Drugs 2004; 64 (23): 2629-2638
0012-6667/04/0023-2629/$34.00/0

Practice Guidelines for Transdermal Opioids in Malignant Pain

Tracy L. Skaer

Pharmacoeconomics and Pharmacoepidemiology Research Unit, Washington State University, Pullman, Washington, USA

Contents

Abstract

Patients with moderate-to-severe malignancy-related pain require opioid pharmacotherapy. Many cancer patients continue to be prescribed subtherapeutic doses of pain medications resulting in undue suffering and diminished quality of life. Pain associated with malignancy and its treatment may exacerbate other symptoms associated with cancer, including nausea, fatigue, weakness, dyspnoea, constipation and impaired cognition. The choice of analgesic pharmacotherapy should be individualised and based on the intensity of pain reported by the patient, rather than its specific aetiology. When selecting pain management pharmacotherapy, the healthcare provider should consider the patient's pain level, activity level and any comorbid illness. Intolerable adverse effects, ineffective pain relief or a change in the patient's clinical status can dictate the need for a new pain management regimen.

Healthcare providers must be able to readily quantify the relative analgesic potency when converting from one opioid to another or from one route of administration to another. Transdermal formulations of fentanyl and buprenorphine are effective pharmacotherapy that can be safely used for cancer patients with pain. However, clinicians need to be cognisant that the US/UK manufacturer's recommendations for equianalgesic dose administration of transdermal fentanyl may result in initial doses that produce subtherapeutic concentrations and unrelieved pain in some patients. A less conservative dose administration algorithm for transdermal fentanyl using a 2 **:** 1 (mg/day of oral morphine **:** μg/h of transdermal fentanyl) conversion ratio that considers both a review of the

literature and clinical experience should help clinicians individualise cancer pain pharmacotherapy.

Management of malignancy-related pain continues to be a major problem for the patient with cancer. Significant pain is reported in at least one-third of newly diagnosed oncology patients and 65–85% of those with advanced disease.[1-4] A broad spectrum of pharmacotherapy is currently available to manage approximately 90% of patients with cancer pain appropriately. Unfortunately, many of these patients receive subtherapeutic doses and continue to experience suboptimal pain control.[3-5] Pain associated with malignancy and its treatment may exacerbate other symptoms associated with cancer, including nausea, fatigue, weakness, dyspnoea, constipation and impaired cognition.[1] In addition, uncontrolled pain diminishes quality of life and patients experiencing pain often hesitate in participating in activities of daily living for fear of worsening their pain. Thus, social and family relationships may suffer as this avoidance behaviour escalates.

A thorough pain assessment must be conducted on each patient. This assessment should include pain severity and aetiology, age, extent of disease, previously effective and ineffective therapies, concurrent medical problems and psychosocial status. It is important to note that the care plan for each patient must be individualised, regularly reassessed, and adjusted, if necessary, to maximise pain control and maximise patient quality of life.[3,6] The patient's self-report is very important here, as it has been documented that both caregivers and healthcare workers tend to underestimate pain severity.[3,7]

The WHO pain management guidelines suggest that the choice of analgesic pharmacotherapy be based on the intensity of pain reported by the patient, rather than its specific aetiology.[8-10] Opioids such as morphine, hydromorphone, oxycodone, fentanyl and buprenorphine have been shown to be highly effective in alleviating moderate-to-severe malignant and nonmalignant chronic pain that is not of neuropathic origin.[11-14]

1. Opioid Rotation

Current practice guidelines for the treatment of pain emphasise individualisation of pharmacotherapy.[15-17] When selecting pain management pharmacotherapy, the healthcare provider should consider the patient's pain level, activity level and any comorbid illness. Cancer pain patients frequently require a change from one opioid to another as a result of intolerable adverse effects, cost considerations or the need for an alternative route of administration. Changing to a non-oral route of administration can ameliorate distressing gastrointestinal adverse effects and should be prescribed in patients with significant gastrointestinal involvement with obstruction, infiltration or compression from the tumour. The Pain Service at Memorial Sloan-Kettering Cancer Center (New York, NY, USA) found that during a 14-week period, 99 of 100 patients had received a median of two (range one to eight) different opioids administered by a median of two (range one to eight) different routes.[18] After the initial evaluation, the Pain Service changed the route of administration in 58 patients. Of the 42 patients whose medication was unchanged after initial evaluation, 22 required subsequent changes in either medication or route of administration. Thus, 80 of the 100 patients required a total of 182 changes be made in pain medication or route of administration prior to death or discharge. While this study documents that opioid switching is a common practice among pain and palliative care specialists, the majority of patients with cancer do not have access to palliative care specialists. Thus, it is unclear how commonly opioid rotation is employed by family practice and internal medicine practitioners involved in the care of patients with cancer-related pain, or in outpatient, hospital or hospice settings.

