Original article

Safety and efficacy of transdermal fentanyl in patients with cancer pain: phase IV, Turkish oncology group trial

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Safety and efficacy of transdermal fentanyl in patients with cancer pain: phase IV, Turkish oncology group trial

We have performed a prospective evaluation of the efficacy, safety and convenience of the transdermal therapeutic system – fentanyl (TTS-F) in Turkish cancer patients when it was newly available in Turkey. Ninety-nine patients with historically confirmed malignancy and pain entered the study; the mean age was 55.1 (16–58) years. The study duration was 28 days. Transdermal therapeutic system – fentanyl was used in opioid-naïve or pre-treated patients. Most patients reported a decrease in pain severity. Use of rescue medication decreased from day 4 to day 28. The majority of patients rated patch convenience of use as excellent. A total of 22.2% of patients experienced adverse events that were either probably related or very likely to be related to the study drug. The majority of the adverse events mentioned were related to the digestive system. Eighteen serious adverse events were reported by 13 patients. Six events were doubtfully related, and 12 events were not related to the study drug. Four patients died during the trial. None of these deaths was attributed to the study drug. In conclusion, the trial showed that TTS-F is easily managed, effective and will help to enable the appropriate opioid administration to patients who are suffering from cancer pain in Turkey.

Keywords: transdermal fentanyl, cancer pain, opioids.

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INTRODUCTION

Transdermal therapeutic system – fentanyl (TTS-F) is an effective transdermal opioid alternative to oral opioids for the control of chronic pain in cancer patients (Yu *et al.* 2005). Compared with morphine, fentanyl exhibits a

higher clearance rate (Morita *et al*. 2005), greater ease in crossing the blood brain barrier (Wuster *et al*. 1980), a higher affinity for the μ-opiate receptor (Wuster *et al*. 1980), haemodynamic stability (Huynh *et al*. 2005) and less histamine release (Hall 1980; Huynh *et al*. 2005). It is useful in managing chronic pain of moderate to severe intensity, since this transcutaneous system provides continuous controlled systemic delivery of fentanyl for up to 72 h. A major area for the use of TTS-F is in the management of terminal cancer-related pain. Transdermal therapeutic system – fentanyl has been approved for marketing in the USA and Canada since 1991. It is now available in more than 25 countries, including Turkey (since 2000). Since its effectiveness and tolerability has not been studied in the Turkish population yet, we performed a prospective evaluation of the efficacy, safety and convenience of TTS-F in cancer patients with pain requiring opioid analgesics.

MATERIALS AND METHODS

This was a phase IV, open, multicentre study. Patients suffering from cancer pain requiring opioids, with a histologically confirmed malignancy at an advanced stage and with an estimated survival of at least 3 months, were enrolled into the study.

Patient population

A total of 100 patients were enrolled into the study; safety data were available from 99. Of the 100 patients enrolled, 74 completed the study. The most frequently mentioned reason for withdrawal was the 'adverse event' ($n = 14$). The safety population excluded one patient who died on the day of enrolment before receiving the study drug. The intention to treat (ITT) population excluded another two patients, in each case the reason being the 'patient does not have at least one post-baseline pain control (VAS) observation'. The per-protocol population excluded a further six patients, the reasons being 'non-compliant in study drug usage', the 'opioid naïve patient started with 50 mcg/h' and the 'patient did not attend'.

Ninety-nine patients (41 men and 58 women) entered the study; the mean age was 55.1 (range 16–58) years. The most frequent six diagnoses are breast (19 patients), lung (16 patients), colorectal (10 patients), gastric (nine patients), prostate (five patients) and ovarian (five patients) cancers. Ninety-three patients mentioned an analgesic history. No specific criteria for pain control or tolerability of current treatment were identified for the eligibility. Patients were admitted to the study regardless of their previous analgesic treatment. All patients received TTS-F every 3 days, and the results were compared with their previous treatment. During the study, oral morphine, codeine and tramadol were used as rescue medication. A dose titration was conducted in 25 μg/h increments based on pain relief. Forty-five patients (44.6%) had previously used weak opioids (tramadol or codeine), 21 patients used strong opioids with an average morphine dose of 29.4 μg/h, and 40 patients were opioid naïve. All patients gave written informed consent before participating in the study.

