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Transdermal Fentanyl

An Updated Review of its Pharmacological Properties and Therapeutic Efficacy in Chronic Cancer Pain Control

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Data Selection

Sources: Medical literature published in any language since 1997 on fentanyl transdermal, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'fentanyl' and 'transdermal'. EMBASE search terms were 'fentanyl' and 'transdermal'. AdisBase search terms were 'fentanyl' and 'transdermal'. Searches were last updated on 2 Nov 2001.

Selection: Studies in patients with chronic cancer pain who received transdermal fentanyl. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Transdermal fentanyl, cancer pain, opioids, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Fentanyl is a synthetic opioid agonist which interacts primarily with the μ-opioid receptor. The low molecular weight, high potency and lipid solubility of fentanyl make it suitable for delivery by the transdermal therapeutic system. These patches are designed to deliver fentanyl at a constant rate (25, 50, 75 and 100 μg/h), and require replacement every 3 days.

Data from randomised, nonblind trials suggest that transdermal fentanyl is as effective as sustained-release oral morphine in the treatment of chronic cancer pain, as reported by patients using visual and numerical analogue scales as well as verbal description scales. No obvious differences in health-related quality of life were found in patients with chronic cancer pain when comparing transdermal fentanyl with sustained-release oral morphine. Nevertheless, significantly more patients expressed a preference for transdermal fentanyl than for sustained-release oral morphine after a randomised, nonblind, crossover trial.

Because of the formation of a fentanyl depot in the skin tissue, serum fentanyl concentrations increase gradually following initial application, generally levelling off between 12 and 24 hours. Thereafter, they remain relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Once achieved, steady-state plasma fentanyl concentrations can be maintained for as long as the patches are renewed.

The most frequently observed adverse events during transdermal fentanyl administration (as with other opioid agonists) included vomiting, nausea and constipation. Data from a nonblind, randomised trials suggest that constipation occurs less frequently in patients receiving transdermal fentanyl than in those given sustained-release oral morphine. The most serious adverse event reported in US premarketing trials was hypoventilation, which occurred with an incidence of approximately 2%. Adverse reactions related to skin and appendages (i.e. rash and application site reactions – erythema, papules, itching and oedema) were reported in 153 patients with cancer at a frequency between 1 and 3%.

Conclusion: Transdermal fentanyl is a useful opioid-agonist for the treatment of moderate to severe chronic cancer pain. The advantages of transdermal fentanyl include ease of administration and the 3-day application interval. These factors coupled with a lower incidence of constipation are likely to contribute to the reported patient preference of transdermal fentanyl over sustained-release oral morphine.

Pharmacodynamic Profile of Transdermal Fentanyl

Fentanyl interacts with the μ-opioid receptor as a pure agonist. The analgesic potency of fentanyl is 75 to 100 times higher than that of morphine, probably because fentanyl is lipophilic, allowing rapid penetration of the blood-brain barrier. The mechanisms of opioid-induced analgesia are only partly understood.

Like other opioid agonists, fentanyl can induce potentially life-threatening respiratory depression. Experiments in cats suggest that fentanyl-induced sustained inspiration (thoracic rigidity) results from increased amplified efferent activity to the spinal cord inspiratory motor neurons. Moreover, studies in rats

suggest that fentanyl, unlike morphine, induces respiratory depression via the μ_1-receptor.

Constipation is a common adverse event after opioid administration. Subcutaneous administration of fentanyl and morphine to rats resulted in an analgesic peak effect at doses of 0.032 mg/kg and 8.0 mg/kg, respectively. This analgesic dose was only 1.1 times higher than the dose required for a 50% inhibition of castor oil-induced diarrhoea for fentanyl, but 36 times higher than that for morphine. These results suggest that fentanyl induces analgesia without incurring the same degree of constipation as morphine. Indeed, transdermal fentanyl administration appears to result in constipation in fewer patients when compared with oral morphine therapy as shown by clinical trials.

Peripheral vasodilation and hypotension have been observed after intravenous morphine administration in surgical patients. In this study, however, such haemodynamic effects were not seen following fentanyl administration. There are two possible explanations for this difference. Firstly, morphine-induced vasodilation has been associated with histamine release. Unlike morphine, however, fentanyl administration did not lead to increased plasma levels of histamine. A second explanation could be that morphine, but not fentanyl, stimulates the release of the potent vasodilator nitric oxide by human endothelial cells *in vitro* by stimulation of the μ_3-receptor.

Pharmacokinetic Properties

Fentanyl can be administered transdermally because of its high solubility in both fat and water and its low molecular weight. The application systems are designed to deliver fentanyl at a constant rate for periods of 72 hours. Currently, patches with a delivery rate of 25, 50, 75 and 100 μg/h are available. Neither local blood flow nor anatomical site of application seem to affect fentanyl delivery. Nonetheless, a rise in body temperature to 40°C may increase the absorption rate by about one-third.

In general, the pharmacokinetics of transdermal fentanyl show interindividual variability. After intravenous administration, fentanyl has a high extravascular volume of distribution (3 to 8 L/kg) in surgical patients. In animals, the drug shows wide physiological distribution to the lungs, kidneys, heart, spleen, brain, muscles and body fat. After transdermal application, an average bioavailability of 92% has been estimated in surgical patients.

Mean maximum plasma concentration (C_{max}) values were 0.6, 1.4, 1.7 and 2.5 μg/L at delivery rates of 25, 50, 75 and 100 μg/h, respectively. Plasma concentrations were proportional to delivery rate. Delays of 34 to 38 hours have been reported between patch application (25 to 100 μg/h) and occurrence of C_{max}. This delay is likely to be due to the formation of a fentanyl depot within the skin before the drug diffuses into the circulation. After several sequential 3-day (72-hour) application intervals, steady-state plasma fentanyl concentrations are achieved, which can be maintained for as long as the fentanyl patches are renewed.

Fentanyl is mainly metabolised by cytochrome P450 (CYP) 3A4. The major metabolite is norfentanyl and minor metabolites include despropionylfentanyl, hydroxyfentanyl and hydroxynorfentanyl, none of which show clinically relevant pharmacological activity. Elimination of fentanyl after patch removal is slow; elimination half-life values of 13 to 22 hours have been reported. The slow elimination is likely to be due to the slow release of the drug from the skin depot. The total body clearance for fentanyl is 34.2 to 52.8 L/h. Since metabolisation of fentanyl is dependent on CYP3A4, coadministration of drugs that inhibit this

isoenzyme may impair fentanyl clearance. Moreover, known CYP inducers may enhance fentanyl clearance.