2. Traditional Opioid Conversion

Table I and table II provide the relative opioid potency conversion commonly used by healthcare

Table I. Opioid potency conversion[17,27] (modified from Breitbart et al.,[27] with permission)

Medication	IM, IV, SC (mg)[a]	Oral (mg)
Morphine	10	30
Hydromorphone	1.5	7.5
Levorphanol	2	4
Pethidine (meperidine)	75	300
Methadone	10	5
Oxycodone	NA	20
Oxymorphone	1	NA

a Although no controlled studies are available, in clinical practice it is customary to consider the doses of opioid given IV, IM or SC to be equivalent.

IM = intramuscular; **IV** = intravenous; **NA** = not applicable; **SC** = subcutaneous.

practitioners.[15,19-24] Unfortunately, these conversion tables are often based on the results of single-dose studies in which patients are receiving low opioid doses for their acute postoperative pain. Studies have reported that the standard conversion tables 'underestimate' the effects of opioids in patients receiving repeated doses.[21,22] In addition, the manufacturer's dose conversion recommendations for transdermal fentanyl provided in table II have been found to underestimate the dose administration needs of chronic pain sufferers.[25,26]

Patients should be titrated to adequate pain relief with short-acting pain medications prior to the initiation of transdermal fentanyl in order to prevent exacerbation of pain- or opioid-related adverse effects.[25] The manufacturer recommends the following steps to convert patients from oral or parenteral opioids to transdermal fentanyl.[23,24]

1. Calculate the previous 24-hour analgesic requirements.

2. Convert this amount to the equianalgesic oral morphine dose (table I).

3. Determine the calculated 24-hour oral morphine dose and corresponding transdermal fentanyl dose (table II).

4. Initiate treatment using this recommended dose and titrate dosage upward (no more frequently than every 3 days after administering the initial dose or every 6 days thereafter) until analgesic efficacy is attained.

It is important to note that the use of these manufacturer guidelines can produce subtherapeutic starting doses and result in breakthrough pain during initial titration because of failure to increase fentanyl dosages upward in the first 72 hours of therapy. A less conservative approach is required in the management of malignant pain. Therefore, when titrating the dosage of the transdermal fentanyl, the healthcare practitioner must consider the daily dose of the immediate-release breakthrough pain analgesics required by the patient during the second and third days after initial patch placement and, if necessary, increase the dose of transdermal fentanyl during this time period. Moreover, transdermal fentanyl has an elimination half-life of 13–22 hours, making it extremely long-acting.[23] Thus, it can take as many as 6 days to achieve steady-state serum fentanyl concentrations. If the initial starting dose is too low, then the dosage titration necessary to achieve adequate pain control may take even longer.[23] Subtherapeutic pain control is quite distressing for the patient, and can lead to therapy failure and/or discontinuance of pharmacotherapy. This problem is accentuated in patients with chronic pain who have been exposed to opioids previously and, therefore, require higher doses of these medications to control their pain. Opioid-naive patients typically need fewer dose adjustments to reach therapeutic concentrations.

Table II. Recommended initial fentanyl doses based upon daily oral morphine dosage in the US and UK[23,24] (reproduced from Breitbart et al.,[27] with permission)

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

There have been four case reports in the literature documenting withdrawal syndromes associated with conversion from oral opioids to transdermal fentanyl.[28,29] Withdrawal symptoms in these cases were linked to physiological effects of too low an estimated equianalgesic starting dose and were not related to psychological dependence. Therapeutic concentrations of fentanyl can take 12–18 hours to occur after initial patch applications. Thus, patients at greatest risk for withdrawal are those who are physiologically dependent and stop taking their oral opioid medication prior to the first application of the transdermal patch and/or prior to the achievement of steady-state fentanyl concentrations. Those patients who are started on a subtherapeutic dose of transdermal fentanyl at the time of dose conversion from opioid pharmacotherapy are also at risk of experiencing withdrawal symptoms and breakthrough pain.

