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# Transdermal fentanyl in combination with initial intravenous dose titration by patient-controlled analgesia

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**Two studies including a total of 70 patients evaluated the efficacy and side effects of a combination of initial patient-controlled analgesia (PCA) for dose finding with transdermal fentanyl administration. Patients, requiring strong opioids for severe cancer pain, received intravenous (i.v.) fentanyl on an on-demand basis over a 24 h period. The amount of fentanyl administered was then used for selecting a suitable transdermal therapeutic system (TTS), which remained in place for 72 h. The size of the second TTS was adjusted according to the amount of supplementary i.v. fentanyl required on day 3. Beginning on day 4, oral or subcutaneous morphine was made available as a rescue medication. The use of TTS fentanyl in combination with initial dose titration using PCA resulted in rapid and statistically significant pain relief in both studies. A respiratory rate below 8 per minute was observed in three patients. Due to adequate symptomatic treatment, other moderate and severe symptoms were relatively rare. TTS fentanyl was shown to be an effective, safe and simple method for long-term pain relief in cancer patients and presents an interesting novel option in the treatment of cancer pain.**

## Introduction

Strong opioids play a major role in the current management of cancer pain. Whenever possible, the use of oral medication is preferable, because it is effective and easy to handle for medical professionals, patients and carers.[1] The availability of sustained-release opioids has eased cancer pain management and improved the relationship between analgesic effectiveness and side effects. Fentanyl administered via a transdermal therapeutic system (TTS) may offer additional advantages by sustaining consistent analgesia for an even longer period of time of up to 72 h. Furthermore, in the terminal phase of the disease, the oral route of opioid administration can no longer be used in many patients, mostly because of other cancer-related effects such as nausea, vomiting or dysphagia.[2,3]

Since the therapeutic window that is associated with comfort and minimal toxicity is narrow in most cancer patients, careful dose titration of opioids is of considerable importance. The previously used dose-finding strategy of converting oral morphine dose equivalents to TTS fentanyl dosage may well be inaccurate, as reliable equianalgesic dose ratios for TTS fentanyl and other opioids are not yet available. In addition, initial treatment should result in rapid pain reduction as most cancer patients suffer from severe pain and have a limited life expectancy. To effect rapid dose titration and initial pain relief, we decided to combine initial patient-controlled analgesia (PCA) using intravenous (i.v.) fentanyl with subsequent TTS fentanyl.

Two studies including a total of 70 patients served to evaluate the efficacy and safety of our approach. The study protocols were approved by the local Ethics Committee of the University of Cologne. All patients gave their written informed consent prior to inclusion in the studies.

## Pilot study (dose finding)

Initially, a 1-week pilot study was performed, including 20 inpatients (10 male; 10 female) with progressive cancer of different sites.[4] Twelve patients suffered from nociceptor pain, eight from neuropathic pain and two from a combination of both pain types. All patients had received either weak opioids or in most cases strong opioids on a regular basis before entering the study. Simultaneous oncological treatment was

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not allowed, but standardised adjuvant drugs according to the analgesic guidelines of the World Health Organization (WHO), i.e. non-opioid analgesics, antiemetics and laxatives, were provided.

## Study procedure

A 24-h period of i.v. fentanyl self-titration administered via a computerised pump was used for dose finding. On the basis of our previous experience with fentanyl, the following parameters were chosen: demand dose, 50 μg; lockout time, 5 min; and hourly maximum dose, 250 μg. Based on the titrated dose and a conversion table (Table 1), the required daily dose of transdermal fentanyl was calculated and the first TTS was applied on the second day. This patch remained in place for 72 h, while i.v. fentanyl was available for a further 48 h. A second TTS was applied to a different body area from day 5–7 which was adjusted in size according to the amount of supplementary i.v. fentanyl required on the second day of transdermal administration. From day 4–7, subcutaneous morphine was available for breakthrough pain as required (Figure 1). Fifteen patients were reconverted to oral or parenteral morphine on day 8 as indicated by the study protocol, whereas five continued with TTS fentanyl for up to 34 days.