Study design

The study duration was 28 days. Assessments were made on three visits (on days 1, 16 and 28) and via seven phone contacts (on days 4, 7, 10, 13, 19, 22 and 25).

The primary objectives of this study were to assess: pain control using visual analogue scales (VAS), and total dose of TTS-F. The secondary objectives were to measure: the convenience of the use of patches, the performance status (using the Karnofsky Performance Status Scale), and the incidence and severity of gastrointestinal adverse events (nausea, vomiting and constipation), which were rated on a four-point scale. All other adverse events were documented when occurring.

The exclusion criteria were alcohol or drug abuse, history of opioid allergy, carbon dioxide retention, active skin disease, serum creatinine >2 mg/dL, bilirubin >2 mg/dL, any coexisting medical condition that is likely to interfere with the study procedures, and/or results (e.g. severe alteration of lung, liver or renal function). Patients who had experienced changes in their hormonal and/or cytostatic medication in the 7 days preceding entry into the study, and those who had received radiotherapy in the preceding 4 weeks were excluded from the study.

The following assessments were performed at visit 1:

- medical history, physical examination and vital signs (weight, height, pulse, systolic and diastolic blood pressure);
- analgesic medication and concomitant therapies over previous 7 days;
- classification of pain according to the International Association for the Study of Pain (IASP) criteria;
- overall evaluation of pain treatment;
- evaluation of gastrointestinal disturbance.

The following efficacy parameters were assessed at visits 2 and 3:

- the dose of TTS-F;
- pain score assessment;

- overall evaluation of the pain treatment;
- nausea and vomiting;
- evaluation of gastrointestinal disturbances;
- convenience of use of patches and treatment preference;
- general condition, performance status and vitals signs;
- disease progression;
- patch adhesion;
- other adverse events.

The patches were replaced either every 48 or 72 h. The initial TTS-F dose was established using an equianalgesic potency ratio of the patient's previous analgesic and fentanyl. This ratio was based on a clinically tested standard narcotic equivalence regimen (Finch & de Kornfeld 1964). Patients used oral or parenteral morphine or tramadol for rescue analgesia. The TTS-F dose was increased every 2–3 days until adequate analgesia was attained.

Statistical analysis

Primary efficacy analysis

The dose of TTS-F observed on different visit days was compared by means of the Friedman test. Pain assessment was summarized over the visits using summary statistics for VAS scores. The baseline and endpoint values of the overall evaluation of pain treatment were compared using the Wilcoxon Matched Pairs Signed Rank Test.

Secondary efficacy analyses

The frequency of constipation, nausea and vomiting at each time point was calculated and compared with baseline using the Cochran Q and McNamara tests. The Karnofsky Performance Status scores at visits 2 and 3 were compared with the baseline score (visit 1) using the Wilcoxon Matched Pairs Signed Rank Test.

RESULTS

Effect on pain

Pain severity decreased sharply after day 2 and continued to decrease throughout the whole study period (Fig. 1). The TTS-F dose used increased gradually until day 21 and then remained stable (Fig. 2). Use of rescue medication (expressed as morphine equivalents) decreased from day 4 to day 28. The morphine equivalent of rescue medication is summarized in Figure 3. The mean amount of rescue medication used on day 28 was 14.5 mg compared with a mean of 17.1 mg on day 4.