Therapeutic Use

Randomised comparative trials in 40 to 127 patients with chronic pain associated with cancer have indicated that transdermal fentanyl 25 to 300 μg/h provides adequate pain control in 66 to 77% of patients. The only double-blind comparative trial of transdermal fentanyl, however, failed to show any statistically significant benefit over placebo. However, this study has not resulted in any significant doubt regarding the analgesic efficacy of transdermal fentanyl; indeed, treatment with transdermal fentanyl is well established and accepted in this indication, as indicated by recent review articles and treatment guidelines. There are a number of possible confounding factors that need to be considered when evaluating this study [including the absence of an active comparator and the possible masking of effects by rescue medication (oral morphine, 51 and 48 mg/day, respectively)].

Data from the two nonblind, randomised trials suggest that transdermal fentanyl is as effective as sustained-release oral morphine in the treatment of chronic cancer pain. No significant differences between transdermal fentanyl and sustained-release oral morphine were found for any of the efficacy parameters in the 2-week trials.

In all trials, patients received oral morphine as rescue medication for breakthrough pain. In the randomised studies, patients were stabilised with morphine before being switched to fentanyl patches. The initial dose of transdermal fentanyl was based on the previous morphine dose as calculated by the conversion table supplied by the manufacturer. In general, the transdermal fentanyl patches were replaced every 72 hours.

Pain control was assessed by the use of visual or numerical analogue scales and verbal descriptions by which patients could express pain intensity. Moreover, in three studies, quality-of-life parameters were assessed by elements from validated survey scales. Patients enrolled were adults experiencing chronic cancer pain and requiring strong opioid analgesia.

Although possible advantages of transdermal fentanyl on health-related quality of life are difficult to appraise methodologically, they embody important elements of palliative care and are an important clinical outcome. A randomised nonblind trial revealed no significant differences in effect on social, physical, role, cognitive or emotional functioning or global quality of life between transdermal fentanyl and sustained-release oral morphine. Nonetheless, significantly more patients preferred transdermal fentanyl than sustained-release oral morphine and there were significant differences in favour of fentanyl in other quality-of-life parameters (e.g. interruption of daily activities of both patients and caregivers, convenience and satisfaction).

Adverse Effects

The most serious adverse event associated with transdermal fentanyl administration was hypoventilation, which occurred in approximately 2% of patients with cancer pain during a premarketing trial. As with other opioid agents, the most frequently observed adverse events during fentanyl treatment are nausea, vomiting and constipation. Nonblind clinical data, however, suggest that fentanyl is associated with less constipation than sustained-release oral morphine as assessed by patient questionnaires. Clinical data in patients with cancer reveal no obvious differences in the occurrence of nausea and vomiting when comparing transdermal fentanyl with sustained-release oral morphine. Adverse reactions related to skin and appendages (i.e. rash and application site reactions – erythema, papules,

itching and oedema) were reported in 153 patients with cancer at a frequency between 1 and 2%. Opioid withdrawal symptoms may occur after discontinuation of transdermal fentanyl administration and after conversion from other opioid analgesics to transdermal fentanyl.

Dosage and Administration

Transdermal fentanyl is contraindicated in patients with acute postoperative pain and should not be administered to children under 12 years of age or to patients under 18 years of age who weigh less than 50kg (110lb). Moreover, the initial dosage should not exceed 25 μg/h in opioid-naive patients and elderly or severely debilitated patients taking less than 135 mg/day oral morphine or equivalent. Doses should be personalised according to the manufacturer's recommended conversion ratio. According to the manufacturer's recommendations, adjustment of the dosage should be withheld until 3 days after initial application and should then occur at 6-day intervals if necessary. It is important to stress that rescue medication such as immediate-release oral morphine should be readily available to the patient, especially during the titration period. The transdermal fentanyl patches should be applied to an intact, hair-free (clipped not shaved) area of the skin.

1. Introduction

Pain and symptom control is one of the priorities of the cancer control programme of the World Health Organization (WHO).[1] In a 1994 US study in 1308 outpatients with metastatic cancer, 67% had had pain or had received analgesic drugs daily during the week preceding the study.[2] Moreover, in 36% of these patients, the pain was severe enough to impair their ability to function. Inauspiciously, 42% of patients with pain were not receiving adequate analgesic therapy.

The WHO has developed a three-step analgesic ladder as a guideline for the treatment of cancer pain (figure 1). In this context, it is emphasised that an important principle in cancer pain management is to individualise treatment to the patient.[1]

The therapeutic goal for moderate to severe, chronic cancer pain treatment with opioids is to achieve maximal analgesia and minimise occurrence of adverse events.[3,4] According to the European Association for Palliative Care (2000), morphine is the opioid of first choice for the treatment of moderate to severe cancer pain.[5] This recommendation, however, is based on familiarity, availability and cost rather than on proven clinical superiority.[5] It is important that alternative opioids and/or routes of administration are considered to optimise the balance between analgesia and adverse events for individual patients.[3,4]

One alternative to oral morphine in the treatment of chronic cancer pain is transdermally administered fentanyl. Fentanyl, [*N*-phenyl-*N*-(1-2-phenylethyl- 4-piperidyl)propanamide] is the prototype of the 4-anilidopiperidine class of compounds.[6] Like

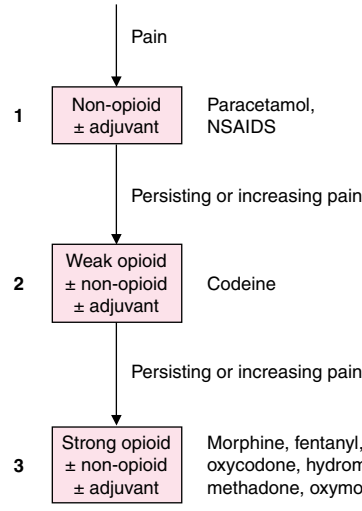

Fig. 1. Schematic overview of the three-step analgesic ladder as proposed by the World Health Organization.[1]

morphine, fentanyl is a pure opioid agonist and has been successfully used as a component of general anaesthetic regimens. The drug is highly lipid soluble, which makes it suitable for transdermal administration. A transdermal therapeutic system has been developed to deliver fentanyl at a constant rate for up to 3 days.

The pharmacological properties and therapeutic efficacy in pain control (including acute, postoperative and nonmalignant pain) of transdermal fentanyl have been reviewed in *Drugs* in 1997.[7] Transdermal fentanyl, however, is contraindicated in acute and postoperative pain (see section 6.2). This review provides an update of the clinically relevant literature published since the previous review. Although transdermal fentanyl is approved for non-malignant pain in the US and other countries, this review focuses on chronic cancer-related pain.

2. Pharmacodynamic Profile of Transdermal Fentanyl

The analgesic properties of fentanyl are well documented.[8] Moreover, the respiratory, gastrointestinal and haemodynamic properties of fentanyl have been reviewed previously.[7] This section provides a brief updated overview of the pharmacodynamic properties of fentanyl relevant to the treatment of chronic cancer pain.

