Anti-Cancer Drugs 1995, **6**, Suppl 3, pp. 50–53

Guidelines for the clinical use of transdermal fentanyl

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Transdermal (TTS) fentanyl therapy has emerged as an effective alternative to the use of oral opioids for the control of pain in certain cancer patients. These patients are those with moderate to severe chronic pain, with a stable baseline pain pattern. Patients receiving this treatment should first be titrated to stable pain relief with oral opioids and should have recourse during therapy to fast-acting, short-duration analgesics for the control of incident pain. TTS fentanyl dosing schedules should be based upon the patient's requirement for rescue dosing and duration of effective pain control. The average requirement to change fentanyl patches is every 72 h, although 48-h dosing is necessary in a few patients. This novel route of fentanyl administration allows convenient outpatient treatment, the possibility of a lower incidence of side effects, and may thus aid compliance.

Introduction

Orally administered opioids have been standard therapy for moderate to severe pain in cancer patients for over 20 years.[1] This bears testimony to their efficacy – there is no good reason to doubt that the opioids are the most effective agents available for the relief of pain in cancer sufferers. However, as in all areas of medicine, there is room for improvement. In the case of opioid treatment, the particular drawback is how to apply therapy in patients who are unable to swallow due to head or neck cancer, or who cannot tolerate oral therapy due to cancer-related nausea and vomiting or dysphagia or because of the side effects of the oral opioid itself.

At present, the available alternative routes of administration are continuous intravenous, subcutaneous or spinal infusion pumps. However, such methods can prove to be expensive, particularly when one considers the additional nursing and physician time required.[2] With the advent of the transdermal therapeutic system (TTS) for opioid administration, physicians and their patients are now offered an alternative non-invasive means of obtaining pain relief. Indeed, data from a number of clinical studies indicate that the application of fentanyl by the transdermal route is of clinical benefit in the control of pain in selected cancer patients. This paper proposes some guidelines for the use of this novel therapeutic modality with regard to patient selection and appropriate methodology, and discusses clinical experience using this approach.

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Guidelines for usage

Patient selection

The first and most obvious requirement in the selection of suitable patients for TTS fentanyl therapy is that the patient is responsive to opioid treatment. In opioid-naïve patients, it is recommended that treatment is started with the lowest dose fentanyl patch and titrated upwards according to patient response.

Since all slow-release transdermal delivery systems take some time to diffuse through the skin, reach the systemic circulation and exert their maximal clinical effects, the clearest indication for TTS fentanyl treatment is in those patients experiencing moderate to severe chronic pain with a stable baseline pain pattern.[3] Clinical experience shows that due to this inherent slow onset of action, with steady-state concentrations being reached within 12–24 h, TTS fentanyl, like the slow-release morphine formulations, is not suitable for the routine management of short-lasting acute pain states.

Although TTS fentanyl represents a significant advance for application of strong opioid therapy in patients with constant and intractable nausea and vomiting or other conditions which render oral opioid administration impossible, and in patients with complicated pain syndromes who are required to take several different drugs for pain control, the favourable efficacy and side effect profile means that TTS fentanyl can be regarded as a true alternative to oral opioids

Table 1. Dose conversion from oral morphine to TTS fentanyl

Oral morphine (mg/day)	Initial TTS fentanyl dose (μg/h)
45–134	25
135–224	50
225–314	75
315–404	100

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Table 2. Mean patient assessment of pain and side effects during morphine stabilisation and TTS fentanyl treatment phases

	Morphine phase	TTS fentanyl phase	*p*
Pain	34.1	37.5	0.287
Sleep quality *	48.5	58.1	0.034 **
Morning vigilance	60.7	51.7	0.018 **
Nausea	0.42	0.25	0.034 **
Vomiting	0.19	0.08	0.016 **
Constipation	0.33	0.19	0.022 **

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as first-line therapy in eligible patients. This has been demonstrated in a study by the TTS Fentanyl Multicentre Study Group[4] involving 40 patients with malignant neoplastic disease requiring opioid analgesia. All patients were stabilised to pain relief with oral morphine for a minimum of 48 h, after which time they were switched to TTS fentanyl using the standard dose conversion chart (Table 1); the dose was then adjusted as required and the patch was replaced every 72 hours. All patients were allowed to take oral morphine on an as needed basis for the control of any incident pain. Several efficacy and tolerability parameters were assessed by the patients using a visual analogue scale during both the stabilisation phase and the nine-day TTS fentanyl treatment phase.

