Review article
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The use of transdermal fentanyl in the treatment of cancer pain

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The management of pain is complex having to take into consideration patient specific characteristics. Drug therapy should be individualized and managed based on numerous factors. The opioid of first choice for the treatment of cancer pain is morphine, according to the European Association for Palliative Care (2000). Transdermally administered fentanyl is one alternative to oral morphine in the treatment of cancer pain. The transdermal systems are designed to deliver fentanyl at a constant rate for periods of 72 hours. Patches with a delivery rate of 25, 50, 75 and 100 μg/h are available. Treatment with transdermal fentanyl is safe and acceptable to many cancer patients. Significantly more patients expressed a preference for transdermal fentanyl than for sustained-release oral morphine. The global score of adverse effects was significantly lower in patients receiving transdermal fentanyl than in those receiving sustained-release oral morphine. The transdermal fentanyl patch is as effective as oral opioids in relieving cancer-related pain, with a safety and side effect profile equal to or better than that of oral opioids.

KEY WORDS: *Neoplasms; Pain; Fentanyl; Administration Cutaneus; Analgesics, Opioid*

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INTRODUCTION

The term cancer pain does not have a specific definition. In fact, cancer patients have some of the most diverse types of pain. Their pain can stem from any of the following: tumor infiltration or compression, surgery and biopsies, radiation damage to tissues, neuropathies, ischemia, inflammation, damaged organ structures (visceral pain), decreased mobility and arthropathies (musculoskeletal pain), pathologic fractures. In addition some pains are constant, others are incidental to specific movements or intermittent. Common words used to describe pain such as chronic pain often do not lead to understanding of the basic mechanism of the pain. Analgesic medication or other pain treatment added to the primary treatment helps to improve patient's experience with cancer treatment and to compliant with treatment protocols. The World Health Organization (WHO) developed a stepwise treatment algorithm as a guideline for the treatment of cancer pain (Figure 1).

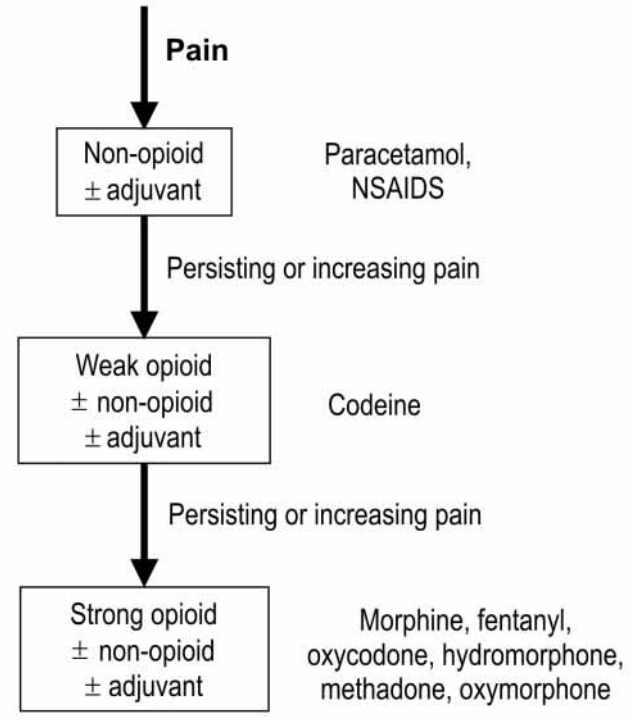

Figure 1. WHO analgesic ladder (1)

This WHO analgesic ladder is composed of three basic steps:

- Step 1: Start with non-opioid analgesic for mild pain
- Step 2: Begin using opioids (codeine, hydrocodeine) for mild to moderate pain

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- Step 3: Use the more potent opioids (morphine, hydromorphine) for moderate to severe pain

Opioids are the mainstay of cancer pain treatment; the therapeutic goal for cancer pain treatment with opioids is to achieve maximal analgesia and minimize occurrence of adverse events. Important principle in cancer pain management is to individualize treatment to the patient. According to the European Association for Palliative Care (2000) the opioid of first choice for the treatment of cancer pain is morphine. This recommendation is based on familiarity, availability and cost rather than on proven clinical superiority (2). However, multiple opioids exist and each has advantages and disadvantages in the clinical care of cancer pain patients. Oral administration of opioids is preferred, but as disease progresses, it may become necessary to use other routes of administration.