3. Dose Administration Algorithm for Transdermal Fentanyl

A more aggressive approach to the initial administration of transdermal fentanyl is recommended for the cancer patient. Care must be taken to avoid a subtherapeutic dose that can compromise patient care and result in uncontrolled pain during the initial conversion and titration period. Of important note is that the conversion table supplied by the manufacturer in Germany (table III) is much less conservative than the US/UK conversion presented in table II.[30] The German conversion rate of approximately 2 : 1 (60 mg/day of oral morphine is equianalgesic to 25 μg/h of transdermal fentanyl) best translates into an optimal initial starting dose for the cancer patient.[30] With this in mind, figure 1 provides a dose administration algorithm for this purpose and table IV extrapolates the recommended dose conversion to transdermal fentanyl from morphine and other commonly employed opioids for moderate-to-severe pain.[15] Once an approximate starting dose is calculated, clinicians should round up or down to the available patch strength (25, 50, 75 or 100 μg/h) on the basis of the clinical status of the patient. If the patient has adequate pain relief from their currently prescribed pain pharmacotherapy it is recommended that the calculated dose be rounded down to the nearest patch size (see figure 2, example 1). However, if the patient is experiencing pain at the time of conversion then the dose should be rounded up to the nearest patch strength (see figure 2, example 2).

Table III. Recommended initial fentanyl doses based upon daily oral morphine dosage in Germany[23,30]

24-Hour oral morphine dose (mg/day)	Transdermal fentanyl dose (μg/h)
0–90	25
91–150	50
151–210	75
211–270	100
Every additional 60mg	25

A multicentre trial conducted by Donner et al.[26] supports the safety and efficacy of the German recommended 2 : 1 ratio. The study involved 98 patients with cancer-associated pain who were converted directly from sustained-release oral morphine to transdermal fentanyl. The initial fentanyl dose was calculated by the dose of sustained-release morphine prescribed to the patient prior to enrolment into the study. The 2 : 1 oral morphine to transdermal fentanyl conversion ratio was employed. For example, patients receiving 30–90 mg/day of sustained-release morphine were initially placed on a 25 μg/h fentanyl patch, those receiving 91–150 mg/day of oral morphine received a 50 μg/h patch, and so forth. Breakthrough pain relief was provided to the patients in the trial through the use of supplemental immediate-release liquid morphine, as needed.

Pain relief with transdermal fentanyl was similar to that of sustained-release morphine, but the use of supplemental liquid morphine for breakthrough pain was significantly higher for those patients receiving transdermal fentanyl. Constipation was less problematic in patients treated with fentanyl. There was no significant difference in vital signs and adverse effects between the two groups. Respiratory depression was not seen; however, three patients experienced morphine withdrawal symptoms within the first 24 hours of transdermal fentanyl therapy. The