## Collected data

Pain, quality of sleep, mood, general state of health, activity, mobility, disease symptoms and adverse effects were assessed for the preceding 24 h using patient-completed visual analogue scales (VAS). Vital functions were monitored four times daily. Pain relief was assessed on the first and fourth day of the study using a five-point scale ranging from 0% to 100% and was compared to the pre-study situation. Plasma fentanyl concentrations were measured daily using a radioimmunoassay technique described by Michiels and co-workers.[5]

**Table 1.** Conversion table for daily parenteral fentanyl dose to TTS fentanyl in the pilot study *

| Total daily parenteral fentanyl (mg/day) (range) | TTS fentanyl delivery rate (mg/day) |
|---|---|
| 0.1–0.8 | 0.6 |
| 0.9 | 0.6 / 1.2 |
| 1.0–1.4 | 1.2 |
| 1.5 | 1.2 / 1.8 |
| 1.6–2.0 | 1.8 |
| 2.1 | 1.8 / 2.4 |
| 2.2–2.6 | 2.4 |
| 2.7 | 2.4 / 3.0 |
| 2.8–3.2 | 3.0 |
| 3.3 | 3.0 / 3.6 |

* In doses higher than 3.3 mg i.v. fentanyl, the same conversion ratio was continued.

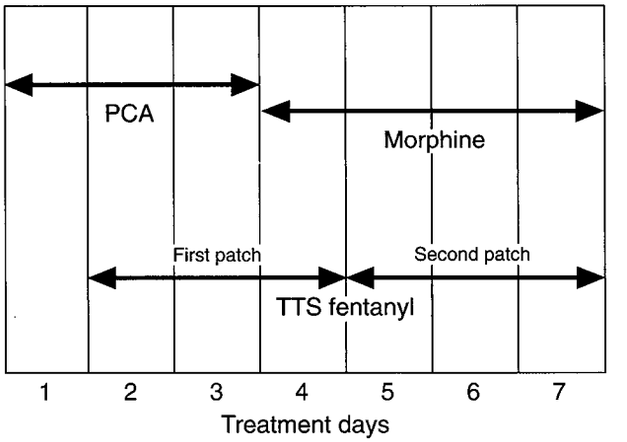


**Figure 1.** Graphic representation of the initial dose titration in both studies. Reproduced with permission from Zech *et al.*[4]

## Results

The results demonstrated a statistically significant reduction of mean daily VAS scores during the PCA period on day 1, from 68 to 34, and a further decrease to values around 26 with the onset of TTS action on the second day. The mean pain relief scores increased from 10% on day 1 to 44% on day 4.

The mean daily PCA fentanyl dose amounted to 1.5 mg during the first 24 h and decreased on days 2 and 3 with the onset of TTS action. The mean daily dose of the first transdermal system was 1.5 mg, whereas additional i.v. fentanyl requirements (which could be administered until day 3) were the basis for an increased daily TTS dose of almost 1.9 mg during days 5–7 (Figure 2). The mean plasma fentanyl concentrations obtained in 15 patients were 1.1 ng/ml during the first 24 h PCA phase which increased to 1.4 and 1.2 ng/ml, respectively, on days 2 and 3, before decreasing to values below 1 ng/ml on day 4. The plasma fentanyl concentration curve from days 5–7 showed a comparable shape but on a lower level. A decline of the fentanyl concentration curve on the third day of transdermal administration was noticed for both patches. A mean plasma fentanyl concentration of 0.3 μg/ml was still apparent on day 8 in four patients who had been already reconverted to morphine. The mean supplementary morphine doses were 25 mg/day on day 4, decreasing on days 5 and 6, before slightly increasing again on day 7. A com-

