

Original article

Dosing fentanyl buccal tablet for breakthrough cancer pain: dose titration versus proportional doses

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Abstract

Objectives:

The aim of this study was to compare the efficacy and safety of doses of fentanyl buccal tablet (FBT) proportional to doses of opioids used for background analgesia versus dose titration starting with the minimal dose for the management of breakthrough cancer pain (BTcP).

Methods:

A total of 82 cancer patients with BTcP who were receiving strong opioids in doses of at least 60 mg of oral morphine equivalents and having acceptable background analgesia, were selected for a multicenter unblinded study. Forty-one patients were randomized to receive FBT in doses proportional to the daily opioid doses for four consecutive episodes of BTcP (group P). Forty-one patients underwent dose titration of FBT, with an initial dose of 100 µg, for four consecutive episodes (group T). Pain intensity and symptoms associated with opioid therapy were measured before administering any dose of FBT (T0) and 15 minutes after (T15).

Results:

In all, 80 patients were considered for analysis (39 and 41 patients in group P and T, respectively). Patients were receiving a mean of 126 ± 100 mg of oral morphine equivalents (range 60–480 mg) for background analgesia. A total of 293 episodes of BTcP (144 and 149 in group P and T, respectively) were treated and considered for analysis. No differences were found in the decrease of pain intensity between the two groups. However, in patients receiving doses of oral morphine equivalents of >120 mg/day, a significant number of patients obtained a decrease in pain intensity $>50\%$ in group P in comparison with group T ($p=0.040$). Also, the need for rescue medication was significantly more frequently reported in group T for the first episode of BTcP ($p<0.0005$). No differences in the level of adverse effects were observed between the two groups. No differences in patients' satisfaction were reported.

Conclusion:

According to the data obtained in this study, there is no evidence for the use of dose titration in the management of BTcP in opioid-tolerant patients. Indeed, doses proportional to basal opioid regimen for background pain seem to be effective and safe in the majority of patients. Further studies should confirm this data in patients receiving higher doses of opioids, with other rapid-onset opioids, and in other settings.

Introduction

Breakthrough cancer pain (BTcP) has been recently defined as a transitory increase in pain intensity that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain¹.

BTcP is a common problem in patients with cancer and is associated with significant morbidity^{2,3}. In different surveys, 50–90% of cancer patients with pain have been reported to experience intermittent flares of their pain, although different definitions and methodologies were used^{1–6}.

The availability of supplemental doses of oral opioids, in addition to the continuous analgesic medication, is the main suggested treatment for the management of pain flares. Given the temporal pattern of BTcP, characterized by rapid onset and short duration, various technologies have been developed to provide rapid onset of effect with potent opioid drugs such as fentanyl (rapid onset opioids, ROOs), delivered by non-invasive routes. It has been suggested that the therapy dose should be individually titrated in order to adapt management of this condition and enable effective analgesia to be delivered while minimizing the risk of clinically significant adverse effects^{1,7}. This statement has been quoted as evidence “B”. However, the need for titrating opioid doses in BTcP may make the practical use of ROOs difficult in daily activity, particularly at home or in outpatient clinics. Most patients may be reluctant to try the medication and avoid the use of an ROO, preferring, in the end, traditional oral dosing of morphine⁸. Moreover, the need for dose titration with ROOs in BTcP, has never been properly assessed and this statement is derived from a series of papers published for regulatory issues. To scientifically affirm the need for titration, a randomized trial should compare a group of patients titrated versus another group of patients who receive proportional doses, and this study design has never been the subject of research. For instance, there is no evidence for dose titration as well as for using proportional doses^{9,10}. The aim of this randomized-controlled study was to compare efficacy and safety of doses of an ROO (fentanyl buccal tablet, FBT), given in doses proportional to opioid daily doses with dose titration, starting with the lowest dose of FBT for the management of BTcP. The primary outcomes were the number of episodes requiring rescue medication after the study dose and the number of episodes with a decrease in pain intensity of $\geq 33\%$ and $\geq 50\%$ 15 minutes after the study dose. The secondary outcome was the number of episodes in which patients reported adverse effects and the level of satisfaction with the treatments.