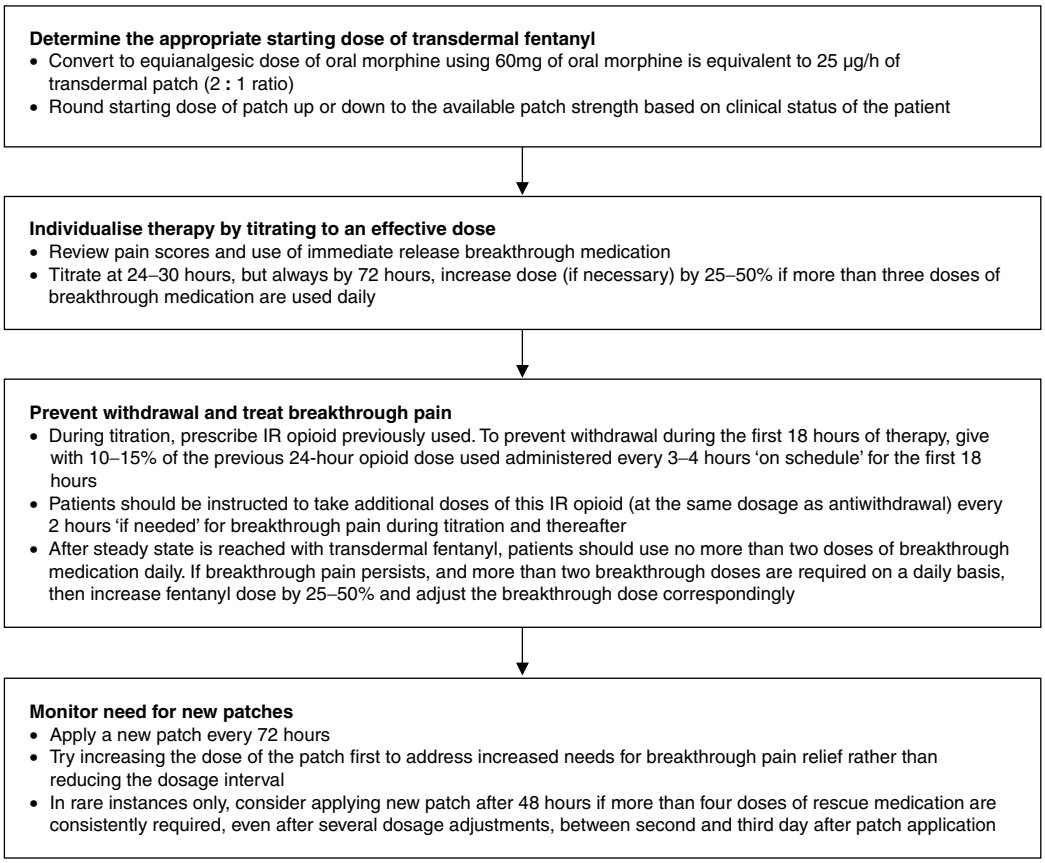

Fig. 1. Dose administration algorithm for transdermal fentanyl in the cancer patient (reproduced from Breitbart et al.,[27] with permission). **IR** = immediate release.

highest dose of transdermal fentanyl administered was 500 μg/h.

Some authors have found intravenous fentanyl to be an effective titration method for cancer inpatients with acute exacerbations of pain.[31-33] A conversion from intravenous fentanyl can be accomplished safely and effectively using a 1 : 1 (intravenous : transdermal) conversion ratio during acute exacerbations of cancer pain.[32,33]

4. Dosage Titration and Breakthrough Pain

Evaluations as to whether the initial starting dose of transdermal fentanyl is providing adequate pain relief should be conducted during the first 72 hours after initiation. If the patient requires more than two doses of breakthrough medication over a 24-hour period for adequate pain relief, than the dose of the patch needs to be increased. At low doses of opioids, the patch is normally increased in 25 μg/h increments. It may be increased in increments of 50 μg/h if the severity of the pain, number of breakthrough doses required and total dose of transdermal fentanyl needed for adequate relief warrants this level of increase. The optimal dose of transdermal fentanyl should be based on an ongoing evaluation of the level of pain relief achieved and the amount of breakthrough medications used. It is important to note that it can take from 12 to 18 hours to reach a clinically relevant serum concentration after initial patch placement. Consistent serum concentrations

Table IV. Recommended dose conversion to fentanyl from other selected opioids[15,17,27]

Transdermal fentanyl	Morphine (mg/day)		Oxycodone (mg/day)		Hydromorphone (mg/day)	
(μg/h)	IM	PO	IM	PO	IM	PO
25	20	60	NA	40	3	15
50	40	120	NA	80	6	30
75	60	180	NA	120	9	45
100	80	240	NA	160	12	60

IM = intramuscular; **NA** = not applicable; **PO** = oral.

are achieved after 16–20 hours, and steady state is attained at about 72 hours.[23]

During dosage titration, and in order to minimise the risk of opioid withdrawal during the first 18 hours of transdermal fentanyl therapy, patients should be instructed to take the prescribed immediate-release opioid every 3–4 hours.[17,27] The dose of antiwithdrawal medication should be equal to 10–15% of the total daily dose of opioid that the patient received prior to the start of transdermal fentanyl pharmacotherapy. As an example, if the patient is applying a fentanyl 50 μg/h patch every 72 hours, the equivalent daily oral dose of oral immediate-release oxycodone is approximately 80mg. Thus, the patient would be prescribed at least 8–12mg (10–15% of 80mg) of oxycodone every 3–4 hours (not as needed) for the first 18 hours of transdermal fentanyl pharmacotherapy. Some patients may require additional immediate-release doses as frequently as every 2 hours, as needed for breakthrough pain. Thus, the use of antiwithdrawal medication must be differentiated from breakthrough pain medication, since the patient in this example should take at least 8mg of oxycodone every 4 hours to abate development of withdrawal symptoms during this first 18-hour phase, regardless of whether breakthrough medication is required.

Breakthrough pain should be treated with the use of agents that are simple to administer, offer rapid pain relief and have a reasonably short half-life.[27] Immediate-release morphine, hydrocodone or oxycodone are commonly used for this purpose.[27] Patients can continue to take the short-acting opioid that was previously effective for breakthrough pain.[27,34] Doses of immediate-release pharmacotherapy for breakthrough pain commonly used are 10–15% of the previous total daily opioid dose given every 2 hours on an 'as needed' basis.[17,34] Ideally, patients should not take more than two doses of immediate-release breakthrough medication each day once a steady-state serum fentanyl concentration has been reached.[17,27,34] If the breakthrough pain is persistent and requires more than two doses of immediate-release medication during a 24-hour period, then the transdermal fentanyl dose should be increased by 25–50%. Patients who require an increase in the dose of their around-the-clock sustained-release pharmacotherapy (transdermal fentanyl) as a result of disease progression or other factors should be given an equivalent increase in the dose of the breakthrough pain medication.

