Original Article

Switching from Transdermal Drugs: An Observational "N of 1" Study of Fentanyl and Buprenorphine

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Abstract

The aim of this study was to confirm that the concomitant presence of transdermal fentanyl (TTS FE) and buprenorphine (TTS BU) may be feasible without important consequences, using doses presumed to be equianalgesic. A prospective "N of 1" study was carried out in a sample of volunteers with cancer pain receiving stable doses of TTS FE or TTS BU, with adequate pain and symptom control. In the study design, each patient provided data before and after a switch from one opioid to the other and then back to the previous one. Sixteen patients receiving daily stable doses of 0.6 or 1.2 mg of TTS FE were switched to TTS BU using an FE-BU ratio of 0.6—0.8. After three days, the TTS BU patch was removed and TTS FE patch was placed for another three days. Six patients receiving TTS BU were switched to TTS FE and then rotated back to TTS BU with the same dosing considerations. No statistical differences in changes in pain and symptom intensity during switching and between the two different sequences were observed. No significant changes in rescue doses of oral morphine were reported at the same intervals. Cancer patients receiving stable doses of TTS FE or TTS BU can be safely switched to the alternative transdermal opioid. Further studies should be performed to gather data about the use of TTS BU with other opioids, at different doses, and in different clinical conditions. J Pain Symptom Manage 2007;34:532—538. © *2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Cancer pain, opioid switching, transdermal fentanyl, transdermal buprenorphine

Introduction

Cancer pain management is based on sequential analgesic administration, as suggested by the World Health Organization, using steps corresponding to drugs with different maximal efficacies.[1] Although this approach has had an impact of paramount importance in terms of

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clinical outcome and educational perspective, unfortunately it lacks necessary information about the possible alternatives, due to the paucity of controlled studies in this field.

Buprenorphine (BU) has been a neglected drug in such a context. The previous available parenteral and sublingual formulations provided an inconvenient bolus effect that seemed poorly tolerated, particularly in the elderly. Other problems have included a presumed ceiling effect at a level which has never been specifically estimated, and concerns about coadministration with other opioids due to its presumed antagonist activity.[2] The use of BU in association with other opioids, for example, during opioid switching, has been of particular concern, because of the possibility of antagonist effects that could reduce analgesia or induce withdrawal symptoms.

BU is known to be a partial mu-agonist and has a slow receptor dissociation, which could potentially impede *in vivo* the full effectiveness of another opioid. Recent experimental studies have confirmed the absence of a refractory period between the offset of action of BU and the onset of action of other opioid mu-agonists. The persistent receptor occupancy has been seen in isolated receptor preparation, whereas under *in vivo* conditions the accessibility of mu-receptor sites is maintained.[3–5] Accordingly, morphine, used as a rescue medication, has been found to be effective in patients receiving BU.[6] Experiences in cancer pain management also showed that patients who switched from other opioids encountered no problems with the conversion, and morphine added to BU did not create problems.[3]

The recent availability of transdermal delivery of BU, avoiding plasma concentration peaks, has made this drug more useful than with previous preparations. The use of transdermal drugs, including transdermal buprenorphine (TTS BU) and transdermal fentanyl (TTS FE), has been increasing during the last years, probably as a consequence of a presumed easy administration, particularly among oncologists.

In the clinical setting, it is often necessary to switch to other opioids for different reasons, including local reactions or the occurrence of adverse effects. Although an approximate conversion ratio of about 1:100 between oral morphine and TTS FE has been established in previous studies,[7,8] no data have substantiated the conversion ratio for TTS BU. Moreover, data about a direct conversion ratio between the two transdermal opioids, without resorting to indirect conversions with morphine equivalents, are lacking.

The aim of this study was to confirm that the concomitant presence of these two transdermal opioids may be feasible without important consequences using doses presumed to be equianalgesic, according to preliminary experience in patients optimally managed for cancer pain.

Patients and Methods

A prospective study was carried out in a sample of consecutive cancer patients receiving stable doses of TTS FE or TTS BU, with adequate pain and symptom control. The design was a within-patient, two-way crossover, in which each patient provided data before and after a switch from one opioid to the other and then back to the previous one.