Patients and methods

A multicenter prospective randomized controlled non-blinded study was carried out in a sample of 82 cancer patients with BTcP who were receiving strong opioids in doses of at least 60 mg of oral morphine equivalents and had an acceptable background analgesia (≤ 4 on a numerical scale from 0 to 10). Patients with more than three

episodes of BTcP/day, relevant co-existing liver or renal disease, cognitive impairment, an expected survival less than 3 months, requiring radiotherapy, or a new course of chemotherapy, were excluded. The study was approved by the local ethical committee of the University of Palermo, and adhered to Helsinki Declaration (Eudract number 03125514, 2010). Informed consent was taken from all patients before participation.

Randomization was computer-generated at the principal investigation center. A total of 41 patients were randomized to receive FBT in doses proportional to the daily opioid doses (for example 100 μg for 60 mg/day of oral morphine, 200 μg for 120 mg/day of oral morphine, and so on) for four consecutive episodes of BTcP (group P). A total of 41 patients underwent dose titration of FBT, with an initial dose of 100 μg . In this group, when BTcP was considered to be unsuccessfully controlled, the dose was progressively increased for the subsequent episodes, up to 200, 400 and 800 μg , to achieve the effective dose (group T). For each episode it was considered the percentage of decrease in pain intensity ($\geq 33\%$ and 50% , respectively), 15 minutes after administration of FBT (see below).

Age, gender, primary cancer, pain causes and mechanisms on the basis of clinical history, known metastases, physical examination, and available investigations were recorded (particularly pain on movement due to bone metastases). The following parameters were collected: pain intensity, measured on a numerical rating scale from 0 to 10¹¹ before administering any dose of FBT (T0) and 15 minutes after (T15), symptoms associated with opioid therapy, such as nausea and vomiting, drowsiness, and confusion, occurring as a new event or a change in intensity as a consequence of FBT administration, assessed by patients, by using a scale from 0 to 3 (not at all, slight, a lot, severe). At the end of the study, patients were asked about their satisfaction regarding the treatment, rated on a verbal scale: excellent, good, sufficient, poor, very poor. Efficacy was assessed by differences in pain intensity for each episode, by the number of episodes successfully treated (decrease of $\geq 33\%$ and $\geq 50\%$ in pain intensity), by the use of rescue doses, by the level of patient's satisfaction, and the number of patients who discontinued the treatment for poor compliance or inefficacy. Safety was assessed by the differences in opioids-related adverse effects or number of patients who discontinued the treatment for adverse effects.

Statistical analysis

Statistical analysis of quantitative and qualitative data, included descriptive statistics, was performed for all the items. Frequency analysis was performed by chi-square test with Yates correction. The paired samples Student's *t*-test was used to compare mean pain intensity scores in

the time periods. The two-sample Student's *t*-test was used to compare parametric variables between groups. All *p*-values were two-sided and *p*-values less than 0.05 were considered to indicate statistical significance. Data were analyzed by the Epi Info software, version 3.2.2, (Centers for Disease Control and Prevention, USA) and the SPSS Software 14.0 version (SPSS, Inc., Chicago, IL, USA).

Results

Patients characteristics are described in Table 1. Two patients in group P were receiving doses of less than 60 mg of oral morphine equivalents and were excluded from the study. In all, 80 patients were considered for analysis (39 and 41 patients in group P and T, respectively). Patients were receiving a mean of 126 ± 100 mg of oral morphine equivalents (range 60–480 mg) for background analgesia.

A total of 293 episodes of BTcP (144 and 149 in group P and T, respectively) were treated and considered for analysis. In all, 71 patients (36 and 35 in group P and T, respectively) received the selected doses for all the four episodes of BTcP. Five patients were excluded because they did not present episodes of BTcP within 3 days (three and two patients in group P and T, respectively). One of the patients in group T was transferred to another unit. Four patients in group T discontinued the treatment due to poor compliance or inefficacy of the treatment and not all the four episodes were recorded (see Figure 1).