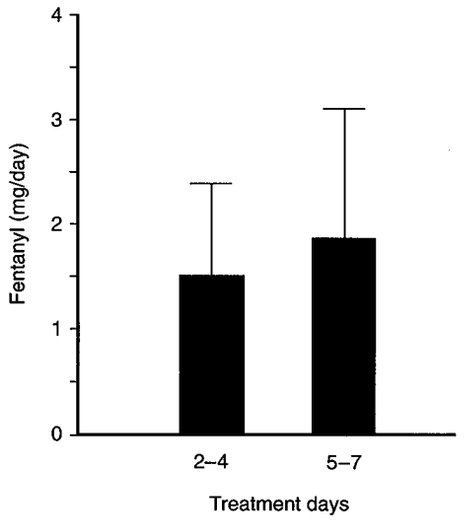


**Figure 2.** Mean (SD) daily doses of the first and second TTS fentanyl applications during the pilot study ($n = 20$). Reproduced with permission from Zech *et al.*[4]

bination of relatively low plasma fentanyl concentrations and relatively high supplementary morphine doses was noted on days 4 and 7.

There was a modest, but statistically non-significant increase in the VAS scores for general state of health, whereas the other quality of life indices showed only very small changes. Severe side effects, such as clinically apparent respiratory depression or significant changes in blood pressure or heart rate, were not observed throughout the pilot study. Four patients presented with a slight and very transient erythema after removing the patch, and one further patient developed minor pustules which resolved spontaneously after a few days. In comparison with the pre-study situation, there was a slight decrease in the VAS scores for constipation, nausea, vomiting, anorexia and fatigue, while other symptoms remained almost unchanged. Main complaints were dryness of the mouth, sweating and constipation, which may have also been influenced by the concomitant application of non-steroidal analgesics, anti-emetics, and other drugs. Overall, there were no statistically significant differences when compared with the pre-study values.

### Prolonged treatment of five patients

In the last five inpatients for whom TTS treatment was allowed to be continued for periods of 20 to a maximum of 34 days, results were inconsistent, with one very difficult case achieving poor pain relief and the remaining four patients having moderate to excellent pain control. The maximum daily TTS dose which was administered in one of these patients was 7.2 mg.

## Main study

These encouraging results with the absence of severe side effects and the excellent patient acceptance led us to perform an open prospective study to evaluate the efficacy, safety and feasibility of TTS fentanyl for long-term cancer pain treatment. We selected patients with cancers of the gastrointestinal tract and the head and neck region for whom TTS fentanyl was expected to be of special value because of their frequent problems with swallowing, nausea and other gastrointestinal symptoms.

Fifty patients (19 female; 31 male), most of whom had advanced gastrointestinal or head and neck cancer, were included in the study. Nociceptor pain was diagnosed in two-thirds of the patients and combinations of nociceptor and neuropathic pain in one-third. Regular administration of weak opioids had failed to provide sufficient pain relief in one-third of the patients, while two-thirds were already being treated with strong opioids, mainly by oral administration.

### Study procedure

In accordance with the pilot study, an initial 24-h period of i.v. fentanyl self-titration was used for dose finding. Based on the titrated dose and a modified conversion table, the required daily dose of TTS fentanyl was calculated. Clinical experience, obtained during the pilot study, led us to increase the i.v. to TTS fentanyl conversion ratio by 50%, from 1:1 to 1:1.5, in this study (Table 2). The first TTS patch was then applied on the second day and was changed every 72 h, and every 48 h, if required, in selected cases. TTS sizes were adapted during treatment if necessary. Due to the delayed onset of maximum TTS action and the individual variance in bioavailability, PCA was available for a further 48 h to provide additional titration. From day 4, oral or subcutaneous morphine was available as rescue medication. Standardised adjuvant drugs were provided according to WHO guidelines, and concurrent radio- and chemotherapy were allowed. Beginning with day 5, patients were allowed to continue TTS as outpatients. Criteria for premature study termination were respiratory depression requiring therapy, other uncontrollable side effects, inadequate pain relief and major surgery.