Selection criteria included volunteers receiving one of the two drugs at stable doses for at least six days, with acceptable analgesia and without relevant adverse effects, and using two or fewer breakthrough doses per day. The duration of adequate analgesia had to be at least three days. Patients with poor performance status, relevant metabolic alterations, cognitive impairment, or an unfavorable balance between analgesia and adverse effects, and those who had unstable pain or the need to change patches at less than three-day intervals were excluded. Patients receiving a new course of chemotherapy or who had recently received radiotherapy were also excluded. Institutional approval and informed consent were obtained.

Patients receiving daily stable doses of 0.6 or 1.2 mg of TTS FE (25 and 50 μg/h, respectively) for more than six days, with no more than two doses of oral morphine (10 and 20 mg, respectively) as needed, were switched to TTS BU using an FE-BU ratio of 0.6–0.8 (0.6–1.2 mg/day of TTS FE equivalent to 0.8–1.6 mg/day of TTS BU). The BU patch was placed whereas the FE patch was removed (T0). After three days (T3), the TTS BU patch

was removed and TTS FE patch was placed for another three days (T6). Patients receiving 1.2 mg (52 μg/h) of TTS BU were excluded, due to the lack of existing intermediate formulation between 0.6 (25 μg/h) and 1.2 mg (50 μg/h) of TTS FE.

Patients receiving TTS BU in doses of 0.8 or 1.6 mg/day (35 and 70 μg/h, respectively) were switched to TTS FE (0.6–1.2 mg/day, or 25 and 50 μg/h, respectively) and then rotated back to TTS BU with the same assessments. Extra doses of oral morphine (10 mg for patients receiving patches of 25 μg/h or 35 μg/h, of TTS FE and TTS BU, respectively) were available orally for breakthrough pain during all the crossover phases. In case of relevant unfavorable clinical changes, opioids and their doses were changed according to the clinical need, and the protocol was interrupted.

Adjuvant drugs, previously administered, were continued at the same doses during the switching. All patients were strictly monitored in the unit, by frequent outpatient visits, or telephone contact to record the following data at T0, T1 (one day after switching), T3 (the day of rotation to the previous drug), T4 (one day after rotation), and T6 (the third day after switching back):

- Age, gender, primary cancer and known metastases, pain causes and mechanisms, and performance status.
- Transdermal opioid doses.
- Symptoms associated with opioid therapy or commonly present in advanced cancer patients, such as nausea and vomiting, drowsiness, confusion, constipation, and dry-mouth, using a scale from 0 to 3 (not at all, slight, a lot, and awful); symptoms were assessed by the patient.
- Pain intensity, measured using the patient's self-report on a numerical 0–10 scale.
- Pain syndromes were considered on the basis of clinical history, anatomical site of primary tumor and known metastases, physical examination, and investigations when available.

Statistical Analysis

For statistical analysis, patients were divided into two groups: 16 patients who were initially switched from TTS FE to TTS BU and six patients who were initially switched from TTS BU to TTS FE. The basic characteristics of the two therapy groups were tested by not-paired samples. Student's *t*-test was used to estimate the treatment effects, within groups and across groups. Analysis of the variance for repeated measures was used to estimate the interaction treatments in time. All *P*-values were two-sided, and *P*-values less than 0.05 were considered statistically significant. Data were analyzed by SPSS Release 13.0 and Systat Software 8.0.

Results

Patient characteristics are shown in Table 1. All patients completed the switching and were rotated back to the original opioid. Sixteen cancer patients receiving TTS FE in doses of 0.6 (patch 25 μg/h) or 1.2 mg/day (patch 50 μg/h), and six patients receiving TTS BU in doses of 0.8 (patch 35 μg/h) or 1.6 mg/day (patch 70 μg/h) completed the study. No statistical differences in gender and age were found between the two sequence groups, or the different dosages. A meaningful treatment interaction was not found. No significant differences were found in symptom intensity scores when considering the pain mechanism or the primary cancer.

