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Transdermal fentanyl: clinical development in the United States

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The first clinical experience in the United States of the transdermal therapeutic system (TTS) for delivery of fentanyl in cancer pain was a small study of five patients. Pain relief was established with intravenous (i.v.) fentanyl. A transdermal system was selected to deliver the same hourly dose while the i.v. infusion was tapered over 6 h. The transdermal system was changed every 24 h for a total duration of 3–156 days. A larger multicentre outpatient trial was conducted in 39 patients for a median of 84 days (range 5–365). The TTS fentanyl dose was established from a conversion table based on the dose of oral immediate-release morphine required to control pain. The TTS fentanyl patches were changed every 72 h. Immediate-release morphine was used on an as required basis for incident pain. The initial study demonstrated that steady-state plasma levels were linearly related to the TTS fentanyl dose. The multicentre trial further demonstrated that patients could be converted from oral morphine to an equianalgesic dose of TTS fentanyl and that pain relief could be maintained for a lengthy period of time on an outpatient basis. The systems were used throughout a variety of concomitant complications of the cancer process. This experience demonstrated the safety and clinical effectiveness of TTS fentanyl in the treatment of chronic cancer pain. TTS fentanyl has been used widely in the USA since it was approved for marketing in 1990.

Introduction

One of the principal objectives in the use of analgesics to relieve chronic pain is to establish and maintain a sustained plasma drug level. A new method of drug delivery, through the intact skin, is a unique way to achieve a continuous infusion of drug. The advent of rate-controlling membranes in transdermal delivery systems further reduces the incidence of fluctuations in plasma drug levels.[1] Such a disposable system is convenient and achieves continuous analgesic administration without the need for a drug-infusion pump.

Fentanyl citrate is a potent synthetic opioid with physicochemical characteristics that are suitable for rate-controlled transdermal delivery. The Alza Corporation first formulated fentanyl into the transdermal therapeutic system (TTS). After it was demonstrated that pain relief could be achieved with these systems by using postoperative pain as a model,[2] the first patients with cancer pain were studied by Miser *et al.*[3] The objective of this paper is to summarise those results and to report on the subsequent multicentre trial carried out in the United States leading to approval of TTS fentanyl for marketing.[4]

Patients and methods

As in the initial clinical trial in postoperative pain, the first five patients with cancer pain were treated with an intravenous (i.v.) infusion of fentanyl to achieve satisfactory pain relief.[3] A transdermal system was then selected to deliver the same μg/h dose, and the i.v. infusion was tapered and discontinued over 6 h. The patients changed the transdermal patch every 24 h. They wore the TTS fentanyl patches for a total of 3–156 days. Plasma fentanyl levels were monitored at regular intervals.

Once it was determined that TTS fentanyl could safely maintain analgesia over a prolonged period of time, a multicentre, open-label study was designed to determine the long-term safety and efficacy of TTS fentanyl in patients requiring opioid analgesics for the treatment of pain due to cancer. Adult patients (who had a primary caregiver) were entered in the study after they signed the informed consent approved by the Institutional Review Board. Patients were not eligible if they were judged to have a life expectancy of less than 30 days. They were also excluded if there was any history of poor pulmonary function with carbon dioxide retention or if they were suffering from widespread active skin disease.

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A total of 39 patients (16 female; 23 male) were entered in the trial – 21 at the Hershey Medical Center and 18 at the University of Cincinnati. Patients were entered from 9 November 1987 to 1 September 1988. The median age was 61 years (range 33–78 years) and the median Eastern Cooperative Oncology Group performance status score at the time of entry was 3 (range 0–4). All patients were suffering from various forms of cancer in advanced stages. The range of diagnoses included: lung cancer (n = 10), breast cancer (n = 9), colon cancer (n = 7), prostate cancer (n = 3), carcinoid (n = 2), unknown primary (n = 2), and one case each of ovarian cancer, pancreatic cancer, bladder cancer, melanoma, sarcoma, and renal cell carcinoma.