Changes in pain intensity, number of episodes with a decrease in pain intensity $\geq 33\%$ and $\geq 50\%$, 15 minutes after the administration of the selected dose of FBT in group P and T are shown in Table 2. The same data in 30 patients who were receiving oral morphine equivalents of ≥ 120 mg/day are presented in Table 3. A significant number of patients obtained a decrease in pain intensity $\geq 50\%$ in group P in comparison with group T patients ($p = 0.040$). The need for rescue medication was significantly more frequently reported in group T for the first episode of BTcP. Eight and 25 episodes in group P and

T, respectively, required a rescue dose after the selected dose of FBT ($p < 0.0005$). This difference was less relevant for the subsequent episodes: rescue doses were given in seven and 11 episodes, respectively, for the second episode of BTcP ($p = 0.341$); in six and four episodes respectively, for the third episode of BTcP ($p = 0.437$); and in five and one episodes respectively, for the fourth episode of BTcP ($p = 0.088$).

No patient developed adverse effects of severe intensity in both groups. The number of patients who developed adverse effects of mild-to-moderate intensity, attributable to study medication are reported in Tables 2 and 3. No differences in adverse effects intensity was observed between the two groups. No differences in patients' satisfaction were reported ($p = 0.106$, Pearson chi-square statistic test).

Discussion

Data from this study suggest that dose titration does not add any advantage in comparison with proportional doses in the management of BTcP, being neither more efficacious nor safer. Doses proportional to basal opioid regimen for background pain are effective, providing optimal analgesia in the majority of treated episodes of BTcP, and are devoid of important adverse effects. Indeed, more patients who underwent dose titration discontinued the treatment for poor efficacy or compliance and required more rescue medications after receiving FBT. As expected, patients given similar doses of FBT of 100 μ g in both arms reported similar outcomes, because they were receiving 60 mg of oral morphine equivalents for their background analgesia. Indeed, differences were observed in patients receiving higher doses of oral morphine equivalents (≥ 120 mg/day), when proportional doses were higher than the initial titration dose. This better outcome was obtained without more adverse effects being reported. This can be explained by the tolerance relative to opioid dose regimen. Finally, patients' satisfaction did not differ between the two groups.

The choice of the dose of an ROO to be prescribed for BTcP has been controversial. Based on analysis of the literature, recent recommendations have suggested that the dose of ROOs to be given for an episode of BTcP should be determined by individual titration¹. However, there are several considerations regarding this statement that should be taken into account. First, about 10–30% of episodes treated may fail during dose titration, especially in patients receiving high doses of opioids^{9,10}. Secondly, dose titration may make the practical use of ROOs difficult in the daily activity, particularly at home or in outpatient clinics. Considering how presentation differs for each episode, titration should potentially be performed in each case. Thirdly, using different pieces of ROO for treating each episode may be time consuming and may well exceed

Table 1. Characteristics of patients.

	Group P	Group T	<i>p</i> -value
Age (mean \pm SD, years)	61.3(9.7)	65.4(10.5)	0.355*
Gender (M/F)	21/15	17/18	0.410†
Primary tumor			
Lung	6	6	
Gastrointestinal	5	10	
Breast	3	3	
Urogenital	8	7	
Other	14	9	
Incident pain due to bone metastases	19/36	24/35	0.173†

*Two-sample *t*-test; †Pearson chi-square statistic test with Yates correction.

