Evidence-Based Treatment of Cancer-Related Breakthrough Pain With Opioids

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Abstract

Opioids are considered important analgesics in the treatment armamentarium for moderate-to-severe background cancer pain. The past decade has seen clinical trials of transmucosal opioid formulations for breakthrough pain in cancer (BTPc), beginning with oral transmucosal fentanyl citrate (OTFC), followed by fentanyl buccal tablet and intranasal fentanyl spray, and most recently sublingual fentanyl tablet, fentanyl buccal soluble film, and fentanyl pectin nasal spray. During that time, enough rigorous evidence has accumulated to support the development of recommendations on treating BTPc with transmucosal formulations. This article describes the randomized controlled trials that have led to the support of the use of transmucosal fentanyl therapies for BTPc, starting in 1999 with OTFC formulations through to the end of 2011. Although oral opioids have been used for historical reasons, evidence supports the use of intravenous morphine or transmucosal fentanyl for treating BTPc, regardless of the opioid being taken to manage background pain. Furthermore, most studies have found no meaningful relationship between the effective dose of transmucosal opioid and the around-the-clock scheduled medication nor the previous rescue medication. The accumulated evidence shows that transmucosal fentanyl formulations provide a rapid effect on BTPc, with adverse events typical of opioids. *(JNCCN* 2013;11(Suppl 1): S37–S43)

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Breakthrough pain in cancer (BTPc) is characterized by intense flares of pain of short duration over a background of controlled chronic pain.[1,2] BTPc commonly has a rapid onset and lasts an average of 30 minutes.[1,3–6] Hence, ideal treatment of BTPc should also have a quick onset and short duration of effect.[1] Classically, treatment of BTPc has involved taking an extra dose of the oral opioid already being taken to relieve background chronic pain, at 5% to 20% of the total daily dose, as "rescue" medication.[3,7,8] This approach, however, may not offer the optimal speed of onset and short duration to match the rapid nature of a BTPc episode. Although oral opioids, particularly morphine as the first-line agent, were previously considered the standard of care for treating BTPc, no well-designed studies supported their use.[9,10] In contrast, recent evidence shows that transmucosal formulations of fentanyl that have become available within the past decade can provide rapid analgesia. This article describes the randomized controlled trials that have led to the support of the use of transmucosal fentanyl therapies for BTPc, starting in 1999 with oral transmucosal fentanyl citrate (OTFC) formulations through to the end of 2011.

The Evolution of Rapid-Acting Formulations for Managing Breakthrough Pain in Cancer

OTFC

Over the course of the past decade, the availability of rapid-acting opioid formulations for BTPc has

evolved substantially. The first Cochrane review[1] of the management of patients with BTPc, which was published in 2006, identified only 4 rigorously designed primary studies for the analysis.[10–13] Instead of morphine, all of the included studies[10–13] in the Cochrane review related to the use of OTFC, the first transmucosal drug formulation developed as a fentanyl-impregnated lozenge-on-a-stick.[10,14] Twenty-five percent of the fentanyl in this formulation is absorbed rapidly through the buccal mucosa, and the remainder is swallowed, of which another 25% of the total dose is absorbed through the gastrointestinal tract.[15] The 4 randomized controlled studies in the analysis included a total of 393 participants and compared reductions in pain intensity and changes in patient global performance scores between different doses of OTFC to either placebo or the active comparator, morphine.[1] Two of the studies assessed effective dosing of OTFC,[11,12] another tested OTFC against placebo,[13] whereas the last study compared OTFC with oral immediate-release morphine sulfate.[10] In the dose-titration studies, a safe and effective dose of OTFC was identified for approximately 75% of the participants; however, no meaningful relationship was observed between the rescue OTFC dose and the scheduled opioid regimen.[11,12] Meanwhile, the comparisons of OTFC with placebo and morphine favored OTFC, as evidenced by significantly better pain relief attained ($P<.0001$ compared with placebo and $P\leq.009$ compared with morphine).[10,13] The most recent study of OTFC compared it directly with intravenous morphine. The study found that both analgesics reduced mean pain intensity from baseline, with intravenous morphine providing a statistical advantage over OTFC at 15 minutes after administration (6.9–4.1 for OTFC vs. 6.9–3.3 for intravenous morphine; $P=.013$), but not at 30 minutes (mean of 2.4 for OTFC vs. 1.7 for intravenous morphine; $P=.059$).[16]

The studies of OTFC collectively indicate that the most frequently reported adverse events are typical of opioids: somnolence, nausea, dizziness, and, in half of the studies, constipation.[10–13]