The TTS developed by the Alza Corporation includes a drug reservoir and rate-controlling membrane which allows a constant rate of diffusion of drug across the stratum corneum of the skin and into the subcutaneous tissue. Fentanyl is released from this system at a rate of 25 μg/h/10 cm². The amount of drug administered can be varied by changing the surface area of the patch; thus, 10, 20, 30 and 40 cm² size patches will deliver 25, 50, 75 and 100 μg/h respectively. Higher doses can be achieved by application of multiple patches. The 40 cm² patch contains a total of 10 mg fentanyl.

Patients were first required to reach a stable morphine dose for at least 3 days prior to being converted to an equianalgesic dose of TTS fentanyl. The conversion rate was based on prior experience with TTS fentanyl and on the assumption that 10 mg morphine i.v. is equipotent to 10 μg fentanyl and that the p.o./i.v. morphine ratio is 6 : 1.[5]

Immediate-release morphine was provided for breakthrough pain. Patients recorded their morphine doses in a diary. Naloxone was provided to the caregiver as a precaution to be used in the event of respiratory depression. Other non-opioid analgesics could be taken as required.

Patients reapplied new TTS fentanyl systems to a hairless area of the skin every 3 days. Application sites were rotated so that consecutive applications were not made on the same site.

Doses of TTS fentanyl were titrated by taking the average amount of supplemental morphine used per day over the previous 3 days. Change in TTS fentanyl dose was judged by the physician based on the patient's updated pain level, satisfaction with analgesia, and amount of supplemental analgesic used.

Patients were seen initially at entry to the trial and then to convert their analgesic from oral morphine to TTS fentanyl. They were seen again after 1 week on study and monthly thereafter. To assess compliance, telephone monitoring was conducted by a nurse on a weekly basis. Home visits were made to some patients by a physician or nurse. Patients completed a 10 cm visual analogue scale (VAS) anchored by 'no pain at all' and 'worst possible pain' at week 1 and at monthly intervals thereafter. The patients also rated their satisfaction with the analgesic regimen on a scale of 1 = excellent, 2 = very good, 3 = good, 4 = fair, and 5 = poor.

Results

In the initial experience with cancer patients studied by Miser *et al.*,[3] satisfactory levels of analgesia were achieved. Furthermore, steady-state plasma fentanyl levels were found to be linearly related to the TTS fentanyl dose in the dose range studied. Serial fentanyl levels were monitored after removal of the systems, and plasma concentrations declined relatively slowly, demonstrating a terminal 50% reduction of drug level after 15 h.

In the multicentre trial, patients were titrated to a level of satisfactory pain relief with a form of oral morphine sulphate. The median pretreatment immediate-release morphine sulphate stabilisation dose was 120 mg/day (range 60–790 mg/day). The median TTS fentanyl dose at the start of the study was therefore 50 μg/h (range 25–150 μg/h) every 72 h (Table 1).

At the week-1 visit, 18 patients (46%) required an increase in TTS fentanyl dose because of frequent use of immediate-release morphine sulphate, as documented in their diaries, or because they were not satisfied with their level of pain control. Only one patient required a decrease in dosage. At 1 month, 13 patients had required additional increases in TTS fentanyl, and 26 were on a stable dosage. There were no further decreases in dosage.

After 1 month, patients' rating of pain by VAS was unchanged from the scores at the time of morphine stabilisation. Scores were 0–5 out of 10 in 35% of

Table 1. Dosage of morphine and TTS fentanyl required

	Median	Range
TTS fentanyl starting dose (μg/h)	50	25–225
TTS fentanyl final dose (μg/h)	150	25–600
Duration of TTS fentanyl use (days)	84	5–365
Supplemental morphine sulphate (mg/day)	105	0–720

Table 2. Concomitant events while using TTS fentanyl

	No. of events
Surgery for pathologic fracture	3
Herpes zoster eruption	3
Chemotherapy infusion	15
Bowel obstruction	4
Thrombotic event	2
Gastric bleed	2

patients at baseline and in 50% of patients at 1 month. The patients rated pain control after 1 month on TTS fentanyl as excellent (n = 1), very good (n = 4), good (n = 12), fair (n = 2), and poor (n = 2). All patients were then given the opportunity to continue using TTS fentanyl.