2.1 Analgesic Effects

Fentanyl is a synthetic opioid agonist of high potency. The drug primarily interacts with the opioid μ-receptor[9] as a pure agonist and shows low affinity for the δ- and κ-opioid receptors.[10] The analgesic potency of the drug is about 75 to 100 times greater than that of morphine.[11,12] This difference in potency is possibly due to the lipophilic nature of fentanyl, which facilitates rapid transfer across the blood-brain barrier.[12,13]

The principal pharmacological effects of fentanyl in the clinical setting are on the CNS. Opioid receptors are located at many points in the pain pathways of the CNS in mammals.[14] The response to pain can be modulated by application of opioids to these receptors. The mechanisms of opioid-induced analgesia in general, however, are only partly understood (for review see Kanjhan[14] and Pasternak[15]).

In opioid-naive patients, the minimum effective analgesic serum concentration of fentanyl ranges from 0.2 to 1.2 ng/ml. The frequency of adverse events increases at serum levels above 2 ng/ml. Both minimum effective concentrations and the concentrations at which adverse events occur vary widely between individuals.[16]

2.2 Respiratory Effects

The most serious adverse event associated with all opioids, including fentanyl, is respiratory depression, which is potentially life-threatening (see sections 5.1 and 6.2).[16] Experiments in cats have revealed that intravenously administered fentanyl (50 or 100 μg/kg) causes disruption of the rhythmic activity of the medullary inspirational neurons.[17] Moreover, the drug caused a complete cessation of activity in the ventral respiratory group of neurons. These neurons are associated with the laryngeal abductor muscles which also aid inspiration.[17]

Interestingly, studies in rats revealed that the respiratory-depressant effect of fentanyl, but not that of morphine, can be prevented by the selective μ_1-receptor antagonist naloxonazine.[18] These results suggest that the μ_1-receptor plays an important role in the respiratory effects of fentanyl and that the mechanism of fentanyl-induced respiratory depression is different from that of morphine.

2.3 Gastrointestinal Effects

A common effect of opioid administration in general is the induction of constipation.[19-21] Binding of opioid agonists to opioid receptors in the gastrointestinal tract (e.g. in the submucosal nerve plexus of the colon) leads to decreased peristalsis, diminished biliary, pancreatic and intestinal secretions and increased ileocaecal and anal sphincter tone.[20] This leads to decreased stool hydration and increased transit time in the colon (allowing increased fluid resorption), both of which can lead to constipation.[19]

Subcutaneous administration of fentanyl and morphine to rats resulted in an analgesic peak effect

doses of 0.032 mg/kg and 8.0 mg/kg, respectively. This analgesic dose was only 1.1 times higher than the dose required for a 50% inhibition of castor oil-induced diarrhoea for fentanyl, but 36 times higher for morphine.[22] These results suggest that fentanyl induces analgesia without incurring the same degree of constipation as morphine.[22] Indeed, transdermal fentanyl administration appears to result in constipation in fewer patients when compared with oral morphine therapy as shown by clinical trials (see section 5).

2.4 Haemodynamic Effects

Peripheral vasodilation and subsequent hypotension have been observed in surgical patients after morphine administration, but not after fentanyl administration, during a randomised study (n = 15), and were attributed to histamine release.[23] Indeed, intravenous fentanyl administration (50 μg/kg) did not lead to increased plasma levels of histamine compared with control levels, whereas plasma histamine levels were significantly increased (from <1 to ≈7 pg/L, $p < 0.005$) immediately after an intravenously administered morphine dose (1 mg/kg).[23] Nonetheless, hypotension occurred in about 3% of opioid-naive recipients of transdermal fentanyl during premarketing trials (see section 5).[16]

Besides histamine release, opioid-induced release of the potent vasodilator nitric oxide by endothelial cells might play a role in vasodilation and hypotension after morphine administration. Data from experiments with human endothelial cells show that these cells express the μ_3-receptor which, when agonised, evokes nitric oxide release.[24] Fentanyl, unlike morphine, proved to have little or no affinity for this receptor and was unable to induce nitric oxide production by human endothelial cells *in vitro*.[24]

3. Pharmacokinetic Properties

Most of the available pharmacokinetic data on transdermal fentanyl are obtained from trials in patients with postoperative pain rather than cancer pain. This section provides an overview of the clinical pharmacokinetics of transdermal fentanyl. Where applicable, pharmacokinetic data obtained after intravenous administration are described. The pharmacokinetic properties of transdermal fentanyl have recently been extensively reviewed by Grond and Lehmann.[25] The pharmacokinetics of fentanyl in general have previously been reviewed by Mather.[26]

It appears that the pharmacokinetics of fentanyl typically show wide interindividual variability.[16] Moreover, the therapeutic window of fentanyl varies widely among patients and is influenced by a number of factors such as pain intensity, μ-receptor regulation, enhancing or inhibiting mechanisms of the nociceptive nervous system and psychological factors. The general pharmacokinetics of transdermal fentanyl are summarised in table I.

Table I. Pharmacokinetic properties of transdermal fentanyl

Absorption
Bioavailabillity after transdermal administration 92% (57 to 146% in surgical patients)[27]
Plasma protein binding (human) 79 to 87%[16,26]
C_{max} 2.6 μg/L after fifth application at a delivery rate of 100 μg/h (in patients with cancer pain, n = 10)[28]
AUC 117 μg/L □h (0-72h) during fifth application at a delivery rate of 100 μg/h (in patients with cancer pain, n = 10)[28]
Distribution
Vd 3 to 8 L/Kg (in surgical patients)[16,27]
Fentanyl shows a wide physiological distribution to lung, kidney, spleen, heart, brain, intestinal wall, liver, muscle and adipose tissue (animal data)[26]
Metabolism
Primarily catalysed by CYP3A4 (human liver microsomes *in vitro*)[16,29]
Major metabolite: norfentanyl;[16,29] minor metabolites: hydroxyfentanyl, hydroxynorfentanyl and despropionylfentanyl (human liver microsomes *in vitro*)[29]
Elimination
$t_{½β}$ after transdermal administration: ≈17 hours (range 13 to 22h)[16] [21.9 hours after five subsequent applications in 10 patients with cancer][28]
Clearance 34.2 to 52.8 L/h in surgical patients (intravenous administration)[30]

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **Vd** = volume of distribution; **CYP** = cytochrome P450; **$t_{½β}$** = elimination half-life.