### Collected data

Pain, mood, general state of health, activity, mobility, disease symptoms and adverse effects were assessed

**Table 2.** Conversion table for daily parenteral fentanyl dose to TTS fentanyl in the main study

| PCA fentanyl dose (mg/day) (range) | TTS fentanyl delivery | |
|---|---|---|
| | Rate (mg/day) | Size ($cm^2$) |
| 0.1–0.6 | 0.6 | 10 |
| 0.6–1.0 | 1.2 | 20 |
| 1.0–1.4 | 1.8 | 30 |
| 1.4–1.8 | 2.4 | 40 |
| 1.8–2.2 | 3.0 | 50 |
| 2.2–2.6 | 3.6 | 60 |
| 2.6–3.0 | 4.2 | 70 |
| 3.0–3.4 | 4.8 | 80 |
| 3.4–3.8 | 5.4 | 90 |
| 3.8–4.2 | 6.0 | 100 |

daily by the patients using a diary. Vital functions were monitored four times daily during the titration period. Plasma fentanyl concentrations were measured daily during dose titration and in free intervals during the rest of the study period.

## Results

*Titration period.* The mean i.v. fentanyl dose during the first 24 h was comparable to that obtained during the pilot study. A comparable decline of the dose curve on days 2 and 3 corresponding with the onset of TTS action was also observed. The mean daily dose of the first TTS application was 2.4 mg/day. Further titration with PCA formed the basis for an increase of the mean daily TTS dose of almost 50% for the second system. At the end of the first week, there was little change in the dose, which demonstrates that a stabilisation was obtained within 5 days (Figure 3). Increased dose requirements between the first TTS and the end of the first week were noted in 79% of the patients remaining in the study. This figure was reduced to 40% when comparing the second TTS with day 8. Due to the increased conversion ratio, mean plasma fentanyl concentrations were significantly higher when compared with the pilot study and were around 2 ng/ml during the first week of the study (Figure 4).

Pain intensity was measured four times daily using a 101-step numeric analogue scale (NAS) completed by the patients. The mean daily NAS scores decreased from an initial value of 45 to 32 on day 1 and subsequently decreased to around 20 during the rest of the week. It has to be noted that patients who were already receiving strong opioids prior to the study were included, independent of the pain relief obtained, i.e. patients with both good and poor results were included.

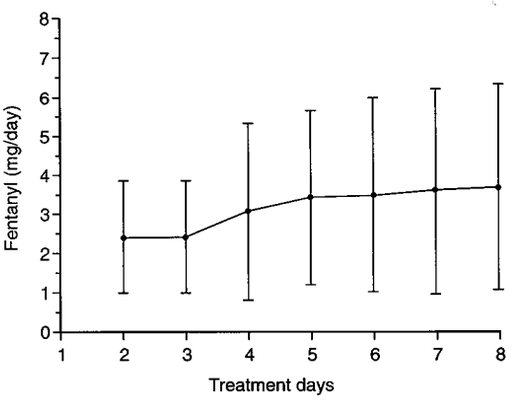


**Figure 3.** Mean (SD) daily TTS fentanyl doses during the first week of treatment with PCA and TTS fentanyl (main study; $n = 50$).

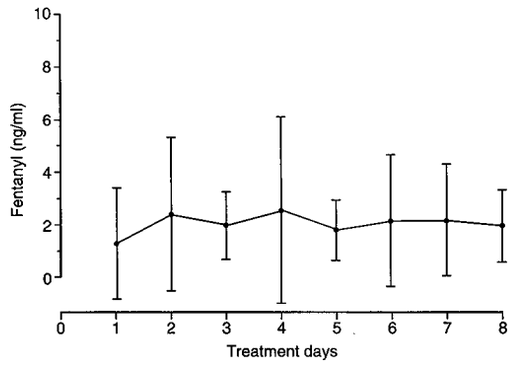


**Figure 4.** Mean (SD) plasma fentanyl concentrations during dose titration with PCA and initial TTS treatment (main study; $n = 50$).

*Long-term treatment.* In the 50 patients in the study, a total of 3,264 TTS fentanyl treatment days were recorded. The mean duration of TTS treatment in the main study was 65 days (range 2–534). Thirty patients were treated satisfactorily until death from the underlying disease.

The majority of TTS fentanyl doses during the whole treatment period were low to medium. The maximum dose administered was 19.2 mg/day and it was effective for a number of weeks. Two patients were treated adequately for more than 1 year. In general, plasma concentrations showed the expected wide variation. The correlation between TTS dose and plasma fentanyl concentration was calculated to be statistically significant.

