Dose titration of sublingual fentanyl, in relation to transdermal fentanyl dosing in cancer patients

Amaniti E MD, PhD, Zaralidou A MD, Maidatsi P MD, PhD,
Mitos G MD, Thoma G MD, Vasilakos D MD, PhD.

ABSTRACT

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Despite stable background pain, most cancer patients suffer 3-4 episodes of breakthrough pain daily. Aim of the present study was the evaluation of potential correlation between effective doses of sublingual fentanyl citrate, administered for controlling breakthrough pain, with transdermal fentanyl used for background pain. Fifty-six cancer patients were prospectivelly recruited. All patients were suffering episodes of breakthrough pain and managed with transdermal fentanyl 25-300μg/h for their background pain. Patients were assigned into two groups, group A (n=26) and group B (n=30), based on their transdermal fentanyl needs, 25-100μg/h or 125-300μg/h respectively. Sublingual fentanyl citrate titration was followed standard protocol, with a starting dose of 100μg. Dose effectiveness was evaluated by the patient, fifteen minutes later. If starting dose was considered inadequate, an extra dose of 100 μg was administered. The subsequent episode was treated with a starting dose of 200μg and an extra dose of 100μg, if needed, following the same stepwise approach to a maximum of 800 μg, per episode. Doses of transdermal fentanyl and sublingual fentanyl, as well as proportion of patients, titrated to 100, 200, 300, 400, 600 and 800μg of sublingual fentanyl were recorded for both groups. Statistical analysis was conducted using χ^2 and Mann Whitney U tests. Correlation between transdermal fentanyl and sublingual fentanyl doses was studied using χ^2 and Spearman rank correlation coefficient r. Level of significance was set at p=0.05. Transdermal fentanyl doses (mean±SD) were 65.38±27.45 and 186.66 ±62.53 μg/h for groups A and B respectively. Sublingual fentanyl doses (mean±SD) were

Chronic Pain Clinic, Anesthesiology and Critical Care Department, AHEPA University Hospital, Thessaloniki, Greece

265.38±26 μg and 396.67±30 μg for groups A and B, revealing significant differences between groups. Proportion of patients titrated to 100, 200, 300, 400, 600 and 800 μg between groups revealed significant association between transdermal fentanyl and sublingual fentanyl. The present study showed that, despite distinguishable characteristics of breakthrough pain, compared to background pain, patients administered high doses of slow releasing opioid regimen for background pain management, required proportionally high doses of rapid onset opioid for their breakthrough pain relief.

INTRODUCTION

Chronic pain is a common problem among cancer patients, particularly in the advanced stages of the disease, resulting in severe physical, mental, social and even financial distress[1]. Pain relief is therefore crucial to cancer pain management. Nevertheless, despite adequate control of chronic stable background pain, patients often experience transient episodes of moderate to severe pain, known as breakthrough pain. Although breakthrough pain episodes are considered short-lived and self-limited, they can contribute to significant physical and psychological impairment. Breakthrough pain management is focusing on reducing both the intensity and the severity of episodes.

The reported incidence of breakthrough pain among cancer patients varies from 24-95%[2]. While these episodes tend to occur frequently, with reported frequencies up to sixty per day, recent studies estimated a median of three to four episodes per day[3]. On the other hand, breakthrough pain characteristics, such as rapid onset and short duration, limited the effectiveness of classic around the clock analgesic regiments for this type of chronic pain. Hence, pharmacologic preparations with rapid onset, relatively short duration are necessary for breakthrough pain relief. New fentanyl formulations, enabling rapid absorption through mucus membranes, like oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablets (FBT) and sublingual fentanyl (SLF), are offering suitable alternatives to the classic rapid onset morphine, administered per os. These preparations are added to the around the clock daily administered opioids, in order to control both background stable and breakthrough pain.