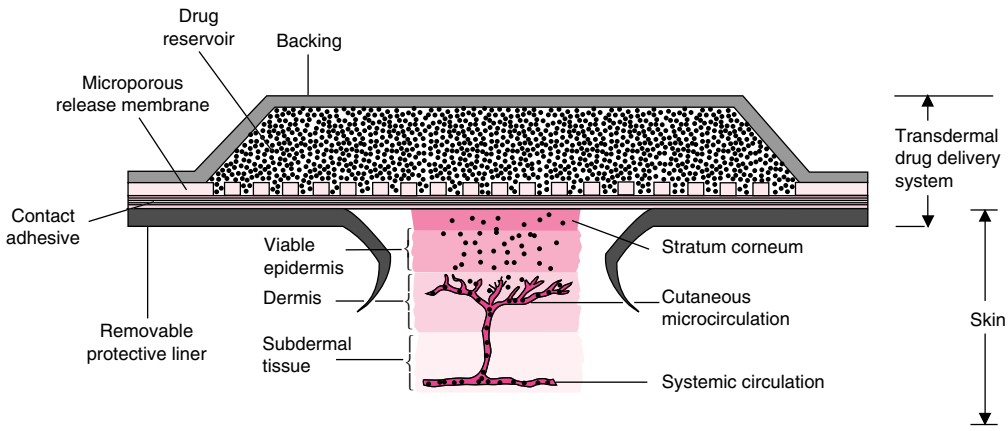

Fig. 2. Fentanyl transdermal system. Schematic representation of the delivery system (not to scale) and the pathway of absorption across the skin.[7]

3.1 Transdermal Delivery System

Fentanyl can be administered transdermally because of its physicochemical properties, i.e. low molecular weight and high solubility in both fat and water. The permeation of fentanyl through the skin is more than 43-fold greater than that of morphine.[31] Moreover, the analgesic potency of fentanyl is up to 100 times greater than that of morphine (see section 2), so that only small amounts of fentanyl have to cross the skin to achieve adequate analgesia.[32] Furthermore, fentanyl does not appear to undergo biotransformation during transdermal permeation.[27]

The transdermal system (figure 2) allows constant delivery of fentanyl for periods of up to 3 days. The fentanyl reservoir is located behind a rate-controlling membrane which reduces variation in fentanyl permeation by about 50%.[33] To overcome limitations of drug release by this membrane, small and clinically insignificant amounts of alcohol are added to the system as a penetration enhancer (0.1 ml/10 cm^2).[16]

3.2 Absorption and Distribution

As shown in table I, fentanyl has a high volume of distribution (3 to 8 L/kg in surgical patients).[16,27] Moreover, studies done in rats show that the drug is widely distributed to the lungs, kidneys, spleen, heart, brain, intestinal wall, liver, muscle and adipose tissue.[26]

The amount of fentanyl delivered is proportional to the surface area of the patch. Currently, systems with delivery rates of 25, 50, 75 and 100 μg/h are available. Although the rate of percutaneous absorption of drugs is potentially dependent on the anatomical site of application, the absorption of fentanyl does not vary to a clinically significant extent between the chest, abdomen and thigh.[34] Moreover, because the permeation of fentanyl through the skin is a much slower process than its removal by the local blood flow, fentanyl absorption is practically unaffected by local blood supply, and would vary only in extreme situations.[33] Absorption of fentanyl, however, has been estimated to increase by about one-third with a rise in body temperature to 40°C.[35] Moreover, anecdotal evidence suggests that, in some circumstances, sweat can accumulate under the transdermal fentanyl patch, which may alter the absorption of fentanyl from the system into the skin.[36]

A mean bioavailability of 92% (range 57 to 146%) has been reported in eight patients with postoperative pain after transdermal administration of fentanyl 100 μg/h for 24 hours.[27] The precision of this study, however, is limited because the

exact content of fentanyl in every individual patch was unknown and was estimated as a mean of 10 similar patches from the same batch. The unbound plasma fraction of fentanyl was 13 to 21%.[26]

Although the duration of the effects of a single intravenous dose of fentanyl is limited by redistribution, plasma fentanyl concentrations become clearance-limited after continuous administration.[26] Maximum plasma concentration (C_{max}; 0.6 to 2.5 μg/L) and time to C_{max} (t_{max}; 33.5 to 38.1h) of fentanyl after transdermal delivery at 25 to 100 μg/h for 72 hours are shown in table II. The serum fentanyl concentrations achieved are proportional to the delivery rate.[16] The relatively high t_{max} values are likely to be due to the formation of a fentanyl depot in the upper skin layers, which subsequently releases fentanyl into the systemic circulation.[37,38]

With continuous application of patches, the fentanyl plasma concentration will continue to rise during the first few applications until steady state is achieved.[16] Steady-state concentrations of fentanyl can be maintained by replacing patches at regular intervals.[16,28] Serum concentrations, however, do vary throughout the 72-hour application interval; concentrations are highest on the first day and decrease slightly during the second and third days.[28,30,37] The mean plasma concentrations in a group of 10 patients who wore two consecutive transdermal fentanyl patches over a period of 144 hours are shown in figure 3 (unpublished data previously reviewed by Jeal and Benfield).[7]

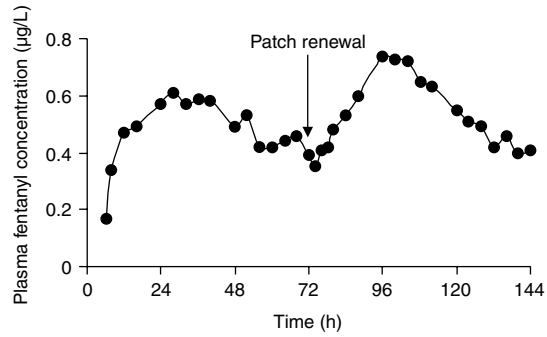

Fig. 3. Mean plasma fentanyl concentration in 10 patients with cancer or intractable pain who wore two consecutive transdermal fentanyl patches (25 μg/h; 72 hours each). Unpublished data previously reviewed by Jeal and Benfield.[7]

3.3 Metabolism and Elimination

Studies using human liver microsomes reveal that fentanyl is mainly metabolised by cytochrome P450 (CYP) 3A4.[16,29,39,40] The major metabolite is norfentanyl[16,29] and minor metabolites include despropionylfentanyl, hydroxyfentanyl and hydroxynorfentanyl.[29] These metabolites show negligible pharmacological activity.[16] The assumption that metabolism is the primary mechanism of elimination is further supported by the observation that the renal clearance of the drug in patients is low: less than 10% of a fentanyl dose is recovered in the urine unchanged.[16] Approximately 9% of an intravenously administered fentanyl dose is found in faeces, primarily as metabolites.[16] The total body clearance for intravenously administered fentanyl in surgical patients ranged from 34.2 to 52.8 L/h.[27]

Table II. Pharmacokinetic values after the first 72 hours of transdermal fentanyl application (US prescribing information, number of individuals or status not reported)[16]

Dosage		Patch size (cm^2)	C_{max} (μg/L)	t_{max} (h)
μg/h	mg/24h			
25	0.6	10	0.6	38.1
50	1.2	20	1.4	34.8
75	1.8	30	1.7	33.5
100	2.4	40	2.5	36.8

C_{max} = maximum plasma concentration; **t_{max}** = time to C_{max}.