Thirty-one patients completed the study and were stabilised, on average, after 4.3 days. As shown in Table 2, there was no significant difference in the patients' assessment of pain during the TTS fentanyl phase compared with the morphine stabilisation phase. Of greater clinical importance was the significant improvement in sleep quality, morning vigilance, nausea, vomiting and constipation with TTS fentanyl as opposed to morphine. Furthermore, the need for oral morphine to control incident pain declined over the fentanyl treatment period, and seven patients had no requirement for additional morphine during this time.

This study therefore demonstrated that TTS fentanyl can provide pain relief in cancer patients equivalent to that achieved with morphine. Furthermore, the additional benefits of reduced side effects may significantly enhance the patients' quality of life. This is an important consideration in a population of patients who are extremely ill and who also have to bear the burden of side effects of any additional therapies being administered. Indeed, in this multicentre study, the majority of patients accepted the offer of remaining on TTS fentanyl therapy after completion of the study.

Dose titration

Prior to initiating TTS fentanyl treatment, patients should be titrated to stable pain relief using immediate or sustained release morphine preparations and then converted to fentanyl for maintenance therapy. In this way, as absorption is relatively slow in comparison with the oral route, peak and trough bolus effects are avoided. According to the findings of the multicentre study described above, the standard conversion table allowed a successful switch from oral morphine to TTS fentanyl, with the initial TTS fentanyl dose being based on the previous 24-h opioid requirement. The initial dose selected is likely to be inadequate in around 50% of patients,[5] and dose titration to achieve maximal pain relief is therefore important. Subsequent fentanyl dosing schedules should be based upon the efficacy of pain control in the patient, taking into account the occurrence and frequency of incident pain and the requirement for rescue pain relief (see below). It is recommended that dose titration is made in 25 μg/h incremental steps. The average duration of effect of a TTS fentanyl patch is approximately 72 h in most patients, although a few patients may require a new patch after 48 h.

Rescue dosing

Since around two-thirds of cancer patients with pain suffer from incident or breakthrough pain, all patients receiving TTS fentanyl therapy should be provided with fast-acting, short-duration oral or parenteral opioids.[3] This is particularly important upon application of the first patch until maximal plasma fentanyl concentrations have been achieved, but is also necessary to control episodes of breakthrough pain after an optimal TTS fentanyl dose titration. Immediate release morphine, oxycodone and hydromorphone have all proved effective in this regard.

The use of agents with a fast offset of action helps to avoid toxicity associated with accumulation of rescue drug on top of the background fentanyl concentration. Patients should be told to expect to require rescue dosing on a prn basis every 3-4 h, particularly at the initiation of fentanyl treatment; rescue dosing requirements in excess of this figure provide an indication for an increase of fentanyl dosage or alternative methods of pain relief.

Skin adhesion / rotation of skin sites

Good adhesion of the fentanyl patch to the skin is essential for efficacy and it is therefore important to instruct patients as to the correct application technique. After removal of the plastic backing, the patch should be applied to a clean, dry, undamaged, non-hairy area of skin and held firmly for around 30 seconds, a finger should be run around the edge of the patch to make sure the edges are stuck down. In the multicentre study, 82% of patients reported no problems with patch adherence.[4] However, extra adhesion with tape may sometimes be required, especially in warm weather or in diaphoretic patients. Rotation of skin sites is necessary in order to minimise changes in blood levels due to a build-up of subcutaneous depots, and the patch should be changed every 72 hours.