Daily NAS scores from four daily measurements for each patient showed a pooling between 0 and 40.

Satisfactory pain control was achieved continuously in those patients with the longest treatment times. Mean daily NAS scores remained below 20 for most of the study period, representing good to excellent pain control. Daily subcutaneous morphine dose requirements were between 0 and 20 mg for most patients. Rescue doses were required in almost 40% of a total of 3,164 treatment days where morphine was available. Mood, general state of health, activity and mobility were improved markedly during treatment with TTS fentanyl.

With regard to side effects, a respiratory rate below 8 per min during sleep was noted in three patients during the titration period. No other signs of respiratory depression were seen and no reversal was necessary. This led to study termination in one of the patients being treated on a normal ward, while the other two patients were monitored closely in a palliative care unit and remained in the study. No other significant changes in vital signs were noticed.

Comparing the incidence of major symptoms such as constipation, nausea and vomiting on days 0 and 3, a marked reduction was noticed during fentanyl treatment, while other symptoms such as sweating, fatigue, dizziness and pruritus were almost unchanged. As careful symptom control was maintained, moderate and severe symptoms were relatively rare during the treatment period and in no case resulted in a patient being withdrawn from the study.

Local skin reactions, which were mild and transient, were observed in nine patients. No treatment measures were necessary, nor were there any complaints from the patients.

Almost all patients interviewed were satisfied with TTS fentanyl, with 97% preferring the transdermal route to their prior treatment. Finally, clinicians found TTS fentanyl to be satisfactory or excellent in 38 (76%) of the 50 patients.

## Discussion and conclusions

From our data we conclude that TTS fentanyl is an effective, safe and simple method for long-term pain relief in cancer patients. It is associated with a low incidence of side effects, if combined with adjuvant therapy, and excellent patient acceptance. TTS fentanyl is especially useful for patients with gastrointestinal and head and neck cancers who often suffer from problems with swallowing and whose opioid intake is provided via indwelling tubes or catheters. However, TTS fentanyl presents not only an alternative to parenteral opioid administration, but may also be of use in patients who have difficulties with a large oral medication intake, a situation which is common in complicated cases. Best suited for TTS fentanyl treatment are patients with low to medium opioid requirements and a stable pain syndrome.

However, some problems have to be considered. Careful dose titration is of considerable importance for TTS fentanyl dose finding. Studies using oral or parenteral morphine failed to demonstrate a quick and marked pain relief, probably because of the considerable inter-individual variations in the bioavailability of oral morphine and the variable equipotency that is reported for fentanyl in comparison with morphine.[6–10] On the other hand, outpatient treatment from the first day is possible with this approach, while a minimum of 5 inpatient days is necessary using the 'invasive' i.v. fentanyl titration. These aspects may be of considerable importance in terminal cancer patients.

In patients with high opioid requirements it may be difficult to find suitable sites for patch application. Two of our patients with daily oral morphine doses of 240 and 720mg, respectively, were unresponsive to fentanyl and the conversion did not succeed, while reconversion to morphine resulted in adequate pain relief.

Many cancer patients suffer from 'breakthrough' or incident pain, requiring supplementation with immediate-release opioids.[11] Since immediate-release formulations of fentanyl, such as oral transmucosal fentanyl citrate, are being investigated clinically, but are not generally available, subcutaneous or oral morphine has had to be used up to now.[12] However, it may be advantageous to use only one opioid for continuous and breakthrough pain. The delayed onset of action of TTS fentanyl makes a quick adaptation of the dosage almost impossible in patients with a rapid escalation of pain intensity due to progressive disease or the development of tolerance.

A few patients were sceptical about transdermal administration or had difficulties at home in handling the patches. Poor compliance was another observation, which is not surprising in patients with head and neck cancers.

To summarise, TTS fentanyl has proven useful in clinical practice and presents an interesting novel option in our armamentarium against cancer pain. To evaluate further the usefulness of TTS fentanyl in cancer pain, a comparison with standard morphine treatment is necessary.

## Acknowledgements

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