Because no meaningful relationship was observed between the successful dose of OTFC and the background opioid, separate titration of OTFC was recommended in the Cochrane analysis.[1] Subsequently, to address the need to quickly identify optimal doses of transmucosal fentanyl to manage BTPc more efficiently, an analysis of pooled data from 3 of the previously mentioned randomized controlled clinical trials[11–13] was conducted to identify a titration strategy.[3] Authors of the article found that BTPc medication doses varied widely among individuals, ranging from 1% to greater than 70% of the 24-hour dose of the regularly scheduled background opioid therapy. Once again, a patient's OTFC dose could not be predicted from doses of previous BTPc medication or daily opioid therapy for background pain.[3] The authors also concluded that the dose of OTFC should be individualized according to a patient's response to BTPc medication and titrated separately from a patient's other opioid therapies.

Fentanyl Buccal Tablet

Fentanyl buccal tablet (FBT) is formulated to have enhanced mucosal permeation through the manipulation of pH, leading to 48% transmucosal absorption.[17,18] Pain relief attained in 2 randomized controlled studies comparing FBT with placebo for BTPc significantly favored FBT (Portenoy et al[19]: $P<.003$ at 15 minutes, $P\leq.0001$ at 30, 45, and 60 minutes; Slatkin et al[20]: $P<.0001$ at 10 minutes and thereafter). The most commonly observed adverse events in these trials were mild to moderate in severity and included nausea, vomiting, dizziness, headache, fatigue, and constipation, as well as somnolence in one study.[19,20]

Intranasal Fentanyl Spray

Intranasal fentanyl spray (INFS) incorporates a phosphate-buffered fentanyl solution at physiologic pH to minimize nasal irritation and in a concentrated volume amenable to nasal cavity capacity.[21,22] (Note: INFS is approved by the European Medicines Agency for use in Europe but has not been approved by the FDA for use in the United States.[23]) In a controlled trial of 113 patients randomized to receive INFS or placebo, a significantly greater difference in pain intensity from baseline was noted in the INFS group compared with placebo, at 10 minutes after administration and at all time points tested thereafter ($P<.001$).[24] In addition, INFS-treated episodes showed significantly higher response rates (assessed as >33% and >50% pain reductions) than those treated with placebo at postdose time points ($P<.001$).[24] The most common adverse events during titration or the randomized phase, aside from

disease-related progression, were vertigo, nausea, constipation, vomiting, and anemia.[24]

In an open-label crossover study including 139 patients, median time of onset of "meaningful" pain relief was reported to be more rapid with INFS (11 minutes) than with OTFC (16 minutes; $P<.001$).[25] The most common adverse events were nausea, vomiting, and constipation.

Comparative Analyses and Recommendations

With limited comparator studies conducted to date, a meta-analysis published in 2010 offered insight into the relative efficacies of the available options.[26] This mixed treatment analysis compared the efficacy of the then-available transmucosal formulations for treating BTPc: OTFC, FBT, and INFS, and oral morphine.[26] Six of the aforementioned randomized controlled trials with similar patient and study characteristics were identified for inclusion in the analysis[26]: 1 of OTFC,[13] 2 of FBT,[19,20] 1 of INFS,[24] 1 of OTFC versus oral morphine,[10] and 1 of OTFC and INFS.[25] Through multiple pair-wise comparisons across these studies, the treatments were compared with placebo, and placebo was used as the common comparator for the mixed analysis.[26] All 3 fentanyl formulations provided superior reductions in pain compared with placebo; however, INFS provided the most substantial reduction.[26]

Furthermore, this analysis showed that oral morphine did not provide pain reduction greater than that of placebo until 45 minutes after administration, at a time when this self-limiting pain may have already subsided naturally. Using oral morphine for BTPc may lead to inadequate acute pain relief and overmedication between pain episodes. Therefore, authors concluded that oral morphine cannot be considered an effective treatment for BTPc.[26]

In 2011, the same groups also used these studies as the basis of a pharmacoeconomic evaluation of OTFC, FBT, and INFS for treating BTPc.[27] Although limited in generalizability by local costs (in this case, specific to Sweden) used in the model, the analysis was an important addition to the limited pharmacoeconomic data available on transmucosal fentanyl formulations. The expected reductions in pain intensity of BTPc that could be avoided for each treatment were estimated, and then translated into gains in quality-adjusted life years and reductions in costs for health resource consumption. Health-associated costs were calculated by summing expenses from general practitioner visits, specialized home care visits, and hospital admissions in Sweden. Direct nonmedical costs, such as those associated with travel to and from the hospital, and indirect costs, such as loss of productivity, were not included. The analysis found that all 3 fentanyl formulations were able to avoid a higher percentage of total BTPc episodes than placebo. The model also predicted that INFS would be more cost-effective than OTFC or FBT.[27] Although the drug acquisition cost would be inherently higher for INFS than FBT and equal to OTFC, using INFS would lead to cost benefits from lower consumption of health resources and better gains in quality-adjusted life years.[27]

