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Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy

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The transdermal route of drug delivery has been used for the effective administration of therapeutic agents for more than a decade. The most important consideration in selecting a drug for transdermal delivery is the potential for improving therapeutic efficacy. The development of a transdermal fentanyl system provided an opportunity to add fentanyl to the armamentarium of strong opioids available for the treatment of cancer pain. The transdermal route of administration has advantages over both the oral and parenteral routes. In addition, patient and caregiver factors allow improved acceptance of and compliance to strong opioids and therefore improved analgesic outcome. Four transdermal fentanyl systems are available, providing delivery rates ranging from 25–100 μg/h; higher rates can be achieved by multiple system application. The system releases fentanyl continuously for 3 days when applied to the skin. Concentrations of fentanyl in the blood are measurable within a few hours of system application. Fentanyl serum concentrations increase gradually, generally levelling off after 12–24 h and remaining relatively constant for the remainder of the 3-day period. Steady state serum concentrations are reached by the second application. Clinical trials have established the efficacy and safety of transdermal fentanyl for the treatment of cancer pain. Transdermal fentanyl is not licensed for the treatment of acute pain, e.g. postoperative pain, and should not be prescribed for this purpose.

Introduction

The development of Duragesic/Durogesic (TTS fentanyl; Janssen Pharmaceutica) has combined fentanyl, an opioid that has been used for over 25 years, with a transdermal drug delivery system (Alza Corporation, Palo Alto, CA) to expand the armamentarium of drugs and routes of administration for the treatment of chronic pain. The ability to administer an opioid transdermally is a significant advance in pain management, particularly for cancer patients, most of whom experience pain during the course of their disease. TTS fentanyl, with its extended 72-h dosing interval and convenient mode of administration (transdermal therapeutic system; TTS), provides a means to achieve sustained, effective analgesia and enhance quality of life.

The development of transdermal technology was initiated almost 25 years ago by the Alza Corporation in Palo Alto, California. Nitroglycerin for the treatment of angina and scopolamine for the prevention of motion sickness were the first drugs to be developed in the transdermal dosage form. Four additional drugs are now available via the transdermal route: oestrogen for hormone replacement, clonidine for high blood pressure, nicotine for smoking cessation, and fentanyl for the treatment of chronic pain.

TTS fentanyl was introduced in the United States in 1991 and in Canada in 1992. In the US it is indicated for the treatment of chronic pain requiring strong opioids. It is not indicated for the treatment of acute pain, e.g. postoperative pain, since it is not possible to individualise and titrate the dose to an effective and safe level in painful conditions requiring short-term treatment.

The value of the transdermal route of administration can best be visualised by the schematic shown in Figure 1, comparing simulated blood concentration of drug administered as a conventional unit dose with

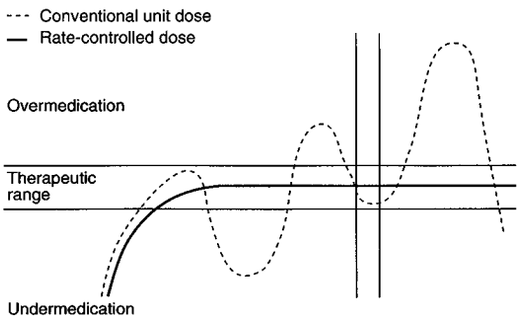

Figure 1. Conventional unit dose compared to rate controlled dose.

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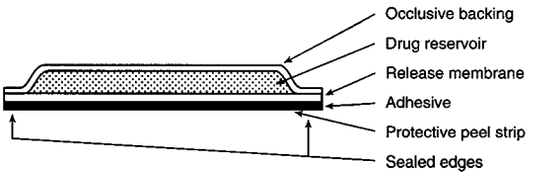

Figure 2. TTS fentanyl schematic.

that of a rate-controlled dose in relation to the therapeutic range. The objective of providing a continuous delivery of drug within the therapeutic range is to improve therapeutic outcome.