Example 1:

Patient 1 is taking two oxycodone 5mg plus paracetamol (acetaminophen) 325mg every 4 hours and has good pain control, but would prefer not to take medication every 4 hours. Determine the dose conversion to initiate transdermal fentanyl patch by converting the total daily dose of oxycodone (5mg × 2 × 6 = 60 mg/day) to an equianalgesic dose of oral morphine (60mg × 1.5 = 90 mg/day). Finally, convert the oral morphine to transdermal fentanyl using the 2:1 (oral morphine:transdermal fentanyl) ratio which equals 45 μg/h of transdermal fentanyl. Since the patient is well controlled, the dose would be rounded to the nearest patch size or 50 μg/h

Example 2:

Patient 2 is on a regimen of 20 mg/day of oral hydromorphone and not obtaining adequate pain relief. Using the 4:1 (morphine:hydromorphone) ratio, the hydromorphone converts to 80 mg/day of oral morphine. Using the 2:1 (oral morphine:transdermal fentanyl) ratio, the oral morphine dose converts to 40 μg/h of transdermal fentanyl. Given the patient's inadequate pain relief, the dose would be rounded up to a fentanyl patch size of 50 μg/h

Fig. 2. Examples of determining the appropriate initial transdermal fentanyl patch size (reproduced from Breitbart et al.,[27] with permission).

5. Patch Application Considerations

Good adhesion of the fentanyl patch to the skin is required for efficacy and patients must be instructed on the proper technique for patch application.[35] To begin with, hair on the skin should be clipped, not shaved, in order to avoid abrasions where the patch is to be applied. This skin should also be clean, dry and undamaged. After removal of the plastic backing, the patch should be held firmly in place for about 30 seconds. A finger should be run around the edge of the patch to ensure that adhesion has occurred around all edges. The TTS (transdermal therapeutic system) Fentanyl Multicentre Study Group[36] reported that 82% of patients had no problems with patch adherence. There are some instances where additional adhesion with tape may be needed, especially in warm weather or in patients who are diaphoretic. Patients should also be instructed to rotate sites when changing patches in order to minimise changes in serum concentrations as a result of a build-up of subcutaneous depots.[35]

For the majority of patients the analgesic effect of fentanyl will last for 72 hours and a new patch should be applied at that time. Changing fentanyl patches more often than every 48 hours is not recommended. Many clinicians recommend increasing the dosage rather than shortening the administration interval. However, in rare instances, a small number of patients may find that the effect begins to decline after 48 hours and only lasts for around 60 hours.[37,38] Therefore, if the patient is consistently requiring more than four doses of breakthrough pain medication over the 24-hour period between the second and third day following patch application, even after several dosage adjustments, the clinician should consider changing the fentanyl patch every 48 hours. This practice should be the exception, not the rule.

6. Adverse Effects, Warnings and Contraindications

The overall tolerability of transdermal fentanyl is very good and limited to an extent by individualised dosage titration and prolonged administration in cancer patients. The most frequently observed adverse effects include nausea, vomiting and constipation.[23] However, a nonblind, randomised, crossover trial revealed that constipation occurred significantly less frequently with transdermal fentanyl ($n = 165$; 27%) compared with sustained-release oral morphine ($n = 155$; 45%; $p < 0.001$) in patients with cancer pain as assessed by a verbal questionnaire.[39] Similar results were found in a nonblind, randomised, crossover trial in 256 patients with chronic non-malignant pain, where 29% (transdermal fentanyl) versus 48% (sustained-release oral morphine) of patients reported constipation.[40] Skin reactions (i.e. rash and application site reactions – erythema, papules, itching and oedema) in cancer patients have been reported at a frequency of between 1% and 2%.[23] Opioid withdrawal symptoms (e.g. nausea, vomiting, diarrhoea, anxiety and shivering) may occur in some patients after discontinuation of transdermal fentanyl, conversion to another opioid or after lowering the fentanyl dosage.[24]