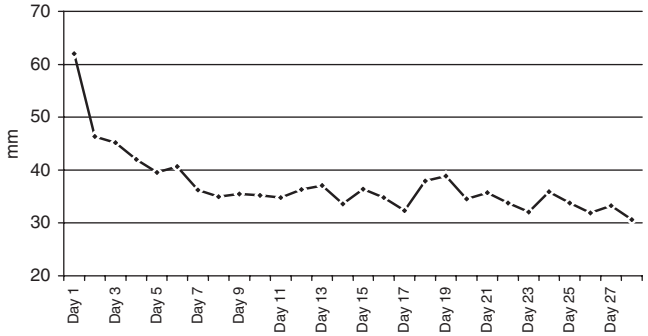

Figure 1. Median pain severity in visual analogue scale.

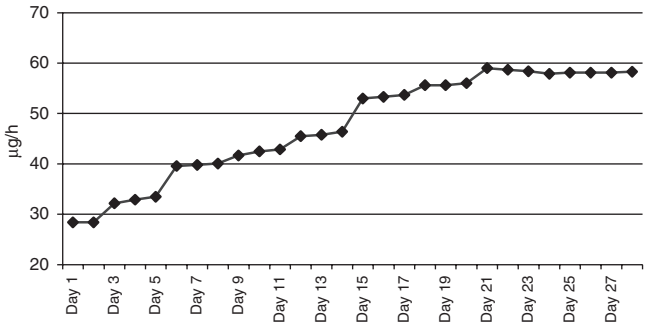

Figure 2. TTS-F dose changes. TTS-F, transdermal therapeutic system – fentanyl.

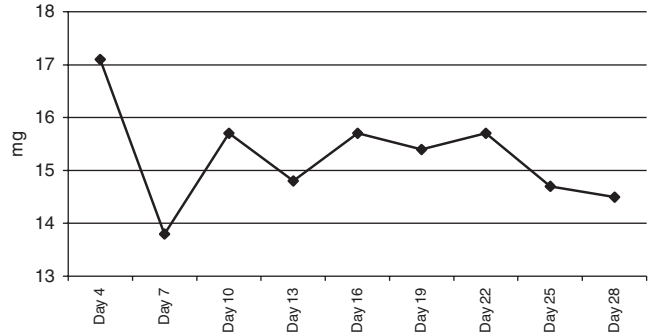

Figure 3. The mean amount of morphine equivalent of rescue medication.

The overall evaluation of pain treatment (pain control, side effects and overall impression) improved significantly from visit 1 to visit 3 (Figs 4–6). The majority of patients rated patch convenience of use as excellent. Only six patients rated the convenience as fair or poor (the ITT population). Thirty-four patients rated the convenience as excellent, and 35 patients rated the convenience as good. Patients' treatment preference favoured for the TTS-F patches, with 24 patients expressing a 'strong preference for TTS-F patches' and 45 patients expressing a 'preference for TTS-F patches'. 'No preference' was expressed by six

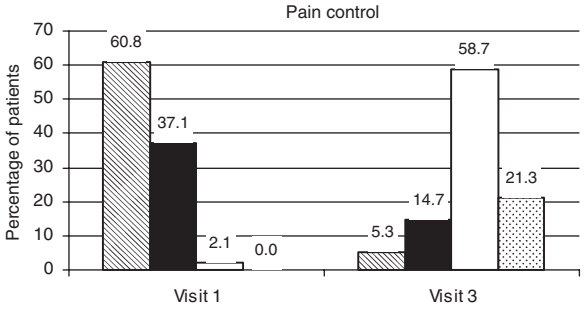

Figure 4. Overall evaluation of pain control from visit 1 to visit 3. (▨ Poor; ■ Fair; □ Good; ⊡ Excellent)

