

Clinical Efficacy of Transdermal Fentanyl in Adults with Cancer-Related Pain: An Open Multicentre Study

Kansere Bağlı Ağrıda Transdermal Fentalinin Klinik Etkinliğinin İncelenmesi

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ABSTRACT Objective: Inadequate pain management has been estimated to occur in most cancer patients. Fentanyl transdermal therapeutic system (TTS) provides continuous controlled systemic delivery of fentanyl for up to 72 hours. In order to assess the efficacy and tolerability of TTS-fentanyl, an open, multicentered, uncontrolled phase IV study was conducted in patients with cancer-related pain. **Material and Methods:** One hundred and forty eight strong opioid-naïve patients started with the lowest TTS-fentanyl dosage available (25 µg/hr). A dose increase was allowed every third day if needed. Primary efficacy measurements were total dose of TTS-fentanyl, Visual Analogue Scale (VAS) score in the patient diary and overall evaluation of the pain treatment. Secondary efficacy measurements were safety concerns. **Results:** Of the 148 patients enrolled, 79 (53.4%) were recorded as opioid tolerant and 69 (46.6%) patients as strong opioid-naïve. Pain control, side effects and overall impression improved from visit 1 to Visit 3 ($p < 0.0001$). Most patients rated the convenience of the patches as excellent. The most frequent mentioned adverse events were nausea (32.4%) and vomiting (18.9%). Only 37.2% of the patients exhibited adverse events, which were related to the study drug. **Conclusion:** Long-term treatment with transdermal fentanyl was safe and tolerable to many cancer patients.

Key Words: Cancer; pain; fentanyl; antineoplastic protocols

ÖZET Amaç: Yetersiz ağrı tedavisi kanser hastalarında sık görülen sorunlardan biridir. Fentanyl transdermal terapötik sistem (TTS) 72 saate kadar sürekli kontrollü fentalin sağlamaktadır. Kansere bağlı ağrısı olan hastalarda TTS fentalinin etkinliğini ve tolere edilebilirliğini saptamak amacıyla açık, çok merkezli, kontrolsüz bir faz IV çalışma düzenlendi. **Gereç ve Yöntemler:** Daha önce güçlü opioid kullanmamış 148 hasta en düşük fentanal dozuyla (25 µg/saat) tedaviye alındı. Hastalar her üç günde bir değerlendirildi ve ihtiyaç duyan hastalarda doz artımına gidildi. Birincil etkinlik parametreleri toplam TTS-fentanal dozu, hasta günlükündeki Görsel Analog Ölçeği (Visual Analog Scale-VAS) puanı ve ağrı tedavisinin genel değerlendirilmesi idi. İkincil etkinlik parametresi olarak güvenilirlik kriterleri dikkate alındı. **Bulgular:** Çalışmaya alınan 148 hastanın 79 (%53.4)'ü opioide toleran ve 69 (%46.6)'u daha önce güçlü opioid almamış olarak değerlendirildi. Ağrı kontrolü, yan etkiler ve genel izlenim, birinci görüşmeden üçüncü görüşmeye dek anlamlı düzeyde ($p < 0.0001$). Hastaların çoğunluğu fentanal bantlarının etkinliğini çok iyi olarak değerlendirdi. En sık görülen yan etkiler bulantı (%32.4) ve kusma (%18.9) idi. Hastaların %37.2'si ilaçla ilişkili olabilecek yan etki bildirdiler. **Sonuç:** TTS-fentanalın kanser hastalarında etkin, güvenli ve iyi tolere edilen bir tedavi seçeneği olduğu kanısına varıldı.