TTS fentanyl was developed with a view towards providing continuous, non-invasive opioid administration in order to improve analgesic outcome and quality of life. Compared with the oral route of administration, TTS fentanyl was intended to extend the dosing interval, from the 4, 8, or 12 h of currently available products, to 72 h (3 days). It was intended to maintain steady serum fentanyl concentrations throughout the entire dosing interval in order to achieve consistent analgesia. The parenteral transdermal route avoids the first-pass liver metabolism and gastrointestinal effects of the oral route. Finally, the transdermal route permits analgesic administration in the presence of nausea and vomiting and in patients who are unable to swallow.

TTS design

TTS fentanyl is a rectangular transparent unit comprising a protective liner and four functional layers. The layers include a backing of polyester film, a reservoir containing fentanyl in a gelled formulation, a rate-controlling membrane, and an adhesive layer (Figure 2). A portion of the drug migrates from the drug reservoir into the adhesive and rate-controlling membrane during initial storage, making it immediately available to the skin upon application. The system controls the release of fentanyl to maintain a continuous and steady supply of drug through the skin. The amount of fentanyl released from each system per hour is proportional to the surface area (25 μg/h per 10 cm^2). The composition per unit area of all four system sizes is identical. Four doses are available: 25, 50, 75, and 100 μg/h. Higher doses may be achieved by using multiple systems.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of TTS fentanyl were evaluated in postsurgical and cancer patients. When the system is applied, the skin beneath it absorbs fentanyl, which initially concentrates in the upper layers of the skin. The drug then becomes available to the systemic circulation. Following the application of the first dose, the serum fentanyl concentration increases gradually; fentanyl can be detected in serum (0.2 ng/ml) after 1–2 h. Fentanyl concentrations generally plateau between 12 and 24 h after the initial transdermal application (Figure 3).[1,2]

Steady state is reached by the second dose, and these concentrations are maintained with repeated application (Figure 4).[3] The concentrations achieved are proportional (approximately 0.5, 1, 1.5 and 2 ng/ml for the 25, 50, 75, and 100 μg/h systems respectively) [Alza Corporation data]. Relatively steady concentrations are maintained for the entire 72-h application period (Figure 5).[3]

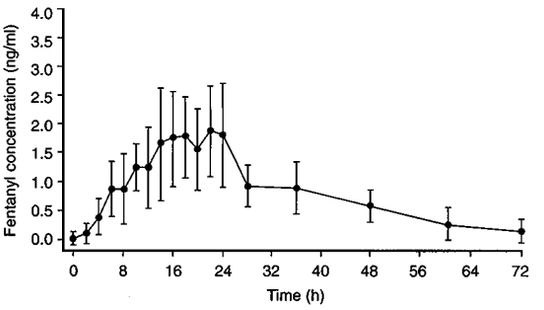

Figure 3. Mean (SD) serum fentanyl concentration for TTS fentanyl 100 μg/h following application of first dose.

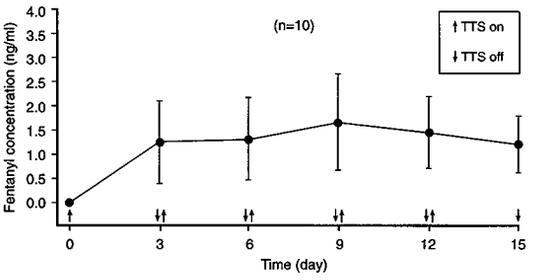

Figure 4. Mean serum fentanyl concentrations during five consecutive 3-day TTS fentanyl 100 μg/h applications.

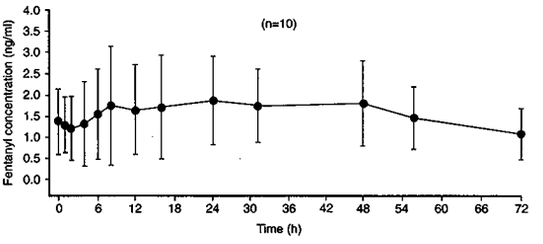

Figure 5. Mean (SD) serum fentanyl concentration for TTS fentanyl 100 μg/h at steady state.