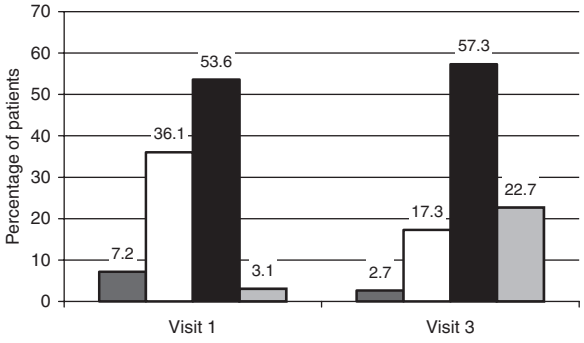

Figure 5. Overall evaluation of side effects from visit 1 to visit 3. (■ Poor; □ Fair; ■ Good; ▨ Excellent)

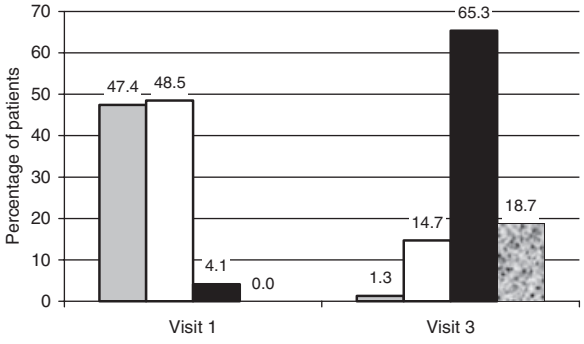

Figure 6. Overall impression from visit 1 to visit 3. (▨ Poor; □ Fall; ■ Good; ▨ Excellent)

patients, while no patients expressed a preference for previous treatment. For patients who expressed a preference for TTS-F patches, the main reason for the preference was: 'better pain relief' (52 patients), 'less side effects' (eight patients), and 'more convenient' (eight patients).

Adverse events

Of the 99 patients enrolled in the safety group, 90 mentioned 556 adverse events. Of these 90 patients, 61 mentioned 246 adverse events that were considered to have no relation to the study drug, and 44 patients mentioned 154 adverse events that were considered to have a doubtful relation to the study drug. Thirty-one patients mentioned 100 adverse events that were considered to be possibly related to the study drug, and 11 patients mentioned 34 adverse events that were considered to be probably related to the study drug. Eleven patients mentioned 22 adverse events that were considered to have a very likely relation to the study drug. Sixty-nine patients mentioned 323 adverse events that were considered mild in severity; 39 patients mentioned 179 adverse events that were considered moderate in severity, and 35 patients mentioned 54 adverse events that were considered severe in severity. The most frequently (more than 20% of patients) mentioned adverse events were: reported nausea in 70 patients, vomiting in 41 patients and constipation in 38 patients. Eighteen serious adverse events were reported by 13 patients. Six events were doubtfully related to the study drug, and 12 events were not. There were four withdrawals due to death. None of these deaths was attributed to the study drug.

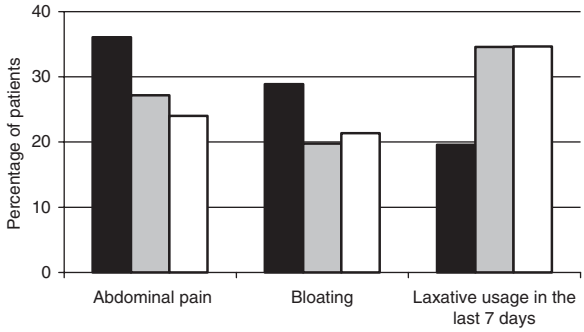

Figure 7. Gastrointestinal disturbances from visit 1 to visit 3. (■ Visit 1; ▨ Visit 2; □ Visit 3)

The maximum number of patients reporting moderate to severe nausea at any one time was 59, and the total number of mentions was 116. The maximum number of patients reporting moderate to severe vomiting at any one time was 23, and the total number of mentions was 33.

The majority of patients did not experience abdominal pain. The number of patients who did experience abdominal pain decreased markedly from visit 1 to visit 3 (Fig. 7). The majority of patients did not experience bloating. The number of patients who did experience bloating decreased from visit 1 to visit 3 (Fig. 7). The majority of patients did not use laxatives during the last 7 days.