Anahtar Kelimeler: Kanser; ağrı; fentanal; kanser tedavisi

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Inadequate pain management has been estimated to occur in 60 to 80% of cancer patients.¹ The choice of drug and the method of administration have been cited as reasons for inadequate analgesia.² The fluctua-

tions in blood concentration caused by oral, intramuscular and IV bolus administered analgesics may be accompanied by clinical responses fluctuating between ineffective analgesia and unwanted side effects such as nausea or sedation.³⁻⁵ Fentanyl TTS, which contains a rate-limiting membrane that provides constant release of the opioid, provides continuous controlled systemic delivery of fentanyl for up to 72 hours. TTS-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-fentanyl allows freedom to maintain a relatively normal lifestyle, thereby enhancing the patient's quality of life.⁶

Over 20 clinical studies to evaluate the safety and efficacy of TTS-fentanyl have been conducted in more than 1000 patients with cancer-related pain. Most of the studies have included strong opioid-tolerant patients and switched them to TTS-fentanyl after a stabilization phase with either short acting strong opioids or intravenous fentanyl. In these studies, TTS-fentanyl was generally well tolerated. The most frequent complaints occurring in more than 10% of patients were nausea, vomiting and constipation. No death was attributable to TTS-fentanyl use and there was no association between deaths and increased doses.^{7,8}

In order to assess the efficacy and tolerability of TTS-fentanyl, an open, multicentre, uncontrolled phase IV study in patients with cancer-related pain was conducted. The primary objective of the study was to assess the efficacy and safety of TTS-fentanyl assessing the total dose of TTS-fentanyl and pain control using VAS, in which 0 point describes "no pain" and 10 point describes the severest pain status.

MATERIAL AND METHODS

Patients with a histologically confirmed malignancy that had either recurred after potentially curative therapy or not amenable to curative therapy, and pain that requires no more than 404 mg of oral morphine daily or the equivalent of 100 µg/hr of TTS-fentanyl, were enrolled in the study.

All patients were over 18 years of age and were required to have an estimated survival of at least 3 months. The protocol was consistent with the Declaration of Helsinki (1989) as reviewed and approved by the local ethical board. The participants read and signed the informed consent before enrollment. Exclusion criteria included history of drug allergy to opioid drugs, narcotic abuse, active skin disease and CO₂ retention (e.g. chronic obstructive pulmonary disease). Patients who received radiation therapy, hormonal and/or cytostatic medication within 7 days of entry into the study, participated in an investigational drug trial within the 30 days prior to selection, with a serum bilirubin level > 2.0 mg/dL (> 34 µmol/L), and a serum creatinine level > 2.0 mg/dL (> 177 µmol/L) and receiving concurrent medication (e.g. severe alterations of lung, liver or renal function) were also excluded. The "seven days period" for radiation, hormonal and cytostatic therapies before entry to the study was considered sufficiently long, because the peak analgesic effects could be detected within this period. Patients with a serious adverse event, severe sedation and/or no reaction to verbal questioning, poor physical condition making the pursuit of the study impossible or unethical, withdrawal of the consent, poor compliance and with the recommendation of the investigator were removed from the study.

Strong opioid naïve patients were to start with the lowest TTS-fentanyl dosage available (25 µg/hr). A dose increase was allowed every third day if needed. For opioid pretreated patients, the initial dose of TTS-fentanyl was to be calculated from the patient's previous daily oral opioid requirement according to the "PO Morphine Sulphate to TTS-fentanyl Conversion Scheme" and the opioid analgesic conversion table. However, rescue medication was expected to be needed during the first days (24 hr to 48 hr) of treatment (to compensate for the insufficient analgesia of TTS-fentanyl before the titration). This was due to the pharmacokinetics of the patch delivering a dose of fentanyl reaching its maximal concentration 17 to 48 hours after the first application.⁹

Patients who had sufficient pain control with < 90 mg supplemental oral morphine per day and who were not experiencing adverse effects were to continue with the same dose of TTS-fentanyl. Patients who had sufficient pain control without additional oral morphine, but were experiencing significant side effects were to continue with a reduced dose of TTS-fentanyl (decrement of 25 mcg/hr). If treatment with TTS-fentanyl was to be stopped, the patient was to receive replacement therapy with a lower equipotent dose of opioid, which was to be increased gradually. Strong opioid-naïve patients were to start with the lowest TTS-fentanyl dosage (25 µg/hr), a dose increase was allowed every third day if necessary.

Patients were visited weekly period (Visit 1-3) to record the possible side effects.