Management of side effects

In clinical trials, the overall tolerability of TTS fentanyl was good, and the majority of reported adverse events were those expected of a potent opioid. Toxicity may be managed by fentanyl dose reduction where appropriate and by the administration of adjuvant therapy. Adverse treatment effects include dry mouth, sweating, nausea, vomiting, constipation, somnolence and confusion, though the incidence of such events appears to be lower than observed with conventional oral morphine treatment. Although there is evidence to suggest that constipation may be less common with TTS fentanyl, it is recommended that all patients receive prophylactic bowel regimens.

Clinical experience with TTS fentanyl at the MD Anderson Cancer Center

Of 5598 DEA schedule 2 outpatient opioid prescriptions written in a six-month period at the MD Anderson Cancer Center, Texas, USA, 560 (10%) were for TTS fentanyl, with 14% of these prescriptions written by the pain service. In order to study TTS fentanyl usage during this six-month period, data from a random sample of 262 patients receiving this treatment were analysed. The data were assessed with respect to adherence to the suggested guidelines for TTS fentanyl therapy as outlined above.

Prior dose titration

Of the 262 patients treated with TTS fentanyl, only 95 (39%) were stabilised on an opioid for a period of more than one week prior to the initiation of therapy. The 61% of patients who were not thus prepared tended to be those who were seen by the primary oncology services, both medical and surgical, and were placed on TTS fentanyl as an initial treatment for pain once it reached the moderate to severe stage.

Rescue dosing

In total, 75% (197) of the patients were given recourse to rescue therapy. In the majority (89%) of the patients, rescue therapy consisted of drugs with a short duration of action, any long-acting drugs being appropriately discontinued prior to initiation of therapy. It is clearly important that the use of rescue dosing is properly explained to the patient prior to the drugs being made available. Several incidences were noted in which patients suffered toxicity as a result of mistakenly taking their rescue medication at regular intervals rather than as required to control emergent pain.

Fentanyl dosing schedule

All 569 patients who received TTS fentanyl therapy during the six-month study period were assessed with regard to the fentanyl dosing schedules employed.

The great majority (87%) of patients were prescribed TTS fentanyl according to a 72 h schedule. However, a small number of patients (n = 18; 3.2%) received treatment on a 48–72 h schedule due to poor pain control after 48 h with an increased requirement for rescue therapy. A few patients (n = 24; 4%) were prescribed TTS fentanyl inappropriately, for example on a prn schedule.

Discussion

It is clear that, when used according to the guidelines outlined above, and in appropriately selected patients, TTS fentanyl represents a useful new therapeutic modality for the control of opioid responsive pain in cancer care. Analysis of the clinical use of TTS fentanyl during a six-month period at the MD Anderson

Cancer Center, Texas, USA, indicates a broad adhesion to the suggested guidelines for TTS fentanyl use, although some further education may be required, particularly with reference to the prior titration of patients to a stable pain level before TTS fentanyl is introduced. Adequate patient and family education to clarify their expectations of treatment is, likewise, important.

This new mode of opioid administration has proved to be as efficacious as oral opioids and has the additional benefit of improving patients' quality of life due to reduced side effects, particularly nausea, vomiting and constipation, which are common complaints with conventional opioids. It is also useful in patients who are unsuitable for oral analgesia because of constant intractable nausea or vomiting or who are unable to swallow because of head and neck or gastrointestinal tract malignancies.

The non-invasive, easy to apply transdermal patch may be an important aid to patient compliance and allows outpatient treatment without the requirement for skilled pharmacy or nursing services. With regard to compliance, experience suggests that TTS fentanyl may not be associated with 'opioid therapy' by many patients and may therefore be viewed as a more acceptable treatment than oral morphine or methadone.

In assessing the value of TTS fentanyl, it is important to allow several weeks for an adequate therapeutic trial so that patients may be properly stabilised prior to the introduction of fentanyl and to allow steady-state plasma levels to be attained. Finally, with regard to the relative utility of TTS fentanyl in comparison with oral opioids (in those able to take them), the principal benefits of this methodology are related to its ease of use, effect on quality of life, and the associated increased compliance.

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