Anti-Cancer Drugs 1995, **6**, Suppl 3, pp. 39–43

Transdermal fentanyl: a new step on the therapeutic ladder

B Donner and Michael Zenz

Universitätsklinik für Anaesthesiologie, Intensiv- und Schmerztherapie, Bochum, Germany.

The high efficacy, low molecular weight and high lipid solubility of fentanyl make it a suitable agent for transdermal administration. Effective plasma concentrations are maintained for up to 48–72 hours after application of a transdermal therapeutic system (TTS) fentanyl patch. In a multicentre study, slow-release morphine was replaced by TTS fentanyl according to a special calculation table (10 mg oral morphine corresponding to approximately 0.1 mg TTS fentanyl). Ninety-eight patients were included in the study. Due to protocol infringements, however, the switch from oral morphine to TTS fentanyl could be assessed for only 38 patients. The changeover at a ratio of 100:1 proved to be safe and effective and a good alternative therapy to conventional strong opioids. The majority of the patients wished to continue TTS fentanyl therapy at the end of the study period. Side effects were similar to those associated with other opioids. However, TTS fentanyl was associated with a distinct decrease in constipation and a significant reduction in the use of laxatives. Furthermore, there were some indications that compliance may be increased with TTS fentanyl. Special indications for chronic pain therapy using transdermal opioids include head and neck and gastrointestinal tract cancer. In these cases, TTS fentanyl may be the final non-invasive form of analgesic therapy which allows the patient to maintain a normal lifestyle. TTS fentanyl thus represents a new alternative for therapy with strong opioids on step III of the World Health Organization analgesic ladder.

Introduction

The μ agonist fentanyl has a potency which is 75–100 times higher than that of morphine. Its high efficacy, low molecular weight, and high lipid solubility make it a suitable agent for transdermal administration. In TTS fentanyl (transdermal therapeutic system), the fentanyl base is present in 25% ethanol, which further increases the solubility of the opioid. The quantity of fentanyl released, at 25 μg/h/10 cm^2, is proportional to the surface area of the system. After release of the priming dose, peak plasma levels are reached after 8–16 h.[1–5] Effective doses of fentanyl are maintained for up to 72 h. In exceptional cases, the patch may need to be changed after only 48 h.[1,6–8] TTS fentanyl patches are manufactured in four different sizes (10, 20, 30 and 40 cm^2) providing four different delivery rates (25, 50, 75 and 100 μg/h). If dosages of more than 100 μg/h (2.4 mg/day) are required, multiple patches have to be used.

The efficacy of transdermally administered fentanyl in the treatment of cancer pain has been proven in a number of clinical studies. However, in the majority of the studies the changeover to TTS fentanyl was made via invasive intermediate stages, making it necessary to admit the patients to hospital.[6,9–19]

In an open multicentre study, a conversion table with a ratio of 100:1 slow-release morphine to TTS fentanyl was tested. The aim was to make it possible to switch patients to TTS fentanyl under outpatient conditions.

Methods

The multicentre study was carried out in accordance with the most recent Declaration of Helsinki and approved by the Ethical Committee of the University of Ruhr in Bochum. After a detailed explanation, the patients gave written consent to take part in the study.

Patients suffering from cancer pain requiring opioid therapy were included in the study. Their established treatment was slow-release morphine, and all patients had equally good pain control with this treatment. A 6-day preliminary phase was used to check therapy adjustment. The patients were then switched from slow-release morphine to TTS fentanyl in accordance with the conversion table (Table 1). They continued to take their non-opioid analgesics in exactly the same dosage and were allowed to use a morphine solution, administered non-invasively, as a

Correspondence to M Zenz
Universitätsklinik für Anaesthesiologie,
Intensiv- und Schmerztherapie
Bergmannsheil, 44789 Bochum
Gilsingstrasse 14, Germany