Most breakthrough pain episodes are related to background pain. Patients with breakthrough pain tended to experience more intense background pain[4]. However, while studies in cancer patients have demonstrated a correlation between opioid needs for controlling background pain and breakthrough pain, other in-

vestigators failed to support this correlation[2]. Aim of the present study was the evaluation of a potential correlation between the effective doses of transmucosal fentanyl preparations, used for controlling breakthrough pain with the effective dose of transdermal fentanyl, administered for background pain management, in cancer patients.

MATERIAL AND METHODS

The study was conducted after Institutional Ethics Committee approval. Outpatients, treated in pain clinic for chronic cancer pain, were eligible for enrollment in the study, after written informed consent was obtained. Inclusion criteria were:

- Age > 18 years
- Presence of chronic cancer pain
- Stable, chronic treatment for background pain with transdermal fentanyl patch (TDS) in doses ranging from 25 μg/h to 300μg/h. Transdermal fentanyl should have been administered at least for a month or more, and should have been effective in controlling background pain. The latter was confirmed by the presence of a score ≤ 4 in the Numeric Pain Rating Scale (NPRS =0--10, where 0 corresponds to no pain and 10 corresponds to the worst pain imaginable)
- Presence of episodes of breakthrough pain. These were defined as transitory exacerbations of pain in patients suffering from chronic stable pain and being adequately controlled with transdermal fentanyl, as mentioned above. Patients were participated if they experienced a minimum of 3 episodes of breakthrough pain per week and a maximum of 4 episodes per day.
- Patients were not considered eligible when presented with pathological lesions in the oral cavity, due to contraindication for oral transmucosal treatment.

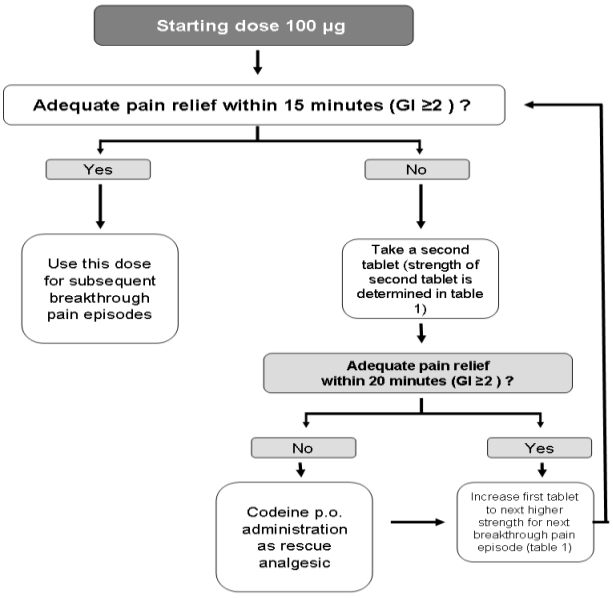
Based on the criteria listed above, a total of fifty six patients (29 men and 27 women) were initially enrolled in the study. Patients we assigned into two different groups, according to their daily TDS requirements for controlling chronic baseline pain.Group A(n=26) comprised patients treated with 25-100μg/h transdermal fentanyl while group B (n=30) comprised patients treated with 125-300μg/h transdermal fentanyl.

After confirmation of baseline pain relief, patients were subjected to breakthrough pain management with oral transmucosal fentanyl preparations (Sublingual Fentanyl Oral Disintegrating Tablets, ODT). A standard protocol of effective sublingual fentanyl dose titration to control episodes of breakthrough pain

was followed for each patient. Titration protocol was preceded by careful patient instruction on proper ODT administration. This procedure included reading Medication Guide and Patients Instruction for use by the patient, as well as discussion of any questions, posed by him with pain specialists.