Following system removal, serum fentanyl concentrations decline gradually, falling by about 50% in approximately 17 h.[2] Since fentanyl continues to be absorbed from the skin after system removal, it disappears more slowly from the serum after transdermal administration than after intravenous administration (half-life is approximately 7 h).[2]

Fentanyl delivered transdermally is not metabolised by the skin and is 92% bioavailable.[2] Absorption continues throughout the entire 72-h dosing interval.[3] Serum fentanyl kinetics are linear within the dose range studied and do not change with repeated applications [Alza Corporation data].[3]

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40°C due to temperature dependent increases in fentanyl release from the system and increased skin permeability. Therefore, patients developing a fever should be monitored for opioid side effects and the dose adjusted if necessary.

Efficacy of TTS fentanyl – Acute postoperative pain model

The analgesic efficacy of fentanyl administered intravenously is well established.[4–7] The efficacy trials for TTS fentanyl were undertaken in the acute and chronic pain models in patients with postoperative pain and cancer pain, respectively. Transdermal fentanyl is not licensed for the treatment of acute pain, e.g. postoperative pain, and should not be prescribed for this purpose.

The efficacy of TTS fentanyl was evaluated in nine controlled clinical trials including over 450 postoperative patients. The TTS fentanyl dose (50, 75, or 100 μg/h) was selected for each trial based upon the severity of pain anticipated for a given surgical procedure (e.g. hysterectomy patients received the 50 μg/h dose and thoracotomy patients received the 100 μg/h dose).

The studies used a similar design and methodology to compare TTS fentanyl with placebo. All were double-blind, randomised, parallel-group trials in patients undergoing surgical procedures expected to produce moderate to severe pain. TTS fentanyl (50, 75 or 100 μg/h) or a transdermal placebo system was applied to the patient's upper torso 0–2 h before surgery requiring regional or general anaesthesia. Patients in both treatment groups were eligible to receive parenteral opioids titrated to their analgesic needs.

The primary measure for evaluating efficacy was the amount of supplementary analgesic used in each treatment group. Pain intensity evaluations were also included to assess the quality of analgesia. Since both the active and placebo groups could be titrated to analgesia with a supplementary analgesic, no differences with regard to pain intensity were anticipated. Both patients and medical observers provided a global rating of pain control for the entire 24-h treatment period.

The efficacy of TTS fentanyl was established in seven of the nine clinical trials. In these seven trials, the TTS fentanyl group used significantly less supplementary analgesic ($P < 0.1$) than patients in the TTS placebo group [Alza Corporation data].[3,8–11] The TTS placebo group used 2–4 times more supplementary analgesic than patients in the TTS fentanyl group. In the other two studies the mean supplementary analgesic requirement was also lower in the TTS fentanyl group than in the placebo group, although the differences were not statistically significant [Alza Corporation data].[12]

Figure 6 illustrates supplementary morphine use in four clinical trials evaluating TTS fentanyl in patients undergoing major surgery (e.g. thoracotomy) [Alza Corporation data]. Efficacy was demonstrated beginning in the immediate postoperative period and continuing throughout the period of TTS fentanyl application ($P < 0.01$).

Although patients receiving placebo had more frequent access to supplemental analgesic than patients have in usual clinical practice, those using TTS fentanyl had significantly lower pain intensity ratings ($P < 0.01$) than the control group (Figure 7). Pain intensity ratings were 40%–60% lower for the TTS fentanyl group than for the placebo group who received i.m. morphine or patient-controlled analgesia (PCA) with morphine. Patients using TTS fentanyl reported excellent pain control with mean pain intensity scores of 2–3 (scale 0–9) during the 12 to 24-h interval after TTS application.

Clinical experience in cancer patients

Expanded clinical trials in cancer patients provide supporting evidence of efficacy and information on the clinical use of TTS fentanyl.