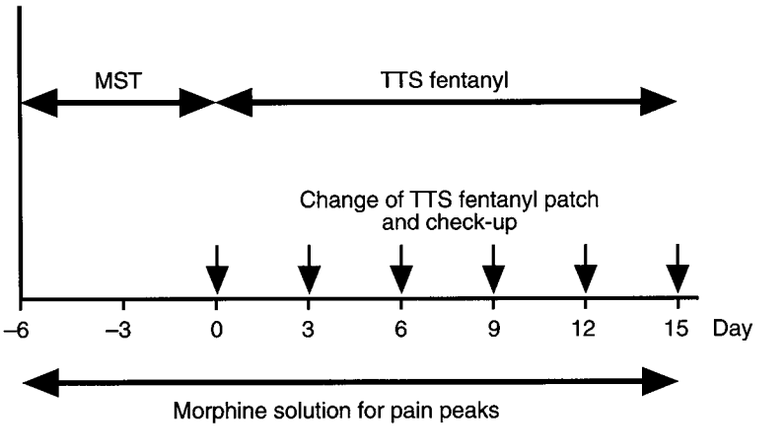

Figure 1. Course of the study.

rapid and short-acting opioid to relieve breakthrough pain. The transdermal system and the site of application were changed every 3 days. Pain reduction, supplementary use of morphine solution, and vital parameters were checked at this time point (Figure 1). Pain reduction was determined three times daily by means of a visual analogue scale (VAS: a line 10 cm long, with 'no pain' at the left end and 'maximum pain imaginable' at the right end).

Patients kept a diary throughout the observation period (day – 6 to day 15) in which they recorded their pain three times daily. They were also asked to record attacks of pain and any side effects of treatment (e.g. nausea, vomiting, diarrhoea, sweating, etc.). The need for additional painkillers was also documented.

The study was concluded on the 15th day of treatment. The patients were then asked to decide whether they wanted to continue treatment with TTS fentanyl or return to their original treatment regime. When protocol infringements were observed during the study, or when tumour progression was assumed, the patient in question was excuded from the evaluation with regard to pain relief and from the oral morphine to TTS fentanyl conversion factor.

Table 1. Conversion table for oral morphine / TTS fentanyl

Oral morphine (mg/day)	TTS fentanyl (mg/day)	TTS fentanyl (μg/h)
30–90	0.6	25
91–150	1.2	50
151–210	1.8	75
211–270	2.4	100
271–330	3.0	125
331–390	3.6	150
391–450	4.2	175
451–510	4.8	200
511–570	5.4	225
571–630	6.0	250
631–690	6.6	275
691–750	7.2	300
For each additional 60	+0.6	+25

Results

A total of 98 patients (45 women and 53 men) were included in the study, aged between 22 and 85 years. The main sites of the underlying malignant disease were intestine, breast, and lung. In the majority of patients, metastasis had already begun. Similarly, most patients had already received previous cancer treatments (e.g. surgery, radiotherapy, chemotherapy). More than 50% of the patients had other diseases which were completely independent of the cancer, and almost all patients were taking other drugs in addition to the opioids administered for pain control. The main concomitant drugs being used were non-opioid analgesics and laxatives. Sixty-three patients were treated as outpatients only, while 31 patients were treated in hospital, and 4 patients were admitted to hospital for some of the time.

Of the 98 patients included in the study, only 38 could be used for the direct analysis of the conversion table. Serious protocol violations were recorded in the other patients or pain had increased due to progression of the tumour.

The 38 evaluable patients took an average of 136.6 mg slow-release morphine and were switched to an average of 1.4 mg TTS fentanyl in accordance with the conversion table. In 16 patients, sufficient pain reduction was achieved with the initially chosen dose of TTS fentanyl, but in the other patients the dose had to be increased, in some by more than 200% (Figure 2). In the regression analysis, the average amount of oral morphine per day in the preliminary phase was correlated with the average amount of TTS fentanyl at the end of the study phase. The ratio of oral morphine to TTS fentanyl was 100:1.44 mg/day (Figure 3). Pain reduction, measured using the VAS, was unchanged during the study phase with TTS fentanyl compared with the preliminary phase with oral morphine. Even at the time of treatment changeover, there was no increase in pain. Similarly, there was no increase in pain peaks. It was noticeable, however, that significantly more patients used morphine solution during TTS fentanyl treatment. The dose was higher for the first few days with TTS fentanyl treatment than with slow-release morphine, but at the end of the study the requirement for morphine solution was the same as in the preliminary phase.