Hypoventilation (defined as respiratory rates of less than eight breaths per minute or a carbon dioxide partial pressure >55mm Hg) was reported in three (2%) of the 153 patients with cancer pain during a premarketing trial.[24] However, clinically relevant fentanyl-induced respiratory depression in patients with chronic non-cancer and cancer pain was not observed in three randomised trials.[39-42] Serious or life-threatening hypoventilation has been documented in opioid-naive patients and in the postoperative setting. Therefore, transdermal fentanyl is contraindicated in the management of acute or postoperative pain and intermittent, mild pain that can be adequately managed with non-opioid agents.[24,30,40] Moreover, transdermal fentanyl should not be administered to children <12 years of age or patients <18 years of age who weigh <50kg (110 pounds).[24] Those patients who are hypersensitive to either fentanyl or the adhesives used in the system should not receive this medication.[24]

Patients should be warned against the use of electric blankets, heating pads, hot tubs, saunas and heat lamps while wearing transdermal fentanyl patches. The heat produced by these items can po-

tentially increase the amount of fentanyl released from the system.[24] Moreover, fever may enhance fentanyl absorption.[24,37] Therefore, patients who are febrile need to be monitored for enhanced pharmacological effects and their dosage adjusted if necessary.

Concomitant use of other centrally acting depressants such as sedatives, other opioids, hypnotics, phenothiazines, tranquillisers, skeletal muscle relaxants, anaesthetics, sedating antihistamines and alcohol can cause hypoventilation, acute sedation or hypotension in patients taking transdermal fentanyl.[24] It is advisable to reduce the dosages of one or all of these agents when polytherapy of this nature is considered.[24] Finally, the transdermal fentanyl system should not be cut or damaged, as the system may then not work properly or not be safe for use. Moreover, safe disposal of the used transdermal fentanyl systems is important in order to prevent accidental poisoning of people, in particular infants or children, or pets.[24]

7. New Transdermal Options

Buprenorphine, a centrally acting opioid analgesic, is now being prescribed in Europe and Australia for cancer pain management.[43-47] Buprenorphine is a synthetic opioid that is lipophilic, water soluble and has a low molecular weight; these properties allow for tissue penetration and make it suitable for transdermal delivery.[43] The buprenorphine is contained in a matrix patch that is applied to the skin for a 3-day duration. The matrix patch differs from the reservoir patch technology used for transdermal fentanyl. In a matrix system, the substance is an integral part of the polymer structure of the patch, rendering the buprenorphine patch more robust in handling. While damaging a reservoir patch might result in 'dose dumping' and potentially overdosing the patient, damaging a matrix patch does not interfere with the controlled release of the medication.[43]

Transdermal buprenorphine is available with release rates of 35, 52.5 and 70 μg/h, which corresponds to daily doses of 0.8, 1.2 and 1.6mg of buprenorphine or approximately 60, 90 and 120 mg/day of oral morphine, respectively.[43-45] Steady-state serum buprenorphine concentrations can take several days to achieve with the transdermal formulation. The terminal half-life of transdermal buprenorphine has been reported as 25–27 hours.[43,44] A clinically effective or analgesia-producing serum concentration is reached in about 12 hours.[44] Therefore, like transdermal fentanyl, it is again important to provide immediate-release opioid medication to assist in the prevention of withdrawal symptoms during initial dosage titration and for treatment of breakthrough pain.

The buprenorphine transdermal therapeutic system has been shown to be quite effective against chronic, severe pain in two multicentre, randomised, double-blind, placebo-controlled, parallel-group studies.[48,49] Patients enrolled in these studies had moderate-to-severe or severe-to-very-severe chronic pain of malignant or nonmalignant origin. In patients who were unsuccessfully treated with weak opioids or morphine, 36.6% and 47.5% of buprenorphine 35 and 52.5 μg/h recipients, respectively, experienced at least satisfactory analgesia and received ≤0.2 mg/day of sublingual buprenorphine compared with a 16.2% response rate for those receiving placebo ($p \leq 0.05$).[48] The requirement for breakthrough medication was reduced from baseline by approximately 50–70% in patients treated with transdermal buprenorphine.[46,48,49] Moreover, those receiving transdermal buprenorphine tended to experience greater pain relief, reduced pain intensity and longer pain-free sleep.