Patients wore the systems for a median of 84 days (range 5–365 days). The reasons for withdrawal were: caregiver decision (n = 1), uncontrolled pain (n = 2), or death (n = 36). All deaths were associated with progression of disease. No death was thought to be related to TTS fentanyl. The median final dosage of TTS fentanyl was 100 μg/h (range 25–600 μg/h). The median supplemental morphine dose was 105 mg/day (range 0–720 mg/day). Over the length of time the patients wore the systems, several concomitant events occurred (Table 2).

A complete battery of laboratory parameters was measured monthly in every patient. There were no changes that could be attributed to fentanyl or to the TTS components. One patient developed a local exacerbation of a generalised dermatophytic infection. When the infection was treated with a systemic antifungal drug, the occlusive dressing effect subsided. Finally, one patient was given a dose of naloxone because of a slow respiratory rate. In retrospect this event was felt to be due to the terminal state of the patient, who had advanced cancer.

Discussion

Patient compliance and acceptance of TTS fentanyl was excellent in both clinical studies based on stable pain scores, overall assessment of pain control, and desire to continue on this form of analgesic.[5] Patients who were on a stable dose of opioid could be converted to TTS fentanyl and achieve an equianalgesic effect.

The conversion ratio was adequate for over half of the patients. An almost equal number used sufficient supplemental morphine in the initial titration period to justify a higher TTS fentanyl dosage. While this indicates a conservative conversion ratio, this is an appropriate guide for widespread usage.

While the median dose of supplemental morphine for breakthrough pain was 105 mg/day, it was surprising to find that some patients used up to 720 mg/day (in divided doses). In some cases, this meant that the patients required this amount of supplemental morphine to control their pain along with the TTS fentanyl. In other cases, despite a careful explanation of the use of TTS fentanyl as a baseline and morphine intended only for supplemental use, patients seemed to be too compliant with their morphine regimen and took it around the clock, whether they truly had breakthrough pain or not. Another possible explanation is that patients used as many as six of the largest size TTS fentanyl systems at once. It may be that inexperience with the product created a bias against using more of the systems at one time. This trial cannot definitely resolve these issues. Further experience and additional studies will hopefully clarify this.

No untoward reactions were attributed to TTS fentanyl. Any reported symptoms could not be distinguished from those judged to be due to supplemental morphine or to the underlying disease. No unpredictable events occurred. Also, any incident or breakthrough pain could be controlled with immediate-release morphine sulphate.

This experience of using TTS fentanyl for a prolonged period of time afforded the opportunity to use the system through varied and typical concomitant events in the natural history of cancer progression. Pain control was able to be maintained during all events. Events such as bowel obstruction and gastrointestinal haemorrhage demonstrated maintenance of pain control with TTS fentanyl when the oral route was temporarily unavailable. Acute exacerbation of pain due to herpes zoster eruption was managed by increasing the TTS fentanyl dose and then decreasing the dose when the pain level abated. Transdermal fentanyl was also continued in combination with sedative–hypnotic drugs for the management of abdominal and orthopaedic surgical procedures.

The rate of dose increase of TTS fentanyl over the duration of the study was within the range seen with continuous infusion of i.v. or s.c. morphine.[6,7] Furthermore, this group of patients was suffering from advancing cancer, so pain levels would be expected to increase.

Patient compliance and acceptance of this form of opioid analgesic was excellent. Transdermal administration provides a convenient method of drug delivery and facilitates maintenance of continuous levels of drug. The method is simple and does not require sophisticated equipment or high levels of profession-

al skill. This method is therefore potentially ideal for long-term administration of opioids in the commonly used dose range. However, patients with severe pain or patients who have developed extreme levels of tolerance requiring high dose levels of analgesics will be limited at some point by the number of systems needed at one time.

A small number of patients will not have an adequate amount of usable skin surface in the usual dose range. The systems may also be dislodged by uncooperative patients. Despite these limitations, the early experience with this approach in the management of cancer pain is encouraging.

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