There was no statistically significant difference between oral morphine and TTS fentanyl with regard to most of the side effects (diarrhoea, nausea, vomiting, dyspnoea, itching, etc.). However, TTS fentanyl was associated with a significant decrease in constipation and a significant reduction in the use of laxatives when comparing the preliminary phase with days 9–14 of the study phase. It was noticed that three patients developed clinical symptoms corresponding to physical withdrawal within the first 24 h after treatment changeover, without signs of psychological withdrawal.

Vital parameters (blood pressure, heart rate, respiratory rate), which were checked at least every 3 days throughout the study, showed no significant changes. Similarly, there were no changes in pupil size. Relevant changes in laboratory parameters were only connected with the underlying disease; they were not considered to be associated with TTS fentanyl therapy in any patient.

The transdermal system was well tolerated on the skin. The most frequent reaction at the application site was erythema, which rapidly receded after the patch was removed. Pruritus, oedema, or formation of papules and pustules were observed only in isolated cases.

Overall, TTS fentanyl therapy was viewed favourably by both the investigating doctors and the patients. Ninety-five per cent of patients wanted to continue with the transdermal route of analgesia.

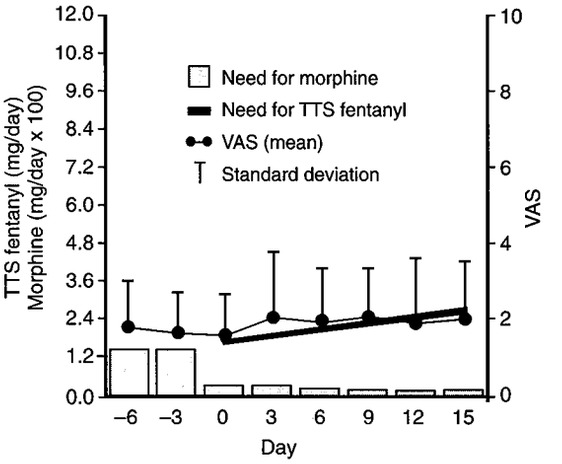

Figure 2. Visual analogue scale (VAS) values, morphine dosage, and TTS fentanyl dosage ($n = 38$).

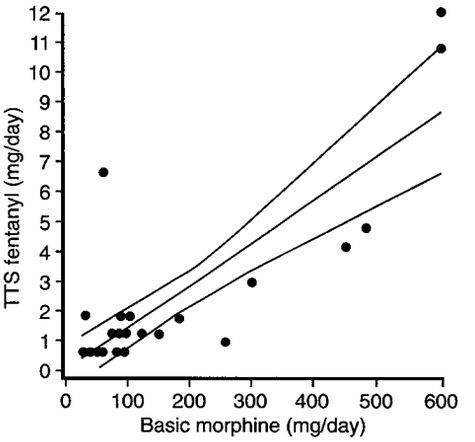

Figure 3. Linear regression analysis ($y = bx + e$). The basic morphine dose is correlated with the TTS fentanyl dose at the end of the study phase. The degree of correlation was between 82.7% and 94.4%.

Discussion

As a supplement to the previous studies [6,8,9,12–21] in which no valid conversion table was available for the changeover from the previous non-invasive form of treatment to TTS fentanyl, this study shows that effective treatment of cancer pain is possible with the aid of transdermally administered fentanyl.

The chosen conversion factor from oral morphine to TTS fentanyl of 100:1 proved to be 'sub-equianalgesic' after evaluation of the study results. This is related to the changeover procedure from one 'con-

