulations are currently on the market or very close to reaching the market. Three of these are intended for oral transmucosal administration and two for nasal administration.
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Bibliography


704 Therapy (2009) 6(5)
72 Simpson DM, Messina J, Xie F, Hale M: Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a


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