Sublingual fentanyl ODT titration protocol included a stepwise increase in the dose of sublingual fentanyl, in order to confirm the effective dose for treatment of single breakthrough pain episode in each patient without non-acceptable side effects (Fig. 1). For this purpose, sublingual fentanyl ODT of different dose strength, were used, containing 100, 200 300, 400, 600 and 800μg fentanyl respectively. Breakthrough pain episodes were initially treated with a single dose of 100 μg sublingual fentanyl ODT tablet. Tablet was placed on the floor of the patients' mouth, under his tongue, according to medication guide. Tablet administration was followed by a period of fifteen minutes, prior to breakthrough pain relief assessment. The latter was achieved using a General Impression (GI) score. GI score was estimated by the patient, using a 5-point verbal rating scale, where 0=poor and 4 =excellent. This initial dose was considered successful if GI score≥ 2 and no serious side effects were present. Moreover, this dose should be adequate in achieving a GI score≥ 2 for at least three subsequent breakthrough pain episodes.

Figure 1. Sublingual fentanyl titration protocol.



This dose was then used for the subsequent breakthrough pain episodes. If the administration of 100 μg was followed by non-acceptable complications, such respiratory depression, excessive sedation, myoclonus, confusion, hypotension, nausea, then the patient dropped out of the study (Fig. 2).

Figure 2. Sublingual fentanyl titration protocol.

Adequate Analgesia (GI≥2)	YES		NO	
Non-acceptable side effects	No	Yes	No	Yes
Decision	Successful therapeutic dose	**One strength down** Drop out for dose 100 μg	One strength up Drop out for dose 800 μg	Drop out

If the initial dose was considered insufficient to control pain (GI score<2) fifteen minutes after administration, then a second dose of 100μg sublingual fentanyl was given (Fig. 1,2). The effect of this additional dose was estimated 20 minutes after administration and if patient continued to experience pain, rescue doses of 30mg codeine p.o. was available. Subsequent episodes of breakthrough pain were then initially managed with a starting dose of 200μg sublingual fentanyl ODT (Fig. 1). Again, the analgesic effect was estimated ten minutes after sublingual fentanyl administration and if considered insufficient (GI score<2), a supplemental dose of 100μg was given, followed by rescue opioids twenty minutes after, if breakthrough pain was still inadequately controlled. Subsequent episodes were then managed with starting doses of 300μg sublingual fentanyl. On the other hand, if administration of sublingual fentanyl caused non acceptable side effects, then patient used one dose strength down ODT tablets for the subsequent pain episodes (Fig. 2). If starting dose for controlling breakthrough pain was ≥400μg, and this dose was considered inadequate ten minutes after, then supplemental doses were 200μg. If doses up to 800μg were considered inadequate to control breakthrough pain, these patients dropped out the study (Fig. 2).

During the sublingual fentanyl titration phase, alterations in background pain were managed with appropriate adjustment of transdermal fentanyl TDS dose, targeting to NPRS ≤ 4 throughout the study period.

Titration of sublingual fentanyl, necessary to control breakthrough pain episodes, was considered successful and effective sublingual fentanyl dose was reached for each patient, when adequate analgesia (GI≥2) through three subsequent breakthrough pain episodes was achieved, with acceptable side effects (Fig. 2).

Variables recorded included the effective dose of transdermal fentanyl for controlling background pain and the effective sublingual dose for controlling breakthrough pain in each patient. Primary outcomes were the doses of transdermal fentanyl, the effective doses of sublingual fentanyl, the number and the proportion of patients reaching an effective sublingual fentanyl dose of 100, 200, 300, 400, 600, 800 μg between two groups.

Data regarding transdermal fentanyl doses for both groups were analyzed using descriptive statistics. Differences regarding sublingual fentanyl effective dose between groups, were analyzed using Mann Whitney U test. Differences between groups, regarding distribution of patients in each dose strength of sublingual fentanyl for breakthrough pain were evaluated using χ^2 test. Moreover, correlation between effective sublingual fentanyl dose and background transdermal fentanyl dose by patient was analyzed by a scatter plot and by compu-

ting Spearman correlation coefficient. Demographic data were analyzed using χ^2 test. Level of significance was set at p=0.05.