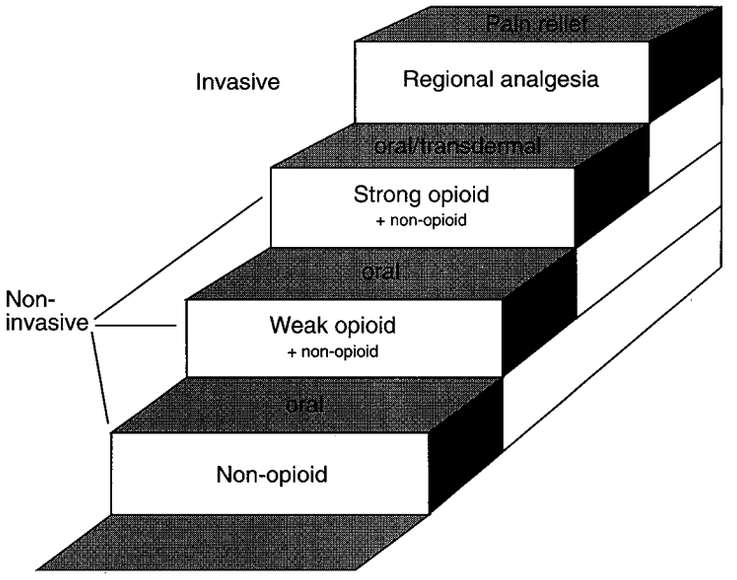

Figure 4. Adapted from the WHO ladder scheme for the treatment of cancer pain.

ventional' opioid to another in the treatment of cancer pain. A slight underdosage in the changeover period is intended to achieve sufficient pain reduction while ensuring that the patient is not in danger of opioid overdosage.[22] Within the following few days, the dose should be adjusted quickly to the needs of the patient. Given the long intervals between applications of TTS fentanyl, it is possible that the adjustment phase can be prolonged with this form of treatment.

Due to the conversion table, a safe changeover of treatment was possible both for inpatients and outpatients. In the vast majority of cases, patients prefer outpatient treatment. In this way, social contacts – which are already affected – are not put under further strain.

The advantages of transdermal fentanyl therapy result from the non-invasive treatment procedure, which allows circumvention of the gastrointestinal tract. The long intervals between applications probably lead to increased patient compliance. A sign of better compliance is the fact that the majority of patients wanted to continue with TTS fentanyl, although the pain reduction was unchanged compared to the previous treatment with slow-release morphine. A further reason could be the significant reduction in constipation.

The disadvantages of this treatment procedure are also due to its pharmacokinetic properties. The long intervals between applications can prolong the adjustment phase. The question of why more patients took morphine solution under treatment with TTS fentanyl remains unsolved. Respiratory depression has been observed in other studies.[14,23] According to the studies to date, the incidence of respiratory depression with TTS fentanyl is 1.4%.[24] If overdosage occurs, continuous antagonism of fentanyl must be established, as the half-life of transdermally administered fentanyl is 16–21 h, due to the existing depot in the skin.[2,3,5,7,11,25,26]

Cancer pain is treated in accordance with the World Health Organization (WHO) analgesic ladder scheme (Figure 4). If curative treatment of the cause of pain is not possible, non-opioid analgesics must be used initially. If pain reduction is insufficient, the non-opioid analgesic is combined with a weak opioid (step II). In step III, if sufficient pain reduction is still not achieved, the weak opioid is replaced by a strong opioid. To date, buprenorphine, slow-release morphine, and methadone have been available as the leading drugs for WHO step III. Fentanyl must also be incorporated into this step, as it is a non-invasive method of administration of a strong opioid. We currently consider the special indications for this new form of therapy to be tumours in the head and neck region, gastrointestinal cancer, patients with severe nausea and vomiting and, according to these results, patients with serious constipation while receiving other forms of strong opioids. The treatment of cancer pain in children and opioid treatment of non-malignant pain may be possible future perspectives.

Acknowledgement

We wish to thank Janssen-Cilag Gmbh, Germany, and STADA AG, Germany for their help with this study.