Transdermal delivery of buprenorphine provides for a slower increase in serum concentration and no peak-and-trough effects as seen with the sublingual route of administration. As a result, there are fewer adverse events reported when using the transdermal delivery system for this medication.[44] Transdermal buprenorphine was usually well tolerated and adverse events reported in clinical trials were generally mild-to-moderate in severity. Adverse effects included local erythema (26.6%), local pruritus (23.2%), nausea (16.7%), vomiting (9.3%), dizziness (6.8%), sedation (5.6%), constipation (5.3%) and erythema (4%).[43,45,48,49] Adverse events could generally be attributed to either local skin reactions

at the application site, buprenorphine (systemic events common to opioid administration) or underlying disease. Adverse events were more frequently reported in patients with malignant pain than those without (46.6% vs 34.2%). Transdermal buprenorphine was associated with a low rate of withdrawals due to adverse events.[43,48,49] In one study, only 10.8% of the patients withdrew because of adverse events during a 15-day treatment period.[48]

On the basis of the currently available clinical trial data, transdermal buprenorphine is a valuable alternative to other available opioids in many chronic pain conditions. However, despite the positive data presented in these two clinical trials, more controlled studies are needed to determine the place of transdermal buprenorphine among current treatment strategies for chronic pain, and to explore if and whether transdermal buprenorphine would be of any value in the treatment of difficult pain conditions such as neuropathic pain.

8. Conclusions and Recommendations

Many pharmacotherapeutic choices are available for the management of cancer pain. Healthcare practitioners must be readily able to quantify the relative analgesic potency when converting from one opioid to another or from one route to another. Transdermal formulations of fentanyl and buprenorphine are effective and safely used pharmacotherapy for the cancer patient experiencing moderate-to-severe pain. Clinicians need to be aware that the relative opioid conversion tables commonly used are often based on the results of single-dose studies and frequently underestimate the dosage required for the patient with cancer-related pain. A more aggressive or less conservative approach to administering transdermal opioids is needed in this patient population. Care must be taken to individualise each patient's pain management in order to prevent opioid withdrawal, and substantially reduce the under treatment of cancer-related pain and its associated negative impact on patients' quality of life.

Acknowledgements

This article was supported by the Pharmacoeconomics & Pharmacoepidemiology Research Unit, Washington State University, Pullman, Washington, USA. The author reports no conflicts of interest.

References

1. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994; 330 (9): 592-6
2. Coyle N, Adelhardt J, Foley KM, et al. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last 4 weeks of life. J Pain Symptom Manage 1990; 5 (5): 83-93
3. Grond S, Zech D, Diefenbach C, et al. Prevalence and pattern of symptoms in patients with cancer pain: a prospective evaluation of 1635 cancer patients referred to a pain clinic. J Pain Symptom Manage 1994; 9 (6): 372-82
4. Simmonds MA. Pharmacotherapeutic management of cancer pain: current practice. Semin Oncol 1997; 24 (5 Suppl. 16): S16.1-16.6
5. Zhukovsky DS, Goroswski E, Hausdorff J, et al. Unmet analgesic needs in cancer patients. J Pain Symptom Manage 1995; 10 (2): 113-9
6. Ferrer-Brechner T. The management of pain associated with malignancy. Semin Anesth 1985; 4: 313-22
7. Bucher JA, Trostle GB, Moore M. Family reports of cancer pain, pain relief, and prescription access. Cancer Pract 1999; 7 (2): 71-7
8. Hanks GW. Cancer pain and the importance of its control. Anticancer Drugs 1995; 6 Suppl. 3: 14-7
9. World Health Organization. Cancer pain relief: with a guide to opioid availability. 2nd ed. Geneva: WHO, 1996
10. Zech DF, Grond SA, Lunch J, et al. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. Pain 1995; 63 (1): 65-76
11. Schug SA, Merry AF, Acland RH. Treatment principles for the use of opioids in pain of nonmalignant origin. Drugs 1991; 42 (2): 228-39
12. Zenz M, Strumpt M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage 1992; 7 (2): 69-77
13. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996; 11 (4): 203-17
14. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain 1988; 33 (1): 11-23
15. Foley KM. The treatment of cancer pain. N Engl J Med 1985; 313 (2): 84-95
16. Cherny NI, Portenoy RK. Cancer pain management: current strategy. Cancer 1993; 72 (11 Suppl.): 3393-415
17. American Pain Society. Principles of analgesic use in the treatment of acute pain and chronic pain. 5th ed. Chicago (IL): American Pain Society, 2004
18. Cherny NJ, Chang V, Frager G, et al. Opioid pharmacotherapy in the management of cancer pain. Cancer 1995; 76 (11): 1283-93
19. Cherny NI, Portenoy RK. The management of cancer pain. CA Cancer J Clin 1994; 44 (2): 262-303

20. Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996; 335 (15): 1124-32

21. Lawlor P, Turner K, Hanson J, et al. Dose ratio between morphine and hydromorhone in patients with cancer pain: a retrospective study. Pain 1997; 72 (1-2): 79-85