No statistical differences in pain and symptom intensity between the two different sequences were observed. Data regarding changes in pain and symptom intensity are reported in Tables 2 and 3. Although no significant changes were observed between intervals examined, some patients reported changes of more than two points in pain intensity during the course of rotation in both directions

Table 1
Patient Characteristics

Age (mean, range, yr)	57 (34–82)
Gender (M/F)	7/15
Primary tumor	
Breast	6
Colon/rectum	5
Lung	4
Melanoma	2
Others	5
Pain mechanisms	
Somatic	11
Visceral	7
Somatic-Visceral	3
Somatic-Neuropathic	1

Table 2

Pain and Symptom Intensity in 16 Patients Who Switched from FE to BU (T0–T3), and Switched Back to FE (T3–T6)

	T0	T1	T2	T3	T4	T5	T6
Pain (0–10)	1.9 (1.3–2.5)	2.1 (1.2–2.9)	1.9 (1.2–2.7)	2.3 (1.4–3.1)	1.9 (1.1–2.7)	1.8 (1.1–2.4)	1.7 (1.1–2.3)
Nausea (0–3)	0.4 (0.1–0.6)	0.4 (0.2–0.7)	0.5 (0.2–0.6)	0.6 (0.3–0.6)	0.6 (0.3–0.9)	0.6 (0.3–0.9)	0.5 (0.3–0.8)
Drowsiness (0–3)	0.3 (0.1–0.6)	0.6 (0.2–0.7)	0.5 (0.2–0.8)	0.6 (0.3–0.8)	0.4 (0.2–0.7)	0.6 (0.2–0.9)	0.6 (0.3–0.8)
Confusion (0–3)	0	0.1 (−0.1 to 0.3)	0.2 (−0.03 to 0.4)	0.2 (−0.03 to 0.4)	0.2 (−0.03 to 0.4)	0.2 (0.03–0.4)	0.1 (−0.1 to 0.3)
Xerostomia (0–3)	0.3 (0.1–0.6)	0.5 (0.2–0.8)	0.6 (0.2–1)	0.7 (0.3–1.1)	0.7 (0.3–1.1)	0.8 (0.3–1.2)	0.6 (0.2–0.9)
Constipation (0–3)	0.7 (0.2–1.2)	0.6 (0.2–1)	0.6 (0.2–0.9)	0.6 (0.3–0.9)	0.6 (0.2–0.9)	0.6 (0.2–0.9)	0.6 (0.2–0.9)

Data are expressed as mean (CI 95%).

(decrease or increase) and both drug sequences (Fig. 1). No significant changes in rescue doses of oral morphine were reported at the same intervals.

Discussion

The results obtained in this study confirm that patients who were successfully receiving a TTS FE or BU maintained their pain control without relevant changes in adverse effects during the crossover switching in each direction. Some individuals, however, demonstrated some changes in pain intensity. These changes were likely to be considered acceptable for patients and no relevant morphine doses were needed, regardless of the sequence used.

We assumed on the basis of a pre-study experience that the equianalgesic ratio between the two transdermal drugs would be 0.6—0.8, and equipotent ratios with oral morphine were estimated to be 1:100 for FE and 1:75 for BU.[6,8] This initial approach was successful in the group of patients studied and no significant changes in opioid doses were necessary. There were no relevant changes in clinical situations, and the stable and favorable balance between analgesia and adverse effects was largely maintained. Of interest, even when rotating back to the first opioid, no relevant changes were observed. Many patients declared that they were unaware of the change, although this information was not systematically collected. These findings suggest that the doses chosen were approximately equivalent and could be interchangeable in the context of patients with an acceptable level of analgesia and adverse effects.

Critical assessment points were T1 and T4, after the switching took place, because significant plasma concentrations of the two drugs coexist, potentially interfering in case of a negative interaction between the drugs, and T3 and T6, when a potential stable concentration of the second drug is achieved. The outcome of this study suggests that no relevant interference exists between these two opioids, at least in the range of the doses used. Consistent concentrations of FE are still present even 24 hours after removing the patch for opioid switching.[9] The offset and the onset of each drug were able to appropriately maintain the

Table 3
Pain and Symptom Intensity in Six Patients Who Switched from BU to FE (T0–T3), and Switched Back to BU (T3–T6)