References

1. Calis KA, Kohler DR, Corso DM. Transdermally administered fentanyl for pain management. *Clin Pharmacy* 1992; **11**: 22–36.
2. Gourlay GK, Kowalski SR, Plummer JL, Cherry DA, Gaukroger P, Cousins MJ. The transdermal administration of fentanyl in the treatment of postoperative pain: pharmacokinetics and pharmacodynamic effects. *Pain* 1989; **37**: 193.
3. Holley FO, van Stevens C. Postoperative analgesia with fentanyl: pharmacokinetics and pharmacodynamics of constant-rate i.v. and transdermal delivery. *Br J Anaesth* 1988; **60**: 608.
4. Latasch L, Lüders S. Transdermal fentanyl against postoperative pain. *Acta Anaesthesiol Belg* 1989; **40**: 113.
5. Lehmann KA, Zech D. Transdermal fentanyl. *J Pain Symptom Man* 1992; **7** (Suppl): 8–16.
6. Grond S, Zech D. Transdermal fentanyl for cancer pain relief. *Euroanaesthesia Mannheim* 1992; Abstract.
7. Janssen Pharmaceutica Inc. *Duragesic Product Information.* Piscataway, 1990.
8. Levy MH, Rosen SM, Kedziera P. Transdermal fentanyl: seeding trial in patients with chronic cancer pain. *J Pain Symptom Man* 1992; **7** (Suppl): 48–50.
9. Herbst LH, Strause LG. Transdermal fentanyl use in hospice home-care patients with chronic cancer pain. *J Pain Symptom Man* 1992; **7** (Suppl): 54–57.
10. Janssen Pharmaceutica Inc. *Product Monograph "Duragesic", Fentanyl Transdermal System.* Mississauga, Ontario, 1991.
11. Larijani GE, Bell SD, Goldber ME, Lessin JB. Pharmacokinetics of fentanyl following transdermal application. *Anesthesiology* 1988; **69** (3A): A363.
12. Maves TJ, Barcellos WA. Management of cancer pain with transdermal fentanyl: Phase IV trial, University of Iowa. *J Pain Symptom Man* 1992; **7** (Suppl): 58–62.
13. Miser AW, Narang PK, Dothage JA, Young RC, Sindelar S, Miser JS. Transdermal fentanyl for pain control in patients with cancer. *Pain* 1989; **37**: 15–21.
14. Payne R. Experience with transdermal fentanyl in advanced cancer pain. *Eur J Pain* 1990; **11**: 98–101.
15. Simmonds MA, Payne R, Richenbacher J, Moran K, Southam MA, Hershey MS. TTS (fentanyl) in the management of pain in patients with cancer. *Proc Am Soc Clin Oncol* 1989; **8**: 324.
16. Slover R. Transdermal fentanyl: clinical trial at the University of Colorado Health Science Center. *J Pain Symptom Man* 1992; **7** (Suppl): 45–47.
17. Zech D, Grond S, Lynch J. Clinical experience. In: Lehmann KA, Zech D, eds. *Transdermal Fentanyl.* Berlin, Heidelberg, New York: Springer-Verlag 1991, 171.
18. Zech D, Lehmann KA, Rupperth J. Current development of pain treatment. *Pain Clinic* 1991; **4**: 177–181.
19. Zech D, Grond S, Lynch J, Lehmann KA. Transdermales Fentanyl zur Schmerztherapie bei Tumoren im GIT und der Kopf-Hals-Region. *Der Schmerz* 1991; **5**: 181.
20. Levy S, Jacobs S, Johnson J, *et al.* Transdermal fentanyl: pain and quality-of-life effects. *Proc Am Soc Clin Pharm* 1988; **7**: 292.
21. Patt RB, Hogan LA. Transdermal fentanyl for chronic cancer pain: detailed case reports and the influence of confounding factors. *J Pain Symptom Man* 1992; **7** (3) (Suppl): 51–53.
22. Jage J, Portenoy RK, Foley KM. Die Bestimmung des i.m. Morphin-Äquivalents zur Therapie des Krebsschmerzes mit verschiedenen Opioiden oder bei Wechsel des Verabreichungsweges. *Der Schmerz* 1990; **4**: 110.
23. Southam M, Gupta S, Knowels M, Hwang SS. Transdermal fentanyl: an overview of pharmacokinetics, efficacy and safety. In: Lehmann KA, Zech D, eds. *Transdermal Fentanyl.* Berlin, Heidelberg, New York: Springer-Verlag 1991, 107.
24. Donner B, Zenz M, Tryba M, Strumpf M. Transdermales Fentanyl in der Tumorschmerztherapie. *Der Schmerz* 1993; **7**: 18.
25. Gupta SK, Southam M, Gale R, Hwang SS. System functionality and physiochemical model of fentanyl transdermal system. *J Pain Symptom Man* 1992; **7** (Suppl): 17–26.
26. Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR. Absorption characteristics of transdermally administered fentanyl. *Anesthesiology* 1989; **70**: 928–934.