All of the aforementioned randomized controlled studies were included in a systematic review of the available evidence on the effectiveness of opioids for treating cancer pain to support the treatment recommendations developed by the European Association for Palliative Care (EAPC). Studies published through July 31, 2009 were included.[2] At this stage, enough evidence had accumulated to permit a recommendation by the EAPC that intranasal or buccal fentanyl preparations could be effectively used to treat BTPc.[2] Furthermore, in some cases these formulations would be preferred because they provide faster relief with a shorter duration of effect than immediate-release oral opioid therapies. Still, the EAPC weakly recommended that predictable BTPc can be managed with immediate-release oral opioids that have short half-lives, taken 20 to 30 minutes preceding the pain-provoking situation.[2]

Evidence Supporting the Use of New Transmucosal Fentanyl Formulations

Since the systematic review by the EAPC, 5 more randomized controlled trials[28–32] published between 2009 and 2011 have added to the rigorous evidence base for treating BTPc with transmucosal opioids.[33,34] These studies include 3 new formulations: sublingual fentanyl (SLF) tablet, fentanyl buccal soluble film (FBSF), and fentanyl pectin nasal spray (FPNS).[28–34]

SLF Tablet

SLF tablet takes advantage of the good permeability and high vascularity of the sublingual cavity, where

it is meant to dissolve completely without sucking, chewing, or swallowing.[28,35] A phase II and a phase III study compared SLF tablet with placebo, with 38 and 131 study participants, respectively, 27 and 61 of whom were randomized and included in the efficacy analysis (intent-to-treat population).[28,29] The design of the phase III study involved a 2-week dose titration period, including doses from 100 to 800 mcg, followed by a 2-week, double-blind treatment efficacy period, ending with a safety phase of up to 12 months.[29] Both studies found that SLF tablet was well tolerated, and compared with placebo yielded a significantly greater difference in pain intensity from baseline (P=.005, both studies) and better pain relief (P≤.049, phase III study) from 10 to 15 minutes after administration, and maintained it throughout the 60-minute assessment period for the phase III study.[28,29] The most commonly noted adverse events were in keeping with those typical of opioids: nausea, vomiting, and dizziness or somnolence.[28,29]

FBSF

A study by Rauck et al[32] compared the efficacy of another novel formulation, FBSF, with placebo. The design of FBSF involves a dual-layer film—one layer that rapidly adheres to the buccal mucosa and delivers fentanyl and another inactive layer that serves as a barrier for diffusion of the active drug into the oral cavity.[32,36] FBSF takes 15 to 30 minutes to completely dissolve, and approximately 50% of the fentanyl is absorbed through the buccal mucosa.[32] The study of FBSF began with a screening period, followed by a titration period of up to 2 weeks. During this second phase, an effective dose of 200 to 1200 mcg was identified for patients to continue on during the double-blind crossover period in which patients received FBSF and placebo in a randomized order. A significant difference (P<.05) in the summed pain intensity difference from baseline between FBSF and placebo was noted beginning at 15 minutes postdose and continued through an hour. The most frequently observed adverse events were somnolence, nausea, dizziness, and vomiting.[32]

FPNS

FPNS is formulated to form a thin layer of flexible gel on contact with the highly vascular nasal mucosa, minimizing runoff and maximizing the fentanyl absorbed through the nasal cavity.[30,37] Two randomized controlled studies examined the efficacy of FPNS for managing BTPc, 1 compared with immediate-release oral morphine (n = 84 patients; 740 BTPc evaluable episodes)[30] and 1 versus placebo (n = 65 patients; 489 BTPc episodes).[31] After a screening period, both studies followed with an open-label titration phase to identify an effective dose, and then a double-blinded treatment period during which as many as 10 episodes of BTPc could be treated.[30,31] Differences between FPNS and placebo were noted in the patients' mean pain intensity scores as early as 5 minutes after administration, and differences were noted from morphine as early as 10 minutes after treatment.[30,31] Scores of the difference in pain intensity from baseline were significantly better for the episodes treated with FPNS than those treated with placebo starting from 10 minutes after administration (P<.01)[31] and better than oral morphine starting from 15 minutes after administration (P<.05)[30]; this significant difference was maintained in both studies throughout the hour-long assessment period.[30,31] Similar to other transmucosal fentanyl formulations, the most common adverse events associated with FPNS were typical of opioids: vomiting, nausea, somnolence, and dizziness.[30,31]