Elimination of fentanyl after discontinuation of transdermal administration is slow. As shown in table I, the elimination half-life after patch removal is about 17 hours (range 13 to 22 hours).[16] This time is 2 to 3 times longer than after intravenous administration.[16,27,38] This is likely to be due to the slow release of the drug from the skin depot into the circulation. In elderly individuals (>60 years of age), the elimination half-life of transdermally administered fentanyl may be significantly longer.[16]

In geriatric, cachectic or debilitated patients, regular dosage assessments should be made because these patients are likely to have altered pharmacokinetic parameters for fentanyl.[16] Limited

data are available on the use of transdermal fentanyl in patients with hepatic or renal disease. Transdermal fentanyl should therefore be used with caution in these patients because of the hepatic metabolism and renal excretion of fentanyl.[16]

3.4 Drug Interactions

When patients are receiving transdermal fentanyl in combination with other opioids or other CNS depressant drugs (including benzodiazepines) the dose of one or both agents should be reduced by 50%. Concomitant administration of CNS depressants with transdermal fentanyl may result in hypotension.[16]

Since the metabolism of fentanyl is dependent on CYP3A4, coadministration of drugs that inhibit this isoenzyme may impair fentanyl clearance. This could result in increased or prolonged opioid effects.[16] Known examples of CYP3A4-inhibiting drugs are macrolide antibiotics, azole antifungal agents and protease inhibitors. Patients receiving one of these drugs in combination with transdermal fentanyl should be carefully monitored and dosage adjustments made if warranted.

Lastly, inducers of CYP (e.g. rifampin, carbamazepine and phenytoin) may enhance metabolism and consequently increase the clearance of fentanyl. Again, caution is advised when coadministering CYP inducers with transdermal fentanyl, and dose adjustments should be made when required.[16]

4. Therapeutic Use

The effectiveness of transdermal fentanyl in the treatment of chronic pain associated with cancer in adult patients has been compared with sustained-release oral morphine in two nonblind randomised trials[41,42] and in a comparative retrospective trial,[43] as well as to placebo in a randomised double-blind trial.[44] Moreover, the use of transdermal fentanyl has been assessed in numerous non-comparative trials,[45-59] The noncomparative trials support the findings of the better designed trials.

In all trials patients received other analgesics (mainly immediate-release oral morphine) as rescue medication for breakthrough pain. The reasons for using rescue medication were two-fold: firstly, because of the often changeable nature of cancer pain and, secondly, for ethical reasons especially in the placebo-controlled study.

In the three randomised studies, patients were stabilised with immediate-release oral morphine before being switched to fentanyl patches, sustained-release oral morphine or placebo. The initial dose of transdermal fentanyl was calculated using the conversion table supplied by the manufacturer (see section 6).[41,42,44] The fentanyl patches were changed every 72 hours, as recommended by the manufacturer. Dosage ranges are presented in table III. Treatment duration in the randomised comparative trials described was 9 to 15 days.[41,42,44]

Pain is an individual and subjective experience and the quantification of pain is therefore not straightforward. Because of this subjectivity, pain can be assessed reliably only by a patient's self report.[3] Moreover, for ethical reasons, placebo-controlled trials are difficult to accomplish. In the trials described below, pain control was assessed by questionnaires, using visual or numerical analogue scales (VAS or NAS) by which patients could express pain intensity, or by verbal descriptions by which patients could rate the efficacy of their pain control [European Organization for Research and Treatment of Cancer (EORTC) questionnaire and the Memorial Pain Assessment Card (MPAC)].

Patients enrolled in the three randomised studies were adult, required strong opioid analgesia (step three WHO analgesic ladder; figure 1) and were already receiving morphine. Patients were excluded if they had a life expectancy of less than 1,[41] 2[42] or 3[44] months, would be unable to complete the assessments[41] or had a Karnofsky performance status of ≤50.[44]

4.1 Pain Control

Randomised comparative trials in 40 to 127 patients with chronic pain associated with cancer have indicated that transdermal fentanyl 25 to 300 μg/h provides adequate pain control in 66 to 77% of patients (table III). The only double-blind comparative trial of transdermal fentanyl, however, failed to show any statistically significant benefit

Table III. Efficacy of transdermal fentanyl in the treatment of chronic pain in patients with cancer in comparative trials. Pain was stabilised with immediate-release oral morphine in all patients before the trials started and the initial fentanyl dosage was established according to the manufacturer's conversion table

Reference (design, duration)	Mean (range) fentanyl dosage (μg/h) [no. evaluable pts]	Mean (range) comparator dosage (mg/day) [no. evaluable pts]	Pain status parameter	Results	
				transdermal fentanyl	comparator
Ahmedzai and Brooks[41] (r, nb,co, mc; 2 × 15 days)[a]	NR (25-300) [127][b]	SROM NR	% pts with adequate pain control (VAS)	77.0	81.1
			Days requiring rescue morphine (% of 15)	53.9	41.5*
			Mean EORTC pain score	45.5	42.0
			Morning MPAC pain score: severity	28.8	27.7
			Morning MPAC pain score: relief[c]	65.7	69.7
			Evening MPAC pain score: severity	29.3	29.5
			Evening MPAC pain score: relief[c]	64.2	67.5
Kongsgaard and Poulain[44](r, db, pc, mc, ITT; 9 days)[d,e]	65 (25-250) [48]	Placebo patches [48]	% pts with adequate pain control[f]	66	48
			Mean rescue morphine day 1 → 9 (mg/day)	30.1→47.7	27.4→51.0
			% pts withdrawn for inadequate pain control[f]	19	27
Wong et al.[42] (r, nb; 14 days)	61 (25-150) [20]	SROM 174 (NR) [20]	Pain intensity (day 1 → 14)[g]	1.4→0.9	1.2→0.85
			Mean rescue morphine day 1 → 14 (mg/day)	49.7→21.0	31.0→26.0

a No washout period.

b Same patients in both groups in crossover trail.

c Higher score indicates more pain relief.

d After 7 days' stabilisation with morphine, all patients received transdermal fentanyl dose-titration (fixed conversion from morphine) over 15 days to achieve at least moderate pain levels before randomisation into the double-blind phase.

e Trial was confounded by limited patient numbers and an unexpectedly high placebo response (see section 4.1 for details).

f Inadequate pain control was defined as the requirement for more than twice the daily amount of rescue morphine that was required immediately before randomisation into the double-blind phase or, in patients requiring no morphine during the prerandomisation phase, >50% increase in the amount of rescue morphine required per day compared with the stabilisation period. If neither criterion was met, pain control was judged adequate.

g Verbal point ranking scale (0 = no pain, to 4 = excruciating pain).

db = double-blind; **co** = crossover; **EORTC** = European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire; **ITT** = intention-to-treat analysis; **mc** = multicentre; **MPAC** = Memorial Pain Assessment Card; **nb** = nonblind; **NR** = not reported; **pc** = placebo-controlled; **pts** = patients; **r** = randomised; **SROM** = sustained-release oral morphine; **VAS** = visual analogue scale; * $p < 0.001$ vs fentanyl.

over placebo (table III). However, this study has not resulted in any significant doubt regarding the analgesic efficacy of transdermal fentanyl; indeed, treatment with transdermal fentanyl is well established and accepted in this indication, as indicated by recent review articles and treatment guidelines.[5,25,60,61] There are a number of possible confounding factors that need to be considered when evaluating this study [including the absence of an active comparator, the possible masking of effects by rescue medication (oral morphine, up to 51 and 48 mg/day, respectively)]. In addition, the trial was conducted after two randomised nonblind studies, that demonstrated transdermal fentanyl had broadly similar efficacy to that of sustained-release morphine.