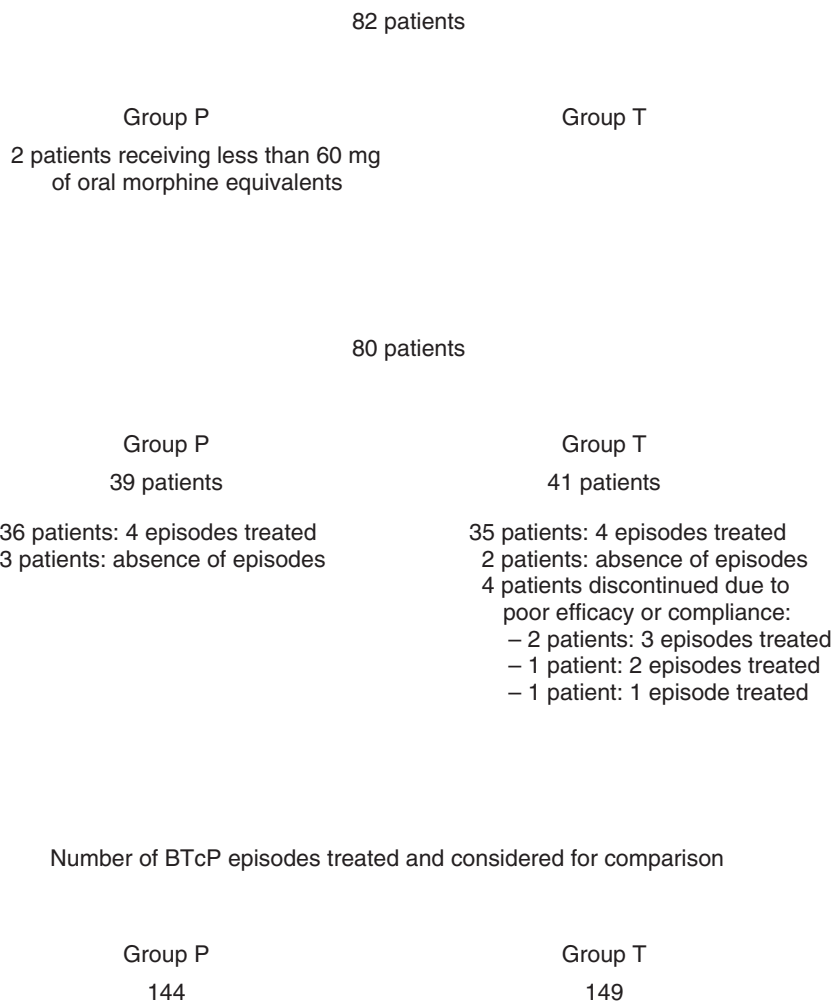


Figure 1. CONSORT flow chart of the study.

Table 2. Pain intensity differences between the two groups for all the episodes of BTcP (n = 284).

	Group P	Group T	p-value
T0, mean (±SD)	7.6 (1.0)	8.1 (1.2)	
T15, mean (±SD)	3.1 (1.7)*	3.1 (1.4)*	
No. of BTcP episodes			
With a decrease >33%	123/144	119/140	0.921†
With a decrease >50%	112/144	104/140	0.490†
No. of BTcP episodes‡			
With AE intensity 1–2	40/144	47/140	0.289†

*p < 0.0005 vs. T0 (paired samples t-test); †Pearson chi-square statistic test with Yates correction; ‡Two-sample t-test.

Table 3. Pain intensity differences between the two groups for episodes of BTcP in patients receiving doses of oral morphine equivalents ≥ 120 mg/day (60 and 60 episodes in groups P and T, respectively).

	Group P	Group T	p-value
T0, mean (±SD)	7.3 (0.9)	8.4 (0.9)	
T15, mean (±SD)	2.8 (1.6)*	3.7 (1.3)*	
No. of BTcP episodes			
With a decrease in PI >33%	52/60	45/60	0.104†
With a decrease in PI >50%	49/60	38/60	0.040†
No. of BTcP episodes‡			
With AE intensity 1–2	22/60	21/60	1.0†

*P < 0.0005 vs. T0 (paired samples t-test); †Pearson chi-square statistic test with Yates correction; ‡Two-sample t-test.

the duration of BTcP which can subside spontaneously, as evidenced by successful placebo-treated patients reported in literature⁹. From a practical point of view, patients should be prescribed more packages with different doses, unless using more pieces of lower doses. Most patients may

be reluctant to try the ROO medication and avoid using these drugs, preferring, in the end, traditional oral dosing of morphine⁴. Fourthly, randomized trials that state the need of dose titration, have never specifically examined this issue, and the information gathered is only a

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consequence of the study design which was aimed to demonstrate the superiority of ROOs over placebo, oral morphine or usual oral opioids, or to evaluate the safety and efficacy of ascending doses of ROOs in dose-finding studies. The titration period was open and not confirmed by comparison with any other method. The reason for the lack of relationship between doses for BTcP and a basal opioid regimen have not been clearly explained, considering that the presence of tolerance would suggest a dose proportional to that used for background analgesia. Of interest, tolerance to adverse effects in patients chronically exposed to opioids has been found, despite serum fentanyl levels as high as 6–8 ng/mL¹².

