Clinical Note

Fentanyl Buccal Tablets for Breakthrough Pain in Highly Tolerant Cancer Patients: Preliminary Data on the Proportionality Between Breakthrough Pain Dose and Background Dose

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Abstract

Context. Cancer patients receiving high doses of opioids as background medication are challenging, and it would be useful clinically to know whether a rapid-onset opioid (ROO) for breakthrough cancer pain (BTcP) may be started at a dose proportional to the background opioid dose.

Objectives. The aim of this study was to assess the efficacy and safety of the fentanyl buccal tablet (FBT) in doses proportional to the opioid dose administered for background analgesia in a sample of patients with BTcP who were receiving high doses of opioids.

Methods. Twelve patients who were receiving opioids for background analgesia at doses equivalent to more than 500 mg of oral morphine and had adequately controlled pain were prospectively recruited. BTcP was treated with proportional doses of FBT: patients receiving 600 mg of oral morphine equivalents were administered 1000 μg of FBT, patients receiving 900 mg of oral morphine equivalents were administered 1500 μg of FBT, and so on. For each episode of BTcP, trained nurses collected pain intensity (on a 0−10 numerical rating scale) and emerging problems when called for increases in pain considered to be severe in intensity by patients (T0) and 15 minutes after FBT administration (T15).

Results. Patients were receiving mean doses of oral morphine equivalents of 1340 mg (±585; range 720−2400). Seventy-nine events were treated with FBT (6.6 ± 4.9 for each patient). The median pain intensity of BTcP events was 8 (range 7−10), and the mean dose of FBT administered was 2233 μg (±975; range 1200−4000). In most events, a decrease in pain intensity >33% and >50% was observed ($n = 14$ and $n = 48$, respectively) 15 minutes after the administration of

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FBT. Data on 11 episodes were missed. Only six events were unsuccessfully treated. In all the patients, the level of adverse effects after FBT administration was mild and indistinguishable from that associated with the background opioid analgesia.

Conclusion. FBT in doses proportional to the high doses of opioids used for background analgesia was efficacious and well tolerated when administered for BTcP. Controlled studies with a specific design and a large number of patients should confirm such preliminary results. J Pain Symptom Manage 2011;42:464–469.

Key Words
Cancer pain, breakthrough pain, opioids, fentanyl buccal tablets

Introduction

In the cancer population, breakthrough cancer pain (BTcP) is a transitory exacerbation of pain superimposed on an otherwise stable pain pattern in patients treated with opioids.[1] BTcP is normally severe in intensity and has a rapid onset. The presence of BTcP has been considered as a negative prognostic factor for adequate pain control and interferes with the quality of life of these patients.[2] The availability of supplemental doses of opioids in addition to the continuous analgesic medication is the main treatment suggested to manage these pain flares, either during dose titration or when basal pain is under control. The use of rapid-onset opioids (ROOs) has been shown to provide pain relief that occurs more quickly than that achieved with an orally administered drug.[3]

The opioid dose to be administered for BTcP is controversial. All the trials with ROOs, including oral transmucosal fentanyl citrate (OTFC) and the fentanyl buccal tablet (FBT), suggest a lack of relationship between the effective the fentanyl dose and a fixed-schedule opioid regimen, regardless of the opioid used.[3] However, in these studies, a substantial proportion of patients failed dose titration of OTFC or FBT,[4] and observations from data pooled from trials of OTFC showed a statistically significant relationship between the breakthrough dose and around-the-clock dose, despite enormous interindividual variability in patients' dose requirements for BTcP.[5] Moreover, an unclear distinction between the basal pain of mild-moderate intensity and BTcP of moderate-severe intensity makes the interpretation of data provided by these studies difficult. The use of proportional doses has been shown to be promptly effective without producing relevant adverse effects in an acute palliative care unit setting.[6–9] A predictable dose may favor an easy prescription, resulting in better patient compliance.

The findings of these studies suggest that patients receiving opioids for chronic cancer pain may not sustain more risk from the administration of a ROO dose that is proportional to the basal opioid regimen, especially if the background opioid dose is relatively high. This can be explained by the protective effect offered by opioid tolerance in patients chronically receiving relevant opioid doses for the management of cancer pain.

It would be useful clinically to know whether a ROO may be started at a dose proportional to the background opioid dose. If the ROO is initiated at too low a dose, in an attempt to titrate the doses individually, this could result in unnecessary suffering, lowered clinical compliance, and refusal to continue the treatment. Patients receiving high doses of opioids as background medication are challenging and have never been the subject of clinical studies. The aim of this study was to prospectively assess the efficacy and safety of FBT in doses proportional to opioid doses for background analgesia given chronically for the treatment of BTcP in cancer patients receiving high doses of opioids.