A nonblind, randomised, crossover trial in 127 evaluable patients with chronic cancer pain suggests that transdermal fentanyl is as effective as sustained-release oral morphine in the treatment of chronic cancer pain, as assessed by pain scores and the number of patients rating pain control as adequate, i.e. 77% for transdermal fentanyl and 81.1% for sustained-release oral morphine (table III).[41] Pain control was assessed by patients using a verbal description scale (EORTC/MPAC) or a VAS

scale. Rescue medication (oral morphine) was self-administered significantly ($p < 0.001$) more often by patients receiving transdermal fentanyl than by those receiving sustained-release oral morphine (53.9 *vs* 41.5% of days). The actual number of doses taken during both treatments, however, was low (1 to 5 per day, dosage not stated).[41]

Similar results were obtained during another nonblind, randomised trial in 40 evaluable patients (table III).[42] Pain control was assessed by patients using a verbal description scale. During this trial no differences in rescue medication use were found. The comparable pain control between transdermal fentanyl and sustained-release oral morphine seen in these two randomised trials was supported by a large multicentre retrospective trial in 504 patients with chronic cancer pain.[43]

Although comparative data on long-term transdermal fentanyl administration are not available, data from some noncomparative studies suggest long-term analgesic efficacy for periods of at least 1 year in patients with chronic cancer pain.[45,49,57]

4.2 Health-Related Quality of Life and Patient Satisfaction

Outcome measures such as patient satisfaction and quality of life are influenced by a number of different factors, such as pain relief, adverse effects, ease of compliance and ability to function. Moreover, fears about disease progression are likely to adversely affect quality of life.[43]

Although quality of life and patient satisfaction are difficult to appraise methodologically, they embody integral elements of palliative care[1] and cannot be neglected as a clinical outcome in the management of chronic cancer pain. Quality of life in patients with chronic cancer pain using either transdermal fentanyl (25 to 400 μg/h) or sustained-release oral morphine (15 to 3000 mg/day) was assessed by elements from various (validated) survey scales in trials summarised in table IV. Scales used were the Functional Assessment of Cancer Therapy-General (FACT-G),[43] the EORTC QLQ-C30 questionnaire[41] and the Technology Assessment Group (TAG) questionnaire.[42] Two of the trials assessing quality of life and patient preference were randomised but nonblind,[41,42] while the third was retrospective.[43]

Verbal ranking scales indicated that there were significant differences in favour of transdermal fentanyl over sustained release oral morphine for patient preference, interruption of daily activities, interruption to caregivers, convenience of medication, satisfaction with, recommendation of, and willingness to continue treatment, and met expectations (the latter three parameters were in men only; table IV). There were, however, no significant differences between the groups in social, emotional, physical, role or cognitive functioning, mood profile, activity status, symptom assessment or global quality of life, as assessed by various scales and questionnaires (table IV).

Assessment of sleep parameters indicated that, while sleep was significantly less disturbed among morphine recipients than among those receiving fentanyl in one trial,[41] there were no significant differences between the groups in this respect in the other two trials (table IV).

5. Adverse Effects

Because transdermal fentanyl is administered for prolonged periods to patients with cancer, optimal dose titration can be achieved. This potentially limits the severity and development of some of the adverse events associated with initial administration of transdermal fentanyl.

As with other opioid agents, the most frequently observed adverse events during fentanyl treatment are nausea, vomiting and constipation. Adverse reactions related to skin and appendages (i.e. rash and application site reactions – erythema, papules, itching and oedema) were reported in 153 patients with cancer at a frequency of between 1 and 2%. Opioid withdrawal symptoms (e.g. nausea, vomiting, diarrhoea, anxiety and shivering) may occur in some patients after discontinuation of transdermal fentanyl, after conversion to another opioid or after lowering the fentanyl dosage.[16]

The premarketing clinical trial adverse event data after long-term administration of transdermal fentanyl (dosage not reported) in 153 patients with cancer pain are shown in table V.[16] Duration of

Table IV. Comparative trials of transdermal fentanyl in cancer pain: health-related quality of life and patient preference

Reference (no. evaluable patients; trial design; duration)	Mean (range) transdermal fentanyl dosage (μg/h)	Mean (range) SR oral morphine dosage (mg/day)	Parameter[a]	Transdermal fentanyl	Morphine
Ahmedzai and Brooks[41] (133-200; r, nb, co, mc; 2 × 15 days)	NR (25-300)	NR	Patient preference[b]	54%*	36%
			Less interruption of daily activities[b]	55%*	20%
			Less interruption to carers[b]	49%*	22%
			More convenient medication[b]	58%*	22%
			Physical functioning[c]	36.7	36.8
			Emotional functioning[c]	66.8	69.2
			Role functioning[c]	24.0	25.4
			Cognitive functioning[c]	66.2	67.6
			Social functioning[c]	42.9	43.2
			Sleep disturbance[c]	32.4	22.4*
			Global quality of life[c]	43.5	45.5
Payne et al.[43] (504; ret, mc, nb; >14 days)[d]	84.4 (25-400)	195 (15-3000)	Social/emotional/functional well-being (FACT-G)	54.35	59.21**
			Sleep (MOS/TAG)	96.00	95.81
			Symptom assessment (MSAS)	98.58	98.63
			Patient satisfaction (TAG)	82.98*	79.81
			Would recommend treatment[e]	96.94*	89.78
			Willingness to continue[e]	94.75*	87.96
			Patient's expectations met[e]	81.12**	67.99
Wong and Poulain[42] (40; r, nb; 14 days)	61.3 (25-150)	174 (NR)	Effect of pain on mood (0-3)[f]	1.25 → 0.8	1.4 → 1.35
			Effect of pain on sleep (0-3)[f]	1.1 → 0.75	1.15 → 1.15
			ECOG activity status (0-4)[f]	1.55 → 1.4	1.55 → 1.75

a Mostly scale 1 to 100; higher score indicates more of the parameter in question.[41,43]

b Verbal questioning; percentage of patients.

c EORTC QLQ-C30 questionnaire.

d Scores adjusted for site, cancer stage, physical well-being and demographics.

e Applies to male patients only, no significant differences were found between groups for female patients.