22. Lawlor PG, Turner KS, Hanson J, et al. Dose ratio between morphine and methadone in patients with cancer pain. Cancer 1998; 82 (6): 1167-73

23. Muijers RBR, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs 2001; 61 (15): 2289-307

24. Janssen Pharmaceutica. Duragesic (fentanyl transdermal system) full prescribing information. Titusville (NJ): Janssen Pharmaceutica, 2001

25. Kornick CA, Santiago-Palma J, Moryl N, et al. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. Drug Saf 2003; 26 (13): 951-73

26. Donner B, Zenz M, Tryba M, et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain 1996; 64 (3): 527-34

27. Breitbart W, Chandler S, Eagel H, et al. An alternative algorithm for dosing of transdermal fentanyl for cancer-related pain. Oncology (Huntingt) 2000 May; 14 (5): 695-705

28. Higgs C, Vella-Brincat J. Withdrawal with transdermal fentanyl. J Pain Symptom Manage 1995; 10: 4-5

29. Zenz M, Donner B, Strumpt M. Withdrawal symptoms during therapy with transdermal fentanyl (fentanyl TTS). J Pain Symptom Manage 1994; 9 (1): 54-5

30. Radbruch L, Elsner F. Clinical experience with transdermal fentanyl for the treatment of cancer pain in Germany. Keio J Med 2004; 53 (1): 23-9

31. Zech D, Grond S, Lynch J, et al. Transdermal fentanyl and initial dose finding with patient controlled analgesia in cancer pain: a pilot study with 20 terminally ill cancer patients. Pain 1992; 50 (3): 293-301

32. Kornick CA, Santiago-Palma J, Schulman G, et al. A safe and effective method for converting patients from transdermal to intravenous fentanyl for the treatment of acute cancer-related pain. Cancer 2003; 97: 3121-4

33. Kornick CA, Santiago-Palma J, Khojainova N, et al. A safe and effective method for converting patients from intravenous to transdermal fentanyl. Cancer 2001; 92: 3056-61

34. Cleary JF. Pharmacokinetic and pharmacodynamic issues in the treatment of breakthrough pain. Semin Oncol 1997; 24 (5 Suppl. 16): 13-9

35. Payne R, Chandler S, Einhaus M. Guidelines for the clinical use of transdermal fentanyl. Anti Cancer Drugs 1995; 6 (3): 50-3

36. The TTS Fentanyl Multicentre Study Group. Transdermal fentanyl in cancer pain. J Drug Dev 1994; 6 (3): 93-7

37. Southam MA. Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy. Anticancer Drugs 1995; 6 Suppl. 3: 29-34

38. Portenoy RK, Southam M, Gupta SK. Transdermal fentanyl for cancer pain: repeated dose pharmacokinetics and efficacy. Anesthesiology 1993; 78 (1): 36-43

39. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manag 1996; 13 (5): 254-61

40. Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001; 322 (7295): 1154-8

41. Wong JO, Chiu GL, Tsaio CJ, et al. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. Acta Anaesthesiol Sin 1997; 35 (1): 25-32

42. Kongsgaard UE, Poulain P. Transdermal fentanyl for pain control in adults with chronic cancer pain. Eur J Pain 1998; 2 (1): 53-62

43. Evans HC, Easthope SE. Transdermal buprenorphine. Drugs 2003; 63 (19): 1999-2010

44. Bohme K. Burprenorphine in a transdermal therapeutic system: a new option. Clin Rheumatol 2002; 21 Suppl. 1: S13-116

45. Budd K. Buprenorphine and the transdermal system: the ideal match in pain management. Int J Clin Pract Suppl 2003; 133: 9-14

46. Radbruch L, Vielvoye-Kerkmeer A. Buprenorphine TDS: the clinical development, rationale and results. Int J Clin Pract Suppl 2003; 133: 15-8

47. Radbruch L. Buprenorphine TDS: use in daily practice, benefits for patients. Int J Clin Pract Suppl 2003; 133: 19-24

48. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther 2003; 25 (1): 150-68

49. Bohme K, Kikar R. Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain: a randomized, double-blind, placebo-controlled study. Pain Clinic 2003; 15 (2): 193-202

Correspondence and offprints: Dr *Tracy L. Skaer*, College of Pharmacy, Washington State University, Wegner Hall, Room 105, PO Box 646510, Pullman, WA 99164-6510, USA. E-mail: skaer@mail.wsu.edu