Discussion

The randomized controlled clinical trials form a strong evidence base supporting the use of transmucosal fentanyl formulations for treating BTPc (Table 1). Most of these efficacy studies had a similar design involving a screening period, followed by a titration period during which an effective dose of test medication was identified, and finishing with a comparison period wherein the identified dose was tested against a comparator: placebo, another titrated analgesic, or a previously used rescue medication. Most of the included studies were double-blinded. The efficacy and outcome measures of the included trials were similar and typically involved measured pain intensity or pain relief, either as differences across time or summed differences of pain intensity or pain relief from baseline. Although all of the studies were randomized, patients in 2 of the studies[11,12] were randomized for titration to determine an effective dose but were not randomized to make a comparison with previous or concurrent rescue medications. Patients in 1 study[28] received different doses of SLF or

Table 1 Randomized Controlled Trials of Transmucosal Fentanyl Formulations for Treating BTPc in Opioid-Tolerant Patients

Formulation and Year of Approval (FDA/EMA)[43]	Study	Comparator	Duration/ Number of BTPc Episodes Treated by Study Drug[a]	Patients Completing Treatment Phase n/N (%)	Outcomes
OTFC (1998/2002)	Farrar et al,[13] 1998	Placebo	2 wk/NR	72/92 (78)	PR and PID significantly higher than placebo beginning by 15 min ($P<.0001$)
	Christie et al,[11] 1998	UBTPM	2 d/NR	47/62 (76)	PR significantly higher and PI significantly lower than UBTPM beginning by 15 min ($P\leq.0002$); PID higher than UBTPM beginning by 15 min ($P\leq.0001$)
	Portenoy et al,[12] 1999	UBTPM	2 d/489	NR/48 (NR)	Significantly higher percentage of total PI reduction vs UBTPM (primary end point) at 15 min ($P<.0001$)
	Coluzzi et al,[10] 2001	Oral IM morphine	NR/NR	84/93 (90)	Mean PI significantly lower, mean PID and PR significantly higher than morphine beginning by 15 min ($P\leq.033$; $P\leq.008$; $P\leq.009$, respectively)
	Mercadante et al,[16] 2007	IV morphine	NR/53	25 (NA)	Change in morphine PI significantly better than OTFC at 15 min ($P=.013$) but not 30 min ($P=.059$)
FBT (2006/2008)	Portenoy et al,[19] 2006	Placebo	21 d/493	68/77 (88)	Mean PID and PR significantly higher than placebo beginning by 15 min ($P<.003$); $SPID_{30}$ (primary end point) significantly higher than placebo ($P<.0001$)
	Slatkin et al,[20] 2007	Placebo	3 wk/493	75/87 (86)	$SPID_{60}$ (primary end point) significantly higher than placebo ($P<.0001$); PR and PID significantly higher than placebo beginning by 10 min ($P<.0001$)
INFS (NA/2009)	Kress et al,[24] 2009	Placebo	3 wk/659	110/111 (99)	Mean PID_{10} (primary end point) significantly higher than placebo beginning by 10 min ($P<.001$)
	Mercadante et al,[25] 2009	OTFC	≤2 wk/577 for each	INFS: (93) OTFC: (92)	Median time to onset of "meaningful" pain relief (primary end point) 5 min earlier than OTFC (11 vs 16 min), with significantly more patients experiencing a faster onset to meaningful pain relief than with OTFC ($P<.001$); mean PID significantly greater than OTFC beginning by 5 min ($P<.001$)
SLF tablet (2011/2008)	Rauck et al,[29] 2009	Placebo	2 wk/393	60/66 (91)	$SPID_{30}$ (primary end point) significantly greater than placebo ($P=.0004$); mean PID and PR significantly greater than placebo beginning at 10 min ($P\leq.0055$, $P\leq.049$)
	Lennernäs et al,[28] 2010	Placebo	NR/NR	23/38 (61)	Mean PID (primary end point) significantly greater than placebo beginning by 15 min ($P=.005$)
FBSF (2009/2010)	Rauck et al,[32] 2010	Placebo	2 wk/394	70/82 (85)	$SPID_{30}$ (primary end point) significantly higher than placebo ($P=.004$); mean PID significantly greater than placebo beginning by 30 min ($P<.05$)
FPNS (2011/2010)	Portenoy et al,[31] 2010	Placebo	NR/459	76/83 (92)	$SPID_{30}$ (primary end point) significantly higher than placebo ($P<.0001$) and for each time point from 10-60 min postdose; mean PI significantly lower than placebo beginning by 5 min ($P<.05$); mean PID significantly greater beginning by 10 min ($P<.01$)
	Fallon et al,[30] 2011	Oral IM morphine	21 d/372	79/84 (94)	PID_{15} (primary end point) significantly greater than IRMS ($P<.05$); mean PID significantly greater than morphine beginning by 15 min and maintained through 60 min ($P<.05$)