An open-label multicentre trial in cancer patients was conducted using an A–B study design.[13,14] The initial TTS fentanyl dose was based upon each patient's clinical history, clinical presentation and previous analgesic requirement (total daily analgesic dose). Patients were titrated to acceptable analgesia with oral morphine. Those on other analgesic regimens (20%) were converted to an equivalent morphine

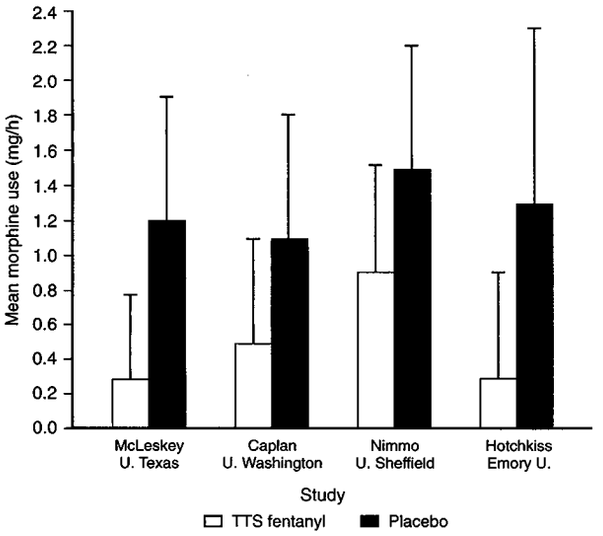

Figure 6. Efficacy: mean morphine use.

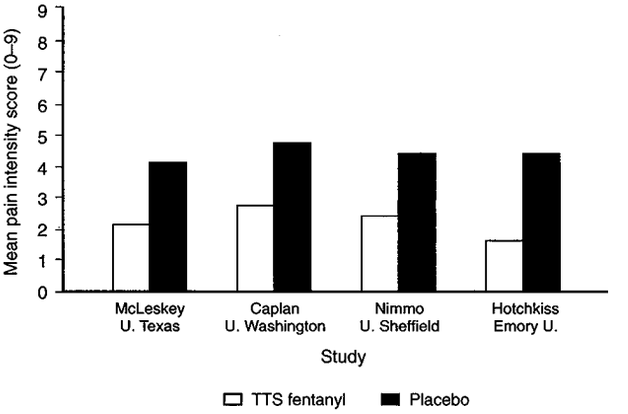

Figure 7. Quality of analgesia: mean pain intensity.

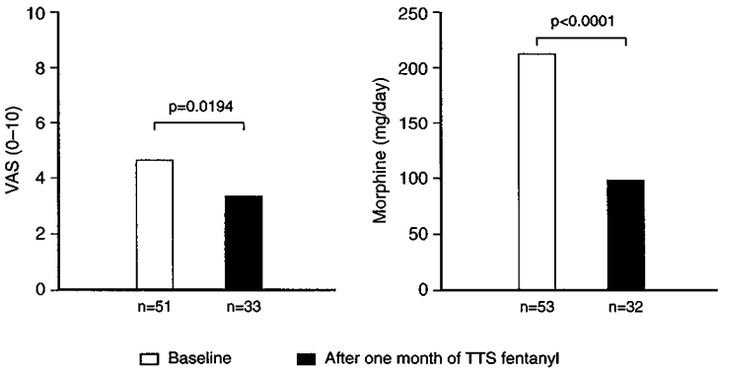

Figure 8. Mean pain scores and morphine use.

dose using standard equivalency tables.[15] The total daily morphine dose was then used as a basis for converting patients to TTS fentanyl based on the scheme presented in Table 1. For example, a patient whose daily oral morphine dose was in the range 315–404 mg was prescribed a TTS fentanyl dose of 100 μg/h. They were then permitted to use morphine as needed. A patient who had not attained acceptable analgesia on morphine could be converted to a higher TTS fentanyl dose. The analgesic outcome was evaluated after 1 month of TTS fentanyl treatment by comparing the reduction of oral morphine use, pain intensity, and pain control satisfaction ratings with prestudy and baseline values.