Patients and Methods

Patients receiving opioids at doses equivalent to more than 500 mg of oral morphine as background analgesia and having pain under control for most daily hours (pain intensity $\leq 4/10$ on a numerical scale of 0–10) were prospectively recruited for this study for a period of eight months. Other medications, including

symptomatic drugs or coanalgesics, when indicated, were added to opioids to maintain a stable analgesia with limited adverse effects. Patients with relevant coexisting liver or renal disease (double values of normal ranges in creatinine, bilirubin, or hepatic enzymes), cognitive impairment, an expected survival of less than one month, requiring radiotherapy, or starting a new course of chemotherapy were excluded. Informed consent and approval by the local ethics committee were obtained.

BTcP was treated with proportional doses of FBT, according to local policy.[9] For example, patients receiving 600 mg of oral morphine equivalents were administered 1000 μg of FBT, patients receiving 900 mg of oral morphine equivalents were administered 1500 μg of FBT, and so on. Tablets were placed between the upper gum and cheek, above and/or below the molar tooth on each side, or on both sides, according to the number of tablets needed to administer the calculated doses.

Patients were treated according to the department policy, that is, patients were encouraged to call when their pain became severe (≥7 on a numerical scale from 0 to 10). For each episode, trained nurses collected changes in pain intensity (on a numerical scale 0−10) and emerging problems when called for pain increases considered to be severe in intensity by patients (T0) and 15 minutes after FBT administration (T15). Daily doses of opioids administered for basal analgesia also were recorded. As a routine, a physician on duty is present in the department and the palliative care team is available on call for any emergency or consultation.

Patients were offered intravenous morphine (about one-fifth of the daily oral dose converted to the intravenous route) if they were not satisfied with the treatment by T15, according to department policy and previous experience.[6,7] The number of patients who reported a decrease in pain intensity of >33% and >50% was recorded 15 minutes after the administration of FBT. Episodes with less than a 33% reduction in pain or requiring further treatment were considered unsuccessful.

Statistical Analysis

Data were collected and analyzed by the SPSS software version 14.0 (SPSS, Inc., Chicago, IL). Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all the items. Bivariate correlations using nonparametric (Spearman's coefficient) correlation analysis were calculated for the association of FBT doses and decrease in pain intensity <33%, >33%, and >50%.

Results

From January to August 2010, 12 patients receiving strong opioids in doses higher than 500 mg/day of oral morphine equivalents were recruited. The mean age was 58.9 (SD ±11.6) years. In total, 79 BTcP events were treated with FBT (mean 6.6 ± 4.9 for each patient).

Patients' characteristics are listed in Table 1. All patients had their background pain under control (pain intensity of 4/10 or less on a numerical scale 0−10) and were receiving mean doses equivalent to oral morphine 1340 mg (±585; range 720−2400). Five patients were receiving pregabalin (Patients 1, 2, 3, and 12) or duloxetine (Patient 6).

On a 0−10 numeric rating scale, the median pain intensity of BTcP events was 8 (range 7−10). The mean doses of FBT administered were 2233 μg (±975; range 1200−4000). In most events, a decrease in pain intensity >33% and >50% was observed ($n = 14$ and $n = 48$, respectively), 15 minutes after the administration of FBT. Data on 11 episodes were missed. Only six events were unsuccessfully treated (decrease of pain intensity 15 minutes after FBT administration of less than 33%). There was no correlation between the FBT doses used and the reduction in pain intensity (>33%, Spearman's correlation coefficient: 0.026, $P = 0.926$; >50%, Spearman's correlation coefficient: 0.132, $P = 0.423$; <33%, Spearman's correlation coefficient: 0.286, $P = 0.260$). In all cases, adverse effects after FBT administration were mild and undistinguishable from those associated with basal opioid analgesia, independent of the dose administered.

Discussion

The aim of this study was to assess efficacy and safety of ROOs commonly used for the treatment of BTcP in patients who were receiving high doses of opioids for background

Table 1
Characteristics of Patients and Data Recorded

Patient Data	Patient Number												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Cancer Mechanism	Testicular Somatic neuropathic	Kidney Somatic neuropathic	Lung Neuropathic	Prostate Somatic	Breast Somatic	Lung Somatic neuropathic	Pancreas Visceral	Lung Somatic	Colon Visceral	Lung Somatic	Colon Visceral	Lung Somatic neuropathic	
Around-the-clock opioids (oral morphine equivalents), mg	1080	1440	1920	1440	1920	720	720	1920	840	2400	960	720	
Dose of FBT, μg	1800	2400	3200	2400	3200	1200	1200	3200	1400	4000	1600	1200	
Number of episodes	2	3	15	8	8	8	4	16	3	8	1	3	79
>33% decrease in pain intensity	2		1			2		8			1		14
>50% decrease in pain intensity		2	10	6	8	4	4	6	3	2		3	48
Unevaluable			4	2						5			11
Unsuccessful		1				2		2		1			6

analgesia. Among the ROOs available for the management of BTcP, FBT was chosen because of its good bioavailability, which yields less dose-to-dose variability than OTFC.[10]