Primary efficacy measurements were the total dose of TTS-fentanyl, VAS score in the patient diary (experienced during the day and night was to be evaluated the next morning) and overall evaluation of the pain treatment (four-point scale; excellent, good, fair and poor). Secondary efficacy measurements were nausea and vomiting (four-point scale for nausea, and frequency of vomiting), gastrointestinal disturbances and bowel function (the number, consistency and passage of stools, the presence of abdominal pain and bloating, and use of laxatives), convenience of the patches and treatment preference. Karnofsky performance status and disease progression were also taken into account for the evaluation. Clinical safety was assessed by patients' reporting of adverse events.

Wilcoxon Signed Ranks test was used to evaluate the evaluation for the efficacy of transdermal fentanyl treatment, whereas the side effects were recorded by descriptive manner.

RESULTS

One hundred and forty eight (148) patients were enrolled in the study. Median age was 53. Of the 148 patients enrolled, 115 patients completed the study. Seventy-one (48.0%) patients were males and 77 (52.0%) females. Sixty-nine (46.6%) of the patients were Caucasian, 48 (32.4%) of the patients were Oriental. Of the 148 patients enrolled, 79

(53.4%) patients were recorded as opioid tolerant and 69 (46.6%) patients were recorded as strong opioid-naïve.

One hundred and thirty eight (93.24%) patients mentioned 523 previous analgesic/adjuvant therapies. The most frequently mentioned previous analgesic/adjuvant therapies were opioids (73.6%), anti-inflammatory/antirheumatic products (45.3%), topical products for joint and muscular pain (41.2%) and antiinflammatory agents (24.8%). One hundred and thirty (87.8%) patients mentioned 694 concomitant medications. The most frequently mentioned therapeutic classes of concomitant medications were laxatives (31.8%), drugs for the treatment of peptic ulcer (23.0%) and propulsives (20.9%). Although bisphosphonate therapy was not changed throughout out the study, no patient declared concomitant use of bisphosphonates, which may be explained by the unavailability of bisphosphonates at the time of this clinical trial.

Sixty-nine (46.6%) participants mentioned 159 previous and 88 (59.5%) patients mentioned 218 concomitant illnesses. The most frequently mentioned illnesses were neoplasms (36.5%), symptoms, signs and ill-defined conditions (12.2%) and diseases of the musculoskeletal system and connective tissue (10.1%). Although all patients included in the study were to have confirmed malignancy, neoplasm was recorded as a concomitant illness for less than half the patients included in the study; however, no fentanyl use was recorded because of the concomitant illnesses, as fentanyl is also labeled for chronic pain from other causes.

Overall evaluation of pain treatment is measured in terms of pain control, side effects and overall impression. All three of these variables improved from visit 1 to visit 3 (Table 1, Figure 1). Most patients rated the convenience of the patches to be excellent. Thirty-seven (35.2%) patients rated the convenience as good and 61 (58.1) patients as excellent, with 44 (41.9%) patients expressing a "strong preference" for TTS-fentanyl patches and 48 (45.7%) patients expressing a "preference" for TTS-fentanyl patches. For patients who expressed

TABLE 1: Pain control, side effects and overall impression.

Category	Pain control		Side effects		Overall impression	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0	0	1	0	0	0
Poor	63	4	33	18	60	4
Fair	51	13	44	19	52	12
Good	16	58	43	42	17	59
Excellent	1	30	10	26	2	30
Total	131	105	131	105	131	105
p-value*	0.0001		0.0001		0.0001	

* Wilcoxon Matched Pairs Signed Rank Test.

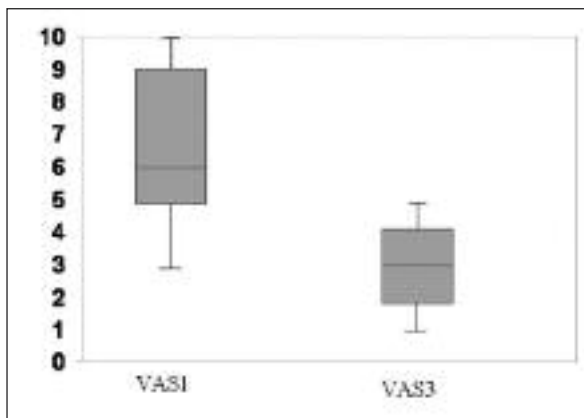


FIGURE 1: Pain control according to the VAS data visit 1 (VAS1) and visit 3 (VAS3) ($Z = -8.173$, $p < 0.0001$).

a preference for TTS-fentanyl patches the main reason for the preference was “better pain relief” (60.0%), “less side effects” (6%) and “more convenient use” (21.0%).