Finally, despite a large interindividual variability in patients' dose requirements, observations from data pooled from the same oral transmucosal fentanyl citrate (OTFC) trials showed a statistically significant relationship between the BTcP and round-the-clock opioid dose, also considering that the protocol was not aimed at demonstrating this¹³. When data were available, a simulation of a calculation of doses of opioids used for background analgesia and those achieved after individual titration showed mean values of proportional doses very close to those found after titration¹⁴.

It could be argued that a proportional dose without titration could expose patients to adverse effects. In practice, although dose titration may appear safer, it requires doses similar to those resulting from proportional doses and may result in more failures, prolonging patients' suffering and reducing their compliance. In a previous small controlled study comparing the use of OTFC and intravenous morphine given at doses proportional to the daily opioid dosage¹⁵, both intravenous morphine and OTFC were effective without producing relevant adverse effects, even when started at high doses in highly tolerant patients. In a study reproducing a clinical scenario of patients receiving opioids for BTcP, the dose of oral opioids used as rescue medication was 18% of the round-the-clock opioid dose, whereas for OTFC, titrated to determine the effective dose, the rescue dose was about 35% of the round-the-clock dose¹⁶, suggesting that the titration process may provide even higher doses than those expected by using proportional doses to the basal regimen.

Preliminary and confirmatory surveys have shown the safety of this approach in a large number of patients with no life-threatening adverse effects which occurs even in older patients treated with large doses of intravenous morphine. Respiratory depression, which is the most feared adverse effect, has never occurred, and no emergency call was needed^{17–19}. As intravenous morphine has the highest intrinsic risk for serious adverse events, one could argue that other drugs with similar rapid effects should be at least as safe. On the other hand experience is quite limited in patients receiving high doses of opioids. All the studies were based on limited maximum doses of

the different ROOs (OTFC, FBT, intranasal fentanyl and sublingual fentanyl, 1600, 800, 200, and 800 µg, respectively). For instance, in a recent preliminary study of the use of FBT in patients receiving high doses of opioids, proportionally higher doses of FBT were effective and well-tolerated by most patients²⁰. 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.

Among the ROOs available at the time of planning the current study, FBT was chosen because of its availability, greater independence from variability associated with the individual use, for example that found with OTFC. The interval of 15 minutes was chosen to evaluate the effectiveness of the treatment, as FBT is expected to produce analgesia within this period²¹.

The principal limitation of this study is the lack of blindness. Regardless of this, the complexity of this procedure in this context, and the associated costs for a study which was spontaneous and not sponsored must be borne in mind. In the same way as the current study design, all titration phases reported in the literature were open and not controlled, as were other studies assessing the efficacy and the safety of opioids given in doses proportional to the opioid basal regimen^{17–19}. These experiences have shown that in patients receiving opioids for chronic cancer pain the risks of administering about 20% of the daily dose of opioids with rapid modalities, intravenously or transmucosally, are minimal, going back to previous recommendations of European Association for Palliative Care, based on clinical experience²². The sample of patients was typical in terms of opioid treatment for background analgesia, ranging from 60 to 480 mg of oral morphine equivalents.

It is likely that differences could be more relevant in a selected population of patients receiving high doses of opioids, as suggested by data of patients receiving ≥ 120 mg/daily of oral morphine equivalents.

In conclusion, a titration process starting with the lowest doses of FBT, does not add any advantage in comparison with proportional doses in the management of BTcP, being neither more efficacious or safer. Doses proportional to basal opioid regimen for background pain seem to be effective and safe in the majority of patients. From a practical perspective, to reduce patients' reluctance in asking for opioid rescue medication^{8,16,23}, a definite indication should be provided and self-titration is unlikely to be accepted, unless performed in an assisted setting. Practical problems, including the need of titration, has probably limited the use of ROOs, despite the superiority over oral opioids and placebo demonstrated in various studies, regardless of the cost. As a consequence many patients will continue to prefer the conventional use of oral morphine, even though most of the episodes will vanish spontaneously⁸, and an uneventful burst of morphine will be gratuitously given. It is also to underline that all the

pioneer controlled studies were designed for approval from FDA. Therefore, indications were dictated by the prudence of managing new delivery systems, which were in their infancy. Further studies should be performed to confirm the data with other delivery systems, selected population, such as elderly, or patients receiving high doses of opioids for chronic cancer pain.

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