The opioid dose to be administered for BTcP is controversial. All the trials with OTFC and FBT suggest a lack of relationship between the effective fentanyl dose and a fixed-schedule opioid regimen, regardless of the opioid used.[3] This finding has suggested the need to begin therapy at a low dose and titrate to higher doses in every case. To affirm that this is the optimal clinical paradigm, these titration methods should be compared with proportional doses in terms of efficacy and safety, but such studies have not been performed so far.[4] Moreover, in the studies that have demonstrated a lack of proportionality, a substantial number of patients failed dose titration, eliminating the chance to clarify the extent of proportionality within the larger opioid-treated population. Interestingly, observations from data pooled from trials of OTFC showed a statistically significant relationship between the breakthrough dose and around-the-clock dose, despite an enormous interindividual variability in patients' dose requirements for BTcP.[5]

The use of proportional doses has been shown to be safe and effective when using OTFC and intravenous morphine, even in patients receiving relatively high doses of opioids for their background pain, and only a minority of patients required further treatment.[6–9] The proportional doses used in these studies were effective and safe, and no patient needed intervention for adverse effects. The use of a dose that is proportional to the background opioid dose may protect patients from failed titration or periods of suffering before achieving the appropriate individualized dose (a time period that could, in certain cases, require weeks, as determined in the controlled studies).

This is the first study assessing the use of high doses of FBT for BTcP, as data on doses higher than 800 μg of FBT have never been published.[11,12] In all previous experiences with FBT, patients who did not obtain satisfactory analgesia with 800 μg discontinued the study.[13] A pharmacokinetic study has shown that higher doses of FBT produce a proportional increase in plasma concentration.[14] As a consequence, further analgesia can be expected when doses

are escalated in patients who are highly tolerant, such as those receiving high doses of strong opioids for background analgesia.

FBT in doses proportional to oral opioids given for background analgesia was safe and effective in this series of patients, reproducing the same effects reported in patients receiving lower doses, but after dose titration.[11,15] Most patients obtained a relevant decrease in pain intensity within 15 minutes, more than 50% in more than 60% of events. Of interest, and in contrast to previous controlled studies of opioid titration, the selection of BTcP events included in this survey may allow a better interpretation of data because the intensity of BTcP (at least 7/10) was clearly distinguished from the intensity of basal pain (no more than 4/10). This means that the confounding influence of the gray area of mild pain for either background analgesia or BTcP often reported in these studies, which may interfere with the quality of the data collected and their interpretation, was limited. Similarly, the cut-off in selecting the events successfully treated was more restrictive (at least a 33% decrease in pain intensity). Despite the uncontrolled nature of the study design, the most strict selection of the BTcP events to be treated offers a clinical outcome reproducible in daily practice. The treatment was safe and effective, and only a minority of patients had an insufficient response. Drugs were given by trained nurses autonomously evaluating BTcP and following the prescription ordered on the clinical sheet, which incorporated the proportional dosing.

Although a certain dose is necessary to cover most BTcP events with severe intensity, the pains may have different presentations and unpredictable courses. It could be argued that this approach could expose patients to adverse effects. However, no patient required a medical intervention, including older patients who could potentially be at risk, regardless of the type of opioid, dose, route, and age. This observation confirms that opioid tolerance, produced by relative high opioid doses used for background analgesia, is a protective factor against the occurrence of severe adverse effects. Preliminary and confirmatory surveys have shown the safety of this approach in a large number of patients; no life-threatening adverse effects occurred, even in older patients. Respiratory depression, which is the most feared adverse effect, has never occurred, and no emergency call was needed.[6–9]

In a recent survey reproducing a real clinical scenario, patients receiving a mean oral morphine dose of 132 mg required 800 μg of OTFC after dose titration,[16] suggesting that the titration process may reveal a need for even higher doses that those expected by using proportional dosing. Similarly, in a recent long-term study of FBT, the mean dose of FBT was 554 μg in patients who were receiving mean doses of 240 mg/day oral morphine equivalents as background analgesia, and approximately half of the patients used the maximum FBT dose of 800 μg during maintenance treatment.[12] These mean doses of FBT (554 μg) were consistently higher than those eventually calculated with a proportional approach (400 μg for mean doses of 240 mg of oral morphine equivalents as around-the-clock analgesia), confirming that overdosing with proportional doses calculated according to the opioid basal regimen is unlikely. These patients, however, needed titration, with evident suffering during the days before achieving the right dose.

In conclusion, FBT in doses proportional to the high doses of opioids used for background analgesia was effective as breakthrough pain medication. This approach did not produce relevant adverse effects. However, these data should be considered with caution, given the preliminary nature of this study. The limited observations in a selected population do not allow broad conclusions of any type, including those focused on safety, particularly given the general concerns about the approach to proportionate dosing of ROOs. Moreover, data were collected in an acute pain relief and palliative care unit offering strict monitoring and should not be extended to other contexts. Controlled studies with a specific design with a large number of patients should be performed to confirm such preliminary results.

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