Of the 148 patients enrolled in the study, 93 (62.8%) patients mentioned 395 adverse events. The most frequently mentioned body system categories were the digestive system (49.3%), body as a whole (22.3%) and the nervous system (20.9%) respectively. The most frequently mentioned adverse events were nausea (32.4%) and vomiting (18.9%). A maximum of 7 patients experienced severe nausea on any of the given days, 21 patients moderate nausea and 35 patients mild nausea. The majority of the patients did not experience abdominal pain and bloating. The number of patients who did experience abdominal pain decreased markedly from visit

1 to visit 3, whereas for bloating there was a slight decrease. The number of patients with constipation decreased from visit 1 to visit 3. The majority of the patients did not experience difficulty or pain when passing stool.

DISCUSSION

Many cancer patients are undermedicated and inappropriately managed for pain, leading to a diminished quality of life. Fentanyl is a synthetic opioid agonist, which interacts primarily with the mu-opioid receptor. The low molecular weight, high potency and lipid solubility of fentanyl makes it suitable for delivery by the transdermal therapeutic system. These patches are designed to deliver fentanyl at a constant rate (25, 50, 75 and 100 $\mu\text{g/h}$) and require replacement every 3 days.

Data from randomized, non-blind trials suggest that transdermal fentanyl is as effective as sustained-release oral morphine in the treatment of chronic cancer pain, as reported by patients using visual and numerical analogue scales as well as verbal description scales.^{7,8}

Because of the formation of a fentanyl depot in the skin tissue, serum fentanyl concentrations increase gradually following initial application, generally leveling off between 12 and 24 hours. Thereafter, they remain relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Once achieved, steady-state plasma fentanyl concentrations can be maintained for as long as the patches are renewed.

In more recent studies, the stabilization phase has been replaced by a titration with TTS-fentanyl patches with encouraging results.¹⁰ Most of those patients had received non-opioids, sometimes combined with weak opioids like codeine (step II of pain management according to WHO), resulting in insufficient pain control. In this study pain control improved from visit 1 to Visit 3 ($p < 0.0001$) and 35.2% of the patients rated the convenience as good and 58.1% rated it as excellent, thus 87.6% expressing a preference for TTS-fentanyl patches. This data is in accordance with randomized, non-blind, crossover trials. Based on the results of these

studies, patients with pain, as well as opioid-naïve patients could be switched immediately to TTS-fentanyl. A dose titration must, however, be performed under close monitoring. In most studies, adequate pain relief was obtained by adding oral morphine as rescue medication to TTS-fentanyl during the first 48 hr until adequate pain control was attained with TTS-fentanyl alone.

The most frequently observed adverse events during transdermal fentanyl administration (as with other opioid agonists) included vomiting, nausea and constipation. Data from non-blind, randomized trials suggest that constipation occurs less frequently in patients receiving transdermal fentanyl than in those given sustained-release oral morphine.^{7,11} In concordance with these findings, analgesic treatment with TTS fentanyl used as a single opioid is effective and safe for cancer pain relief, in patients requiring strong opioid analgesics even if they were naive to strong or mild opioids.¹² In the present study, at each visit the majority of patients did not experience abdominal pain, bloating or had used laxatives during the last 7 days. Ab-

dominal pain and bloating decreased from visit 1 to visit 3, but the use of laxatives increased slightly between the visits. Overall bowel function improved from visit 1 to visit 3. The main reasons for preference were better pain relief, less side effects and more convenience. Only 37.2% of the patients exhibited adverse events, which were related to the study drug. We can thus conclude that the study drug does not cause any untoward serious adverse events.

CONCLUSION

Transdermal fentanyl is a useful opioid-agonist for the treatment of moderate to severe chronic cancer pain. The advantages of transdermal fentanyl include ease of administration and the 3-day application interval. These factors coupled with a lower incidence of constipation are likely to contribute to the reported patient preference for transdermal fentanyl over sustained-release oral morphine. We conclude that long-term treatment with transdermal fentanyl is safe and tolerable for many cancer patients.

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