Abbreviations: BTPc, breakthrough pain in cancer; EMA, European Medicines Agency; FBSF, fentanyl buccal soluble film; FBT, fentanyl buccal tablet; FPNS, fentanyl pectin nasal spray; IM, immediate-release; INFS, intranasal fentanyl spray; IRMS, immediate-release morphine sulfate; IV, intravenous; NA, not applicable; NR, not reported; OTFC, oral transmucosal fentanyl citrate; PI, pain intensity; PID, pain intensity difference; PR, pain relief; SLF, sublingual fentanyl; SPID, summed pain intensity difference; UBTPM, usual BTPc medication.
[a]Duration describes the randomized treatment period for the randomized controlled trials.

placebo in random order. Intravenous morphine was used as a comparator in 1 study,[16] and oral morphine was the comparator in 2 studies.[10,30]

Other notable differences between the included trials included dissimilarities in pretreatment breakthrough pain intensity levels, titration protocols, methods of identifying effective doses, intervals between assessments of pain, study end points, and use of rescue medications. Use of a second dose of the investigational drug was allowed in some studies, whereas others specified use of the previous rescue medication if needed, and the timing of this second dose varied and was often vague as to when it was administered (ranges of time were reported). All of the randomized controlled trials, however, showed that transmucosal fentanyl can provide rapid analgesia, which is in keeping with the characteristics of BTPc.

As advances in oncology improve the survival of patients, the long-term safety of opioids is of increasing interest. Long-term, open-label studies published on OTFC, FBT, INFS, SLF tablet, and FPNS found similar opioid adverse events as those previously noted in the short-term studies, and acceptable safety profiles overall.[24,29,38–42] Furthermore, most patients in these studies did not require dose changes over time.

The evidence base is substantial enough now to permit recommendations on treating BTPc with rapid-acting opioids.[2] Because their pharmacodynamics closely mirror the common characteristics of BTPc, the EAPC recommends that transmucosal fentanyl formulations may be preferable to immediate-release oral opioid therapies in some cases.[2] Intravenous morphine has been compared with transmucosally delivered opioids, and both have been found to effectively provide rapid analgesia. Meanwhile, the oral route is more commonly used, but it has not been formally tested; furthermore, in studies in which it has been used as a comparator, oral opioids have been inferior.

Conclusions

The largest number of studies on the treatment of BTPc and the strongest evidence for rescue medication efficacy have been demonstrated for opioids administered via the transmucosal route. These studies show that these formulations work quickly, and serve as the basis for several guidelines on the management of BTPc. In addition, most studies have found no meaningful relationship between the effective dose of transmucosal opioid and the around-the-clock scheduled medication nor the previous rescue medication; therefore, rescue medication should be titrated separately and tailored for each individual. Further research is needed to develop a therapeutic algorithm for managing BTPc.

Acknowledgments

The author gratefully acknowledges the contributions of the following individuals who participated in the discussion that shaped the content of this article: Augusto Caraceni, MD; Hernán Cortés-Funes, MD, PhD; Andrew Davies, MB BS, MSc, MD, FRCP; Guido Fanelli, MD; Paul Glare, MD; Andreas Kopf, MD; Paolo Marchetti, MD; Didier Mayeur, MD; Sunil Panchal, MD; Philippe Poulain, MD; Carmen Rubio, MD, PhD; Alain Serrie, MD, PhD; Raymond Voltz, MD; and Jamie Von Roenn, MD. The roundtable discussion was supported by Archimedes Development Ltd. Technical and editorial assistance was provided by Rebecca Bachmann, Sharon Suntag, and Julie Gerke of Quintiles Medical Communications, Parsippany, NJ, and was supported by Archimedes Development Ltd, Nottingham, UK.

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