f Verbal ranking scale; lower values are better; baseline to day 14.

co = crossover; **ECOG** = Eastern Cooperative Oncology Group Scale; **EORTC** = European Organization for Research and Treatment of Cancer; **FACT-G** = Functional Assessment of Cancer Therapy-General; **MSAS** = Memorial Symptom Assessment Scale; **MOS** = Medical Outcomes Study; **NR** = not reported; **ret** = retrospective; **SR** = sustained release; **TAG** = Technology Assessment Group; * $p < 0.05$; ** $p \leq 0.001$ *vs* morphine.

treatment with transdermal fentanyl in this group varied: 56% of patients received the drug for more than 30 days, whereas 28 and 10% of patients were treated for longer than 4 months and 1 year, respectively. Hypotension and hypertension were observed in 3% and 1% of opioid-naive patients, respectively (both postoperative patients and patients with cancer). A number of other noncomparative trials, however, have described transdermal fentanyl use for periods of at least a year without the occurrence of serious adverse effects.[45,49,50,52,57]

Interestingly, a global score for adverse effects (22 *vs* 31; $p < 0.001$) was significantly lower (more favourable) in patients receiving transdermal fentanyl (25 to 400 μg/h) than in those receiving sustained-release oral morphine (15 to 3000 mg/day) in a retrospective study (n = 504, >14 days).[43] This score is a global measure of adverse effects which embodies frequency and impact of these events (TAG questionnaire). Moreover, 68% of patients receiving transdermal fentanyl reported no adverse effects or not being bothered by adverse

Table V. Adverse events associated with transdermal fentanyl: summary of adverse events occurring in more than 1% of patients with cancer in premarketing trials (dosage not reported; n = 153). A causal relationship was not always established and some patients received other opioids concomitantly. Postmarketing experience indicates that oedema (general), tachycardia (cardiovascular), weight loss (metabolic/nutritional) and blurred vision (senses) may also be associated with fentanyl use[16]

System affected	Incidence		
	>10%	3-10%	1-2%
General		Abdominal pain	
		Headache	
Cardio-vascular			Arrythmia
			Chest pain
Digestive	Nausea	Anorexia	Flatulence
	Vomiting	Diarrhoea	
	Constipation	Dyspepsia	
	Dry mouth		
Nervous	Somnolence	Dizziness	Tremor
	Confusion	Hallucination	Abnormal coordination
	Asthenia	Anxiety	Agitation
		Depression	Paranoid reaction
		Euphoria	Amnesia
		Nervousness	Paraesthesia
			Syncope
			Speech disorder
			Abnormal thinking
			Abnormal gait
			Abnormal dreams
Respiratory		Dyspnoea	Haemoptysis
		Apnoea	Pharyngitis
			Hypoventilation
			Hiccups
Skin/Appendages	Sweating	Pruritus	Rash
			Application site reactions (erythema, papules, itching, oedema)
Urogenital		Urinary retention	

effects compared with 46% of those receiving morphine ($p = 0.001$). The results from this study, however, must be interpreted with caution because of the retrospective design.

5.1 Respiratory Effects

The most serious adverse event observed was hypoventilation (defined as respiratory rates of less than 8 breaths per minute or a pCO_2 greater than 55mm Hg), which occurred in three (2%) of the 153 patients with cancer pain during the previously mentioned premarketing trial.[16] Clinically relevant fentanyl-induced respiratory depression, however, was not observed during the three randomised trials described in section 4.[41,42,44] Hypoventilation was observed in 1 of 20 patients receiving transdermal fentanyl (25 to 150 μg/h) during the randomised trial by Wong et al.[42]

5.2 Effects on Bowel Function

Like other opioid analgesics, fentanyl can cause constipation.[16] A nonblind, randomised, crossover trial, however, revealed that constipation occurred significantly less frequently with transdermal fentanyl (n = 165; 27%) than with sustained-release oral morphine (n = 155; 45%; $p < 0.001$) in patients with cancer pain as assessed by a verbal questionnaire.[41] This is confirmed by similar results found

during a nonblind, randomised, crossover trial in 256 patients with chronic noncancer pain, where 29% (transdermal fentanyl) versus 48% (sustained-release oral morphine) of patients reported constipation ($p < 0.001$).[62]

5.3 Vomiting and Nausea

Vomiting and nausea are frequent in cancer patients and are often caused by chemotherapy or the disease process. Nonetheless, nausea and vomiting are common adverse events reported after opioid administration in general. Comparative clinical data from nonblind trials reveal no obvious differences in the occurrence of nausea and vomiting between transdermal fentanyl and sustained-release oral morphine administration in patients with cancer[41,42] and in patients with chronic noncancer pain.[62]

5.4 Sedation

Data from a randomised, nonblind trial[41] suggest that transdermal fentanyl is less sedative than sustained-release oral morphine. Administration of transdermal fentanyl was associated with significantly ($p = 0.015$) less daytime drowsiness than sustained-release oral morphine as assessed by a VAS (mean percentage area under the curve was 34.0 for fentanyl *vs* 43.5 for morphine).

6. Dosage and Administration

In the US, transdermal fentanyl is indicated for the treatment of chronic pain (not restricted to cancer pain) that: (i) cannot be managed by lesser means such as paracetamol-opioid combinations, nonsteroidal analgesics or administration of short-acting opioids as required and (ii) requires continuous opioid administration.[16] Likewise, in Germany, transdermal fentanyl is indicated for chronic pain that can only be treated effectively with opioids.[63] In the UK, however, transdermal fentanyl is indicated only for chronic intractable pain due to cancer.[64]

The dosage of transdermal fentanyl should be individualised according to the pain state of the patient. Regular dosage assessments should be made, particularly in geriatric, cachectic or debilitated patients, as they are likely to have altered pharmacokinetic parameters for fentanyl (section 3).[16] Unless these patients are taking more than 135 mg/day of oral morphine or equivalent opioids, they should not be started on dosages higher than 25 μg/h of transdermal fentanyl.[16]

The conversion of patients from other opioids to transdermal fentanyl should be carried out as follows:

- calculate the patient's analgesic requirements for the previous 24 hours
- convert this value to the equianalgesic dose of oral morphine
- select the transdermal fentanyl dose based on the manufacturer's recommendation as indicated in table VI.

The conversion table supplied by the manufacturer (e.g. US and UK, table VI) is conservative; a number of patients will require an increase in dosage.[16] As shown in table VI, a less conservative conversion table is recommended in Germany.[63]

Table VI. Recommended initial transdermal fentanyl dose based upon daily oral morphine dose in the US/UK and Germany[a]

Oral 24-hour morphine (mg/day)	Transdermal fentanyl dose (μg/h)
US/UK prescribing information:[16,64]	
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
German prescribing information:[63]	
0-90	25
91-150	50
151-210	75
211-270	100
Every additional 60mg	25

a This table should not be used to convert from transdermal fentanyl to other opioids as consequent overdose of the other opioid may occur.