The overall number of patients with constipation decreased from visit 1 to visit 3 (Fig. 8). The percentage of patients with constipation in the cohort who had been opioid tolerant prior to initiation in the study decreased

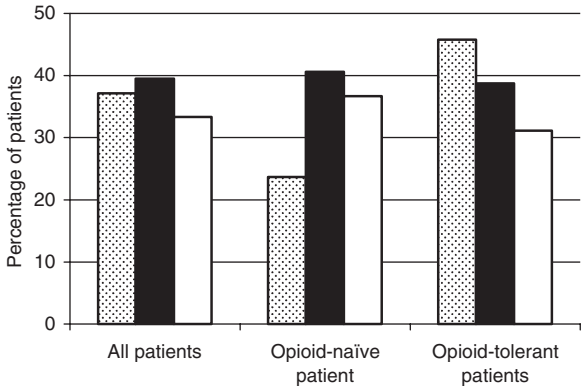

Figure 8. Percentage of the patients experiencing constipation from visit 1 to visit 3. (▨ Visit 1; ■ Visit 2; □ Visit 3)

from visit 1 to visit 3. In the group of patients who had been opioid naïve prior to the start of the study, the percentage of patients with constipation increased from visit 1 to visit 3 (Fig. 8). The number of patients who had diarrhoea fluctuated between the visits. The number of patients who had passed stools 3 or more days per week on average decreased from visit 1 to visit 3. The majority of patients experienced no difficulty or pain when passing stools (visit 1: 52 patients, visit 2: 54 patients, and visit 3: 48 patients). Very few patients experienced difficulty and pain all of the time (visit 1: six patients, visit 2: two patients, and visit 3: one patient).

The majority of patients passed formed stools (visit 1: 52 patients, visit 2: 54 patients, and visit 3: 49 patients).

The median Karnofsky Performance index at baseline, visit 1 and visit 2 was 70 (range 50–100), 70 (range 30–100) and 80 (range 20–100) respectively. No large improvements were found regarding Karnofsky Performance Status scores from visit 1 to visit 2 ($P = 0.14$) or from visit 1 to visit 3 ($P = 0.44$).

Disease remained 'stable' for the majority of patients (46.4% of patients in the ITT population). Disease had markedly deteriorated in 4.1% and mildly deteriorated in 17.5% of patients. Disease improved in 8.2% of patients, and data were missing in 23.7% of patients.

DISCUSSION

A major area for TTS-F use is the management of cancer-related pain. Inadequate pain management has been estimated to occur in 60–80% of cancer patients (Markman 2005). The choice of drug and the method of administration have been reported as reasons for inadequate analgesia (Foley 1981). The changes in blood concentration caused by oral, intramuscular (IM) and intravenous (IV) bolus administered opioid analgesics may be accompanied by clinical responses fluctuating between ineffective analgesia and unwanted side effects (such as nausea or sedation) (Austin *et al*. 1980; McGivney & Cooks 1984; Homesley *et al*. 1986). Transdermal therapeutic system – fentanyl provides continuous opioid delivery without the need for special equipment. The non-invasive transdermal delivery route does not expose patients to the risks and discomfort of the IV or subcutaneous route of drug administration. The simplicity of TTS-F allows freedom to maintain a relatively normal life, thereby enhancing the patient's quality of life.

The transdermal delivery route in Turkey was first used for a nitroglycerine drug in cardiac patients, and the majority did not tolerate it well. Since TTS-F is new in Turkey and has not been studied yet in the Turkish population in terms of effectiveness and tolerability in cancer pain, we conducted this prospective study to evaluate its usefulness.