	T0	T1	T2	T3	T4	T5	T6
Pain (0–10)	1.8 (−0.1 to 3.6)	1.8 (0.3–3.6)	1.6 (−0.2 to 3.3)	1.8 (0.3–3.4)	2.9 (1.1–4.7)	2.3 (0.9–3.6)	1.8 (0.2–3.3)
Nausea (0–3)	0.8 (0.8–2.9)	0.9 (−0.1 to 1.1)	0.8 (0.4–1.3)	0.8 (−0.05 to 1.5)	0.7 (0.1–1.2)	0.7 (0.1–1.2)	0.6 (0.2–0.9)
Drowsiness (0–3)	0.2 (−0. to 0.6)	0.7 (0.1–1.2)	0.9 (0.2–1.6)	0.6 (−0.1 to 1.1)	0.4 (−0.1 to 0.9)	0.6 (−0.1–1.1)	0.6 (−0.1 to 1.1)
Confusion (0–3)	0	0.2 (−0.3 to 0.6)	0.2 (−0.3 to 0.6)	0	0	0.2 (0.3–0.6)	0.2 (−0.3 to 0.6)
Xerostomia (0–3)	1 (0.3–2.3)	1.3 (0.1–2.6)	0.8 (0.0.4–1.6)	0.8 (0.2–1.7)	0.8 (0.04–1.6)	1 (−0.1 to 2.1)	1 (−0.1 to 2.1)
Constipation (0–3)	1.2 (−0.4 to 2.7)	0.3 (−0.5 to 1.2)	0.3 (−0.5 to 1.2)	0.7 (−0.2 to 1.5)	0.8 (−0.2 to 1.9)	0.6 (−0.4 to 1.4)	0.2 (−0.3 to 0.6)

previous analgesic level in both directions, producing a clinical carry-over effect that is consistent with a raw clinical scenario, where no therapeutic gaps should be allowed, particularly in volunteers who had a well-balanced condition before initiating the study. Of interest, in some patients, changes in pain intensity of more than two points on the numerical scale were observed in both directions of opioid rotation. For example, one patient (Patient 3 in Fig. 1) showed a progressive decrease in pain intensity after being switched to TTS FE and then had a worsening when rotated back to TTS BU to achieve a final potential benefit in comparison with the initial pain score intensity. On the contrary, Patient 4 showed an increase in pain intensity after switching back to TTS BU. One patient (Patient 9) showed an increase in pain intensity, which persisted after switching back to TTS FE. Patient 22 had an increased pain level after switching to BU TTS, which resolved in the following days without important changes after being rotated to FE TTS.

All these findings could be explained by individual responses to drugs with different activities on opioid receptors. Alternately, it could be attributed to spontaneous changes in pain intensity in patients assumed to be stable, independent of the drug effects as a consequence of the study design. Globally, these changes were not considered to be relevant by patients, and opioid consumption did not change, even in individuals who had more relevant changes in pain intensity.

We also recognize that stable plasma concentrations with TTS drugs may require more than three days, which was the interval chosen in the protocol. In the clinical setting, however, this is the common interval used to make a decision, again reproducing clinical practice. On the contrary, in some patients, the effect of the patch may last less than 72 hours. However, only patients with a constant analgesia with change intervals of three days were selected. Finally, BU could be expected to provide prolonged analgesia, after removing the patch, due to a longer binding with the receptor. This, however, did not have any clinical influence when rotating to FE.

There is paucity of data in the literature about switching between TTS drugs. The findings of this study confirm preliminary