In a clinical trial using the UK/US conversion table,[41] 47.1% of patients required at least one dosage increase. Dosage titration may occur 3 days after initiation of therapy and at 6-day intervals thereafter.[16] Dosage adjustments should be based on the daily supplementary analgesia use; a ratio of 25 μg/h transdermal fentanyl to 90 mg/24h of oral morphine is recommended according to US prescribing information.[16] For dosages above 100 μg/h, multiple systems may be applied.[16] A small number of patients require administration every 48 hours; however, a higher dose should be considered before the dosage interval is decreased.[16]

During transdermal fentanyl administration, and especially during dosage titration, rescue medication (e.g. immediate-release oral morphine) should be available to the patient.

It is important that patients prepare the application site correctly. The fentanyl transdermal system should be applied whole to an intact area of skin. The area should be prepared by clipping any hair, cleaning with water only (not soap, alcohol or lotions that might irritate the skin) and thorough drying.[16] Patients should hold the transdermal system on the application site for at least 30 seconds, if the edges lift, the manufacturer recommends the use of first-aid tape.[16]

6.1 Discontinuation

To avoid possible opioid withdrawal symptoms, it is recommended that discontinuation of transdermal fentanyl is conducted slowly with downward titration. It is advised that patients who require abrupt discontinuation of transdermal fentanyl because of adverse events are closely monitored for at least 12 hours after the removal of the system. This is because an estimated 17 hours or more are required for a 50% reduction in plasma fentanyl concentrations (see section 3.3).[16]

6.2 Contraindications and Warnings

Serious or life-threatening hypoventilation has been associated with transdermal fentanyl, especially in opioid-naive patients and in the postoperative setting (see section 5.1). Transdermal fentanyl is therefore contraindicated in the management of acute or postoperative pain and intermittent and mild pain which can be adequately managed with non-opioid agents.[16,63,64] Moreover, transdermal fentanyl should not be administered to children under 12 years of age or patients under 18 years who weigh less than 50kg (110lb).[16] Patients who are hypersensitive to either fentanyl or the adhesives used in the system should not receive transdermal fentanyl.[16]

Patients wearing transdermal fentanyl patches should be warned against exposure to external heat sources such as heat pads, electric blankets, hot tubs, saunas and heat lamps, since heat potentially increases fentanyl release from the system.[16]

Likewise, fever may enhance fentanyl absorption (see section 3.2).[16,35] Therefore, patients who develop fever should be monitored for opioid adverse events and the transdermal fentanyl dosage should be adjusted if necessary.[16]

Hypoventilation, hypotension and acute sedation are possible with concomitant use of other centrally acting depressants such as sedatives, other opioids, anaesthetics, hypnotics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcohol. It is advisable to reduce the dosages of one or all of the agents by 50% when polytherapy of this nature is considered.[16]

The transdermal fentanyl system should not be cut or damaged, as the system may then not work properly or not be safe to use. Moreover, safe disposal of used transdermal fentanyl systems is important to prevent fentanyl poisoning of infants, children, pets and adults.[16]

7. Place of Transdermal Fentanyl in the Management of Chronic Cancer Pain

An important principle of cancer pain management is to individualise treatment to the patient, with an optimal balance between analgesia and adverse events as the main therapeutic goal.[1,3,4] As different patients respond differently to various opioids, alternatives to morphine (see figure 1) should be considered to achieve optimal pain treatment.[3,4]

At present, oral morphine is the standard step three opioid analgesic on the WHO analgesic ladder

for the treatment of chronic cancer pain as recommended by the European Association for Palliative Care.[5] This recommendation, however, is not based on proven clinical superiority of morphine, but on reasons such as familiarity, availability and cost.[5]

Transdermal fentanyl fits in the third step of the WHO analgesic ladder as a strong opioid. Nonblind, randomised clinical trials confirm that transdermal fentanyl is as effective as sustained-release oral morphine in the management of chronic cancer pain (see section 4.1).[41,42] Transdermal fentanyl, however, potentially has a number of advantages over sustained-release oral morphine and other oral opioids as listed below.

Alternative routes of opioid administration (e.g. subcutaneous morphine and transdermal fentanyl) have a number of advantages over oral opioid administration. For obvious reasons, transdermal fentanyl could be an alternative in patients who are unable to swallow or where vomiting affects drug absorption. Moreover, fentanyl is parenterally administered using a noninvasive technique, which has advantages in patients with poor venous access. Further advantages over oral opioid administration are that the transdermal delivery system results in a pharmacokinetic profile comparable to that of intravenous administration and that first-pass metabolism is avoided. Once steady state is achieved, relatively constant plasma concentrations of fentanyl can be maintained for prolonged periods.

The transdermal fentanyl system is relatively easy to apply, generally requiring replacement every 72 hours. This is likely to result in a high compliance with and acceptance of therapy by patients. Therefore, transdermal fentanyl is likely to have less effect on daily routines of patients and caregivers than daily oral medication. This was confirmed by questionnaire data from a nonblind, randomised trial, during which transdermal fentanyl was compared with sustained-release oral morphine (section 4.2).[41]

Although clear differences in health-related quality of life have not been found in clinical trials comparing transdermal fentanyl with sustained-release oral morphine, there are indications that constipation occurs less often in transdermal fentanyl recipients than in those receiving sustained-release oral morphine (section 5.2).[41]

The main disadvantage of transdermal fentanyl is the delay of onset of action after application of the first system. Moreover, it takes some time before dosage adjustments start to have an effect. It is therefore important that rescue medication (e.g. immediate-release oral morphine) is readily available to patients receiving transdermally administered fentanyl. Availability of rescue medication is also important to overcome possible breakthrough pain. Further disadvantages of transdermal fentanyl are that optimal dosing may not always be possible because patch sizes are fixed and, lastly, that relatively large skin areas are required to administer higher dosages of fentanyl.

Nevertheless, significantly more patients expressed a preference for transdermal fentanyl than for sustained-release oral morphine after a randomised, crossover trial (section 4.2).[41] The reason for this difference is unknown, but is likely to be related to the advantages of transdermal fentanyl listed above.

Although the analgesic efficacy of transdermal fentanyl in the treatment of chronic cancer pain has not been assessed by double-blind trials with active comparators, treatment with transdermal fentanyl is well established and accepted in this indication, as indicated by recent review articles and expert reports.[5,25,60,61]

In summary, transdermal fentanyl is an effective opioid analgesic agent (as recommended on step 3 of the WHO analgesic ladder) in the management of chronic pain in patients with cancer. Clinical trials suggest that transdermal fentanyl is as effective as sustained-release morphine and is generally well tolerated. The typical properties of the delivery system, i.e. convenience of use and the 3-day application interval and the reduced constipation compared with morphine therapy are likely explanations for the reported preference of patients for transdermal fentanyl over sustained-release oral morphine.

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