Fentanyl is a synthetic opioid agonist, which interacts primarily with the mu-opioid receptor. Activation of mu-receptor results in analgesia, euphoria, respiratory depression, nausea, vomiting, decreased gastrointestinal motility (constipation), tolerance and dependence. Fentanyl is 75 to 100 times more potent than morphine, probably because fentanyl is lipophilic, allowing rapid penetration of the blood-brain barrier. Fentanyl increases billiary tract pressure and the tone of urinary tract smooth muscles. The drug may be given intravenously, intramuscularly, intrathecally, via mucous membranes or through the skin. Transdermally administered fentanyl is one alternative to oral morphine in the treatment of cancer pain (3-8).

FENTANYL TRANSDERMAL SYSTEM (DURAGESIC®)

Pharmacokinetic properties

The low molecular weight, high potency and lipid solubility of fentanyl make it suitable for delivery by the transdermal therapeutic system (3,6,9). Transdermal administration of fentanyl was introduced in United States in 1991.

The transdermal systems (figure 2) are designed to deliver fentanyl at a constant rate for periods of 72 hours (3,10).

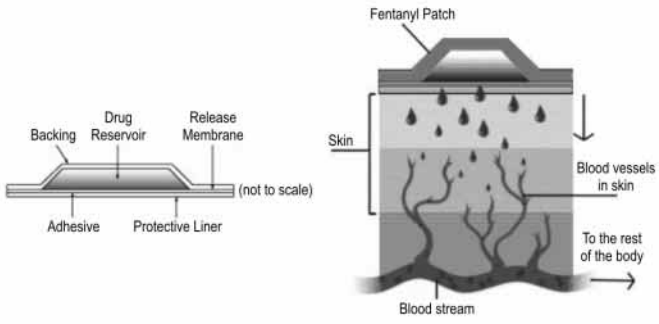

Figure 2. Fentanyl transdermal system

Patches with a delivery rate of 25, 50, 75 and 100 μg/h are available. The amount of fentanyl delivered is proportional to the surface area of the patch (3). Neither local blood flow, nor anatomical site of application seems to affect fentanyl delivery. The absorption of fentanyl does not vary between the chest, abdomen and thigh. A rise in body temperature to 40˚C may increase the absorption rate by about one-third. Sweat can accumulate under the transdermal fentanyl patch, which may alter the absorption of fentanyl from the system into the skin.

Fentanyl does not appear to undergo biotransformation during transdermal permeation (11). Serum fentanyl concentrations increase gradually following initial application, generally leveling off between 12 and 24 hours (Table 1) (10). Thereafter, they remain relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Concentrations are highest on the first day and decrease slightly during the second and third day.

Tabele 1. Pharmacokinetic values after the first 72 hours of transdermal fentanyl application (3)

Dosage		Patch size	C_{max}	t_{max}
µg/h	mg/24h	(cm^2)	(µg/h)	(h)
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}

Fentanyl is mainly metabolized by cytochrome P450(CYP)3A4 (12). The major metabolite is norfentanyl and minor metabolites include despropionylfentanyl, hydroxyfentanyl and hydroxynorfentanyl. These metabolites show negligible pharmacological activity. Unlike other opioid medications, the metabolism of fentanyl is even unaffected by liver disease, and because fentanyl does not have active metabolites, its actions are also unaffected by renal failure. Coadministration of drugs that inhibit CYP3A4 may impair fentanyl clearance and result in increased or prolonged opiod effects (12). CYP3A4-inhibiting drugs are macrolide antibiotics, azole antifungal agents, protease inhibitors; CYP3A4-inducers are phenytoin, and carbamazepine. Patients receiving one of these drugs in combination with transdermal fentanyl should be carefully monitored.

Dosage and therapeutic use

Transdermal fentanyl is recommended for use in patients with stable pain who have trouble using oral medications or who are active and find regular oral dosing inconvenient. As with any long-acting preparation, breakthrough medication should be provided in addition. In 11 countries worldwide including the US, its use is not restricted to cancer pain; the drug is also available for treatment of severe chronic pain of nonmalignant origin (13).

Table 2 displays the range of 24-hour oral morphine doses that are recommended for conversion to each transdermal fentanyl (DURAGESIC) doses. The dosage should be individualized according to the pain state of the patient (14). This starting dose is recommended to minimize the potential for overdosing patients

with the first dose. The conversion tables recommended in UK and US are conservative. Less conservative table is recommended in Germany.