The results showed a statistically significant reduction ($P = 0.001$) in morphine use and in pain intensity scores 1 month after treatment initiation, compared with baseline. The mean pain intensity score was 3.3 cm vs 4.6 cm at baseline ($P = 0.0194$) (Figure 8). Pain intensity ratings were the same or better for 73% of the patients, who also reported good to excellent satisfaction with their pain control [Alza Corporation data].

Dose conversion

The method of conversion from conventional oral opioids proved conservative and thus ensured safety upon treatment initiation. No patient received an excessive initial dose which had to be decreased. In fact, approximately 50% of patients required a dose titration upward after the first week of treatment [Alza Corporation data]. Since TTS fentanyl was available in 25 μg/h dose increments, patients could easily be individually titrated to an efficacious dose.

Table 1. TTS fentanyl dose prescription based upon daily oral morphine dose

Oral 24-hour morphine (mg/day)	TTS fentanyl dose (mg/h)
45–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

During initial application of transdermal fentanyl, patients should use short-acting analgesics for the first 24 h, as needed, until analgesic efficacy with transdermal fentanyl is attained. Thereafter, some patients may require periodic supplemental doses of short-acting analgesics for breakthrough pain.

Extent of exposure

More than 17,000 patient days of TTS fentanyl use were accrued in five clinical trials at 10 different institutions. Patients received TTS fentanyl doses in the range 25–600 μg/h for 1–866 days. More than 50% of these patients used TTS fentanyl for over 1 month and 10% continued use for more than 1 year [Alza Corporation data].

Patients in these clinical trials were considered as representative of many who will be candidates for treatment with TTS fentanyl. Although receiving opioids orally or parenterally, the majority were not achieving adequate control of pain associated with cancer with conventional analgesic regimens and for this reason were considered for TTS fentanyl use.

More than half of the patients were 60 years of age or older (range 16–81). The malignancies most frequently reported were those of the breast, lung, and gastrointestinal tract, and the prognosis for most patients was poor. All patients were receiving palliative therapy for cancer or associated symptoms.

Safety

The safety of TTS fentanyl has been evaluated in 357 postoperative patients and 153 cancer patients. Hypoventilation was the most serious adverse reaction, occurring in 13 (4%) postoperative patients and three (2%) cancer patients.

Withdrawal from chronic treatment

The majority of cancer patients continued TTS fentanyl use until death. Only 11 (7%) withdrew from treatment because of inadequate pain control. While disease progression could not be documented in all cases, it probably contributed to intensified pain in this subset of patients. Adverse experiences accounted for the withdrawal of 13 (9%) patients. Nausea and vomiting were cited as the reasons for approximately half of these withdrawals. Multiple opioid-related side effects accounted for an additional three withdrawals during the first 7 weeks of therapy. None of these effects was considered serious. One additional patient withdrew because of bacterial sepsis and hypotension, and another had renal dysfunction and became comatose;[6] both were seriously ill from cancer at the time of study entry.

Adverse experiences

TTS fentanyl was generally well tolerated by the patients who used it chronically for cancer pain. Hypoventilation occurred in only three patients (2%). The most frequently reported complaints were nausea (23%) and vomiting (22%). Other reactions reported in 10% or more patients included constipation, dry mouth, somnolence, confusion, asthenia and sweating. In view of the advanced disease states and adjunctive treatments in these patients, the precise role of TTS fentanyl in causing these symptoms is uncertain.

Topical effects

The topical effects observed during TTS fentanyl use have been minimal. Only 4% of patients have reported an application site reaction. There have been no complaints of sensitisation. When skin sites were evaluated under double-blind conditions in postoperative studies, the topical effects of TTS fentanyl could not be distinguished from those of transdermal placebo [Alza Corporation data].

Conclusion

The TTS fentanyl delivery profile can provide 72 h of pain control from a single dose, reduces the frequency of re-medication, and promotes good compliance – all optimising the opportunity to achieve good pain

control. The simplicity of the TTS fentanyl regimen is a major advantage for both patients and caregivers.

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