RESULTS

All fifty six patients initially enrolled, completed the study. Groups A and B were comparable, regarding men/women ratio (p<0.05). The doses of transdermal fentanyl (as means± ±SD) for group A and B were 65.38μg/h ± ±27.45μg/h and 186.66μg/h ± 62.53μg/h respectively.

The proportion of patients reaching an effective sublingual fentanyl dose of 100, 200, 300, 400, 600 and 800μg in groups A and B is shown in Figure 3. The effective doses of transmucosal fentanyl (as means ± SD) for group A and B were 265.38μg±26μg and 396.67μg±30μg respectively. Analysis revealed significant difference between groups (p= =0.014). Moreover, significant differences, regarding patients distribution in each effective transmucosal fentanyl dose, were demonstrated between groups (p=0.0240).

Scatter plot between effective sublingual fentanyl dose and background transdermal fentanyl dose by patient is shown in Figure 4. Spearman Rank Correlation coefficient measurement, demonstrated a statistical dependence between two variables (Spearman Correlation Coefficient r_s = 0.6830, p<0.0001).

Figure 3. Proportion of patients effectively titrated to 100, 200, 300, 400, 600 and 800 μg of sublingual fentanyl between groups.

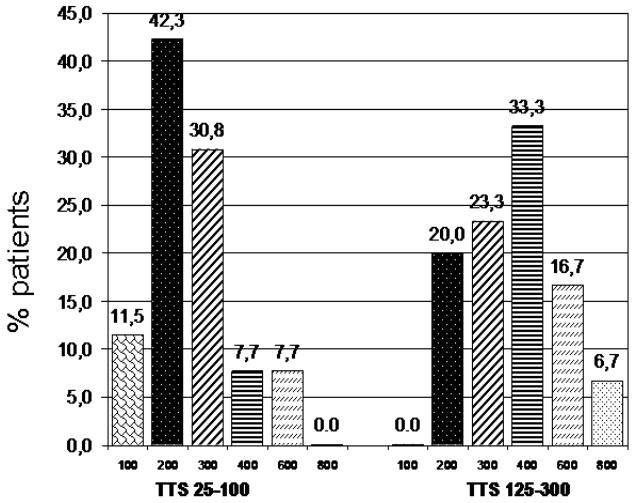
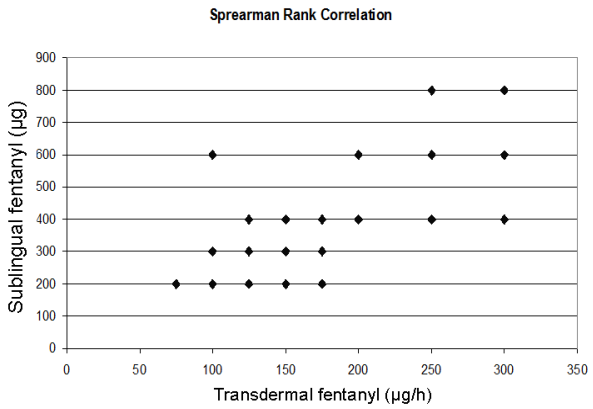


Figure 4. Scatter plot showing transdermal and sublingual fentanyl doses for each patient.



DISCUSSION

Titration of opioids for controlling breakthrough pain is a considerable issue in the management of cancer patients. European Association for Palliative Care (EAPC) recommendations suggested that the effective dose