At study entry, the prognosis of our patients was poor, and several were at the terminal stage. In some cases, it was not possible to clearly separate events related to disease progression (including death) or underlying medical conditions from events related to TTS-F treatment. Adverse events were distributed relatively evenly throughout the study period. Since several trials report that nausea and vomiting occur mostly at the start of treatment, and that they decrease over time, those adverse events might be mostly disease-related. Clusters of adverse events did not appear at the initiation of TTS-F therapy. No deaths were attributable to TTS-F use, and there was no association between deaths and increased doses.

Most studies have included strong opioid-tolerant patients and switched them to TTS-F after a stabilization phase with either short-acting strong opioids or IV fentanyl. In more recent studies, the stabilization phase has been replaced by a titration with TTS-F patches with encouraging results (Joranson *et al*. 2000; Tawfik *et al*. 2004). In another study that included opioid-naïve patients as well, it was reported that these patients tolerated TTS-F well (Van Seventer *et al*. 2003). In our study, 40 patients were opioid naïve. We also did not notice the increased prevalence of side effects. These experiences have shown that both opioid-naïve and opioid-tolerant patients with chronic cancer pain requiring strong opioids [step III of World Health Organization (WHO) pain management] may be treated with TTS-F without a prior stabilization. A dose titration must, however, be performed under close monitoring.

The majority of the adverse events were related to underlying disease progression. Fifty-six out of 556

adverse events were probably or very likely related to TTS-F. The adverse events related to TTS-F were typical for opioids, and they did not differ significantly between the opioid-naïve and opioid-tolerant patients. The most common adverse events were mainly gastrointestinal and tended to decrease from visit 1 to visit 3. Of these, nausea and vomiting were the most common symptoms in our study. Other trials comparing TTS-F with other opioids revealed a lower rate of nausea and constipation (Ahmedzai *et al*. 1994; Yeo *et al*. 1997; Van Seventer *et al*. 2003).

The majority of patients (92%) preferred TTS-F to their previous treatment, and an overall evaluation of 'excellent and good' pain control increased significantly from visit 1 to visit 3. The overall impression of TTS-F was good to excellent for 84% of patients, related to good pain relief and good tolerability. This impression is similar to that seen in previous studies (Van Seventer *et al*. 2003; Mystakidou *et al*. 2004; Tawfik *et al*. 2004). The mean starting dose of TTS-F was low (29.4 μg/h) since 40% of patients were not first stabilized on oral morphine before being initiated on TTS-F. During the study, the mean dose of TTS-F increased gradually and stabilized gradually after the second visit. Related pain severity on VAS decreased, and the mean rescue medication remained constant after the first week of the study period.

The percentage of patients reporting constipation was significantly higher in opioid-tolerant patients than in opioid-naïve patients at visit 1. The percentages of the two groups became similar at visits 2 and 3. The patient's use of laxatives increased from baseline and remained constant by visits 2 and 3.

The findings related to nausea/vomiting and constipation are comparable with previous studies (Ahmedzai *et al*. 1994; Lorvidhaya *et al*. 2004).

Respiratory depression is the most serious adverse event related to opioids possible, patients. In this study, we noticed no respiratory depression. This shows that TTS-F can be used safely even in opioid-naive setting in patients with no history of CO_2 retention. This finding is consistent with that of previous studies (Vielvoye-Kerkmeer *et al*. 2000; Van Seventer *et al*. 2003; Tawfik *et al*. 2004).

Pain is the most frequent symptom in advanced cancer. It often remained inadequately treated due mainly to a reluctance to use opioids and to concerns surrounding possible drug addiction. However, the data show that when opioids are used to treat pain, the incidence of drug abuse is very low. Opioids are the first-line drugs used to treat severe cancer-related pain. Although slow-release morphine is still considered to be the gold standard against which other opioids are measured, a lot of data demonstrating that TTS-F is as suitable as slow-release morphine in the treatment of severe pain have now been collected. Our trial confirmed that TTS-F is effective and safe for the management of cancer-related pain.

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