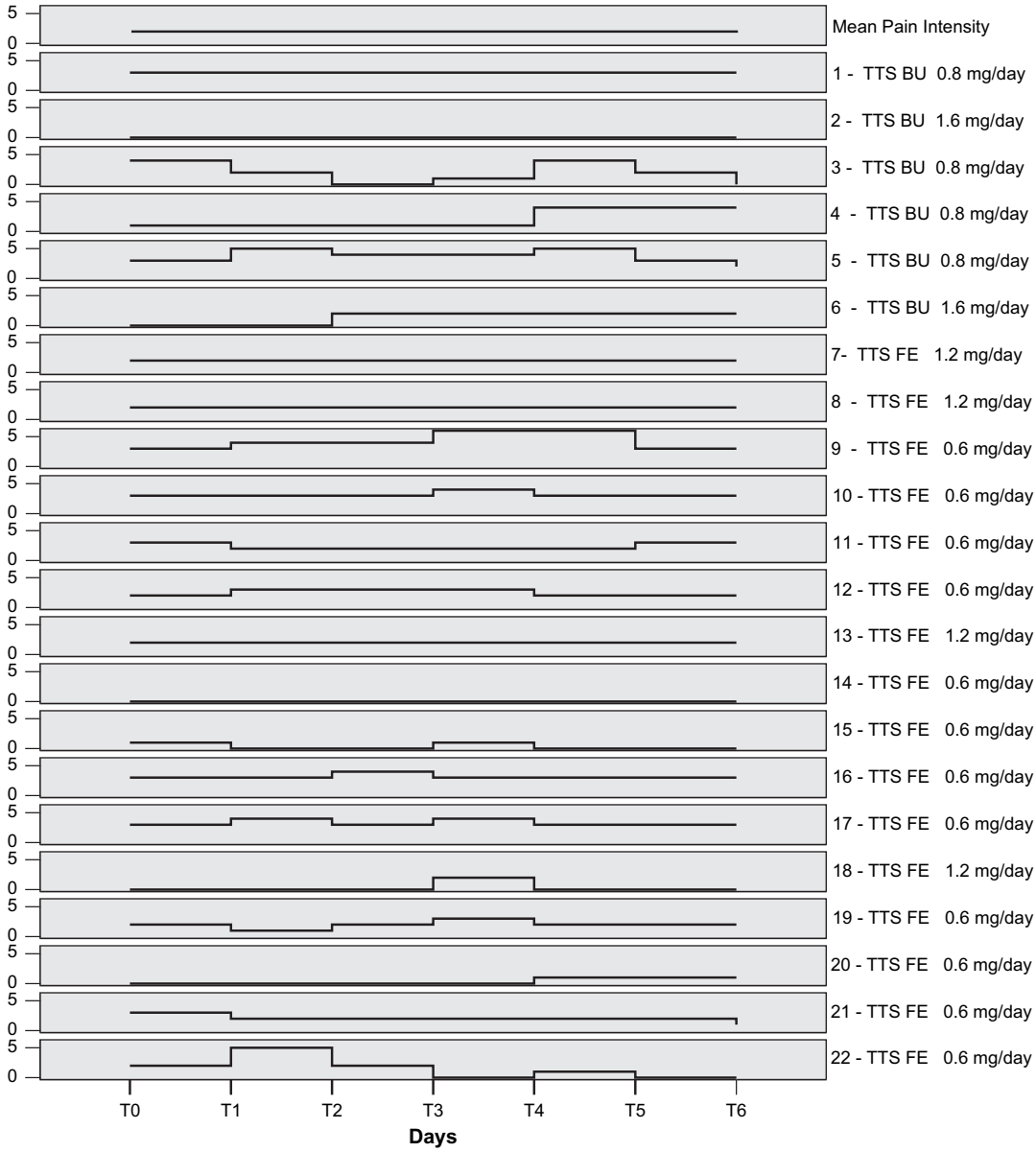

Fig. 1. Changes in pain intensity during BU-FE-BU sequence (Patients 1–6) and FE-BU-FE sequence (Patients 7–22). Initial doses of TTS BU and TTS FE.

observations in unstable patients who were switched successfully from prior analgesic therapy with large doses of other opioids.[10–12] In non-cancer patients with neuropathic pain, the efficacy of three escalating doses of TTS FE and BU was compared (25, 50, and 75 μg/h and 35, 52.5, and 70 μg/h, respectively). The two substances provided similar analgesia, but BU produced more sedation, constipation, and local skin problems. The protocol proposed, however, did not follow a proportional dose increase ratio, as doses of FE were tripled, whereas BU doses were just doubled.[11] Data were incomplete for an appropriate comparison with the present results.

A retrospective analysis showed lower calculated equipotent oral morphine doses in TTS BU groups compared with TTS FE groups, suggesting an equipotency ratio of about 1:110. However, this observation was not drawn from clinical data, but from a database containing numbers concerning drug prescriptions of patients who had received long-term

treatment with TTS FE and TTS BU, who were presumed to have similar intensity.[13]

There are some limitations to this study, including the number of patients and selection criteria in the range of low level of pain intensity. However, the study was viewed as preliminary and the first step was to assess what happens in patients using presumed equivalent doses of transdermal drugs in patients with adequate pain control and no adverse effects.

In conclusion, cancer patients receiving TTS FE or BU may be switched to TTS BU or FE, respectively, without encountering relevant clinical problems. Although the results present here do not provide conclusive evidence, they provide an indicator for a suitable conversion ratio to be used in future studies to gather data about the use of TTS BU in other contexts, with other opioids, at different doses, and in different clinical conditions.

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