of opioids for controlling breakthrough pain should be a percentage of patients' daily opioid dose[5]. However, these recommendations were based on expert advice without any strong evidence regarding their accuracy and mainly referred to the use of oral opioids, especially morphine, for breakthrough pain relief. New formulations, delivering fentanyl through oral or nasal mucus membranes and providing rapid onset analgesia, including sublingual fentanyl ODT tablets, have not been considered suitable for administration at fixed doses, proportional to "around the clock" opioid doses. Instead, dose escalation following specific algorithms and individual dose titration are suggested, in order to enable effective analgesia and minimizing adverse effects[6-8]. This practice poses difficulties in daily practice, on the assumption that patients directly participate in dose titration. Patients need to begin therapy at a low dose and to titrate to higher doses in every case. Studies regarding patients' compliance to breakthrough pain opioid regimen have shown that most patients do not take breakthrough medication every time they experience pain, often due to concerns about overdosing or tolerance[9]. Consequently, any possible adjustment of the titration protocol to patients' current opioid needs, in order to achieve rapid effective dose determination, should possibly enhance the use of rapid onset opioids for breakthrough pain.

The possible correlation between around the clock opioid for background pain and rapid onset opioid for breakthrough pain is still controversial. Previous studies have failed to show any correlation between the basal opioid regimen and the dose of rapid onset opioid. This lack of correlation was observed for different rapid onset opioid formulations, including transmucosal fentanyl citrate (OTFC)[10-11] fentanyl buccal tablets[12,13] and sublingual fentanyl tablets (SLF)[14]. However, in these studies, a substantial proportion of patients failed dose titration of OTFC and FBT and when pooling the same data from all the trials, a statistically significant relationship between the breakthrough dose and around-the-clock dose was found[15]. Other studies have confirmed this correlation. Mercadante et al, evaluating patients at high doses for background pain and receiving buccal tablets for breakthrough pain, showed proportionality between breakthrough pain dose and background dose[16]. These studies are in accordance with the results of the present study, suggesting a correlation between background and breakthrough pain opioid doses.

Opioid needs,especially in cancer patients with advanced disease, are influenced by pharmacologic tolerance. The presence of tolerance should suggest proportionality between breakthrough pain and background pain opioid needs[17]. However, while long term exposu-

re to one opioid often results in the development of tolerance to the effects of other opioids, a phenomenon known as cross tolerance, it is rarely complete[18]. Consequently, a possible explanation for the discrepancy in results regarding opioid dose correlation could be attributed to the differences among studies, regarding opioids used for background pain. The present study enrolled patients treated with transdermal fentanyl for their background pain, excluding patients treated with other opioids like morphine. Provided that the same pharmacologic agent, fentanyl in different formulations, was used for both background and breakthrough pain could influence the observed correlation between doses.

All fifty six patients entered the titration protocol completed the study and titrated to doses 100-800μg of sublingual fentanyl, suggesting high success rates regarding titration. These data are in constrast to previous titration studies, where a considerable part of patients initially enrolled in the study, failed to titrate to effective doses[10,19,20]. High success rates, observed in the present study, could be attributed to the relative small transdermal fentanyl doses, administered for background pain management. Low dose regimens may suggest limited development of pharmacologic tolerance among patients entered the study, leading to successful titration process to doses up to 800μg of sublingual fentanyl.

In conclusion, breakthrough cancer pain consist an entity with special characteristics, such as rapid onset and short duration, necessitating a different pharmacologic approach, compared to constant background pain management. Rapid onset opioids formulations, especially for breakthrough pain management, have been shown to be highly effective and well tolerated in the treatment of breakthrough pain. However, while previous studies failed to show any correlation between breakthrough pain and background pain opioids, there is still a controversy regarding the existence of proportionality between these two entities. The present study, despite its preliminary results, showed correlation between transdermal fentanyl and sublingual fentanyl doses. Further studies are necessary to confirm these data. The existence of proportionality between background and breakthrough pain opioid needs may facilitate the titration phase, and leading faster to efficient dosing.

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Keywords: Breakthrough pain, sublingual fentanyl, transdermal fentanyl, cancer pain.

CORRESPONDING AUTHOR:

Amaniti Ekaterini

Anesthesiology and Critical Care Department, AHEPA University Hospital,

Thessaloniki, 54636, Greece

tel: +302310994862

e-mail: amanitoula@gmail.com