Tabele 2. Recommended initial transdermal fentanyl dose based upon daily oral morphine dose in US/UK and Germany (3, 12)

US/UK prescribing information:		German prescribing information:	
Oral 24-hour morphine (mg/day)	Transdermal fentanyl dose (μg/h)	Oral 24-hour morphine (mg/day)	Transdermal fentanyl dose (μg/
45-134	25	0-90	25
135-224	50	91-150	50
225-314	75	151-210	75
315-404	100	211-270	100
405-494	125	Every additional 60	25
495-584	150	mg	
585-674	175		
675-764	200		
765-854	225		
855-944	250		
945-1034	275		
1035-1124	300		

Geriatric, cachectic or debilitated patients should not be started on dosages higher than 25 μg/h of transdermal fentanyl, unless they are taking more than 25 mg/day oral morphine or equivalent opioid (12). Coadministration of transdermal fentanyl and centrally acting depressants (sedatives, other opioids, anesthetics, hypnotics, phenothiazines, skeletal muscle relaxants, sedating antihistamines, alcohol) may result in hypoventilation, hypotension and acute sedation.

Transdermal fentanyl is contraindicated in the management of acute or postoperative pain and intermittent and mild pain, which can be adequately managed with non-opioid agents (12). It should not be administered to patients who are hypersensitive to either fentanyl or any other component used in the system, to patients with increased intracranial pressure, severe respiratory failure, and severe liver or renal insufficiency. It should not be administrated to children less than 12 years of age or patients less than 18 years of age weighing less than 50 kg (3).

Fentanyl in the form of the Duragesic patch should be applied whole to an intact area of skin. It is important that patients choose site to apply a patch where is no hair, taking care to avoid sensitive areas or areas of excessive movement and prepare the application site correctly. The area should be prepared by clipping the any hair (not shave, shaving irritates the skin), cleaning with water only (not soap, alcohol or lotions that might irritate the skin). Before put a new patch on, patient should always remove and dispose of the used patch properly. Application of a transdermal patch to different sites on the body reduces the risk of adverse reactions or toxicity. Repeated exposure of the transdermal patch to the same area can potentially increase toxicity or adverse drug reactions. Patient may shower, wash or bathe with the patch on. Some people even swim while wearing it. Patch will not work properly and may not be safe to use if it is cut or damaged. Transdermal fentanyl patches should be warned against exposure to external heat sources such as heat pats, electric blankets, hot tubs, saunas and heat lamps, because heat may increase fentanyl release from the system (12).

Adverse effects

Global score of adverse effects was significantly lower in patients receiving transdermal fentanyl than in those receiving sustained-release oral morphine (3). The most serious adverse event associated with transdermal fentanyl administration is respiratory depression. The most frequently adverse events during fentanyl treatment are nausea, vomiting and constipation. Adverse reactions related to skin sensitivity (erythema, papules, itching, edema) occurred in 1-2% of patients (8,9).

Hypoventilation (respiratory rate less than 8 breaths per minute or a $PaCO_2$ greater than 55 mm Hg) occurred in approximately 2% of patients during transdermal fentanyl patch treatment. The mechanism of fentanyl-induced respiratory depression is different from that of morphine. Mu1- receptors play an important role in the respiratory effects of fentanyl and these effects can be prevented by the mu-receptor antagonist naloxon (1,15). No significant respiratory depression was associated with fentanyl during observations of patients receiving transdermal fentanyl in UK (16).

Fentanyl, like other opioids, increases the tone and decreases the propulsive contractions of the gastrointestinal tract, diminished billiary, pancreatic and intestinal secretions and increased ileocaecal and anal sphincter tone. This can result in constipation. Constipation is less frequent with transdermal fentanyl than with sustained-release oral morphine (3,8,17,18). In cancer patients, the incidence of constipation was reduced by up to two-thirds after switching from oral morphine to transdermal fentanyl (13). The majority of patients (78%) did not experience any constipation during the study in UK (16).

Vomiting and nausea are frequent in cancer patients and are caused by chemotherapy or by cancer disease process. Fentanyl like other opioids can cause vomiting and nausea. Comparative clinical data from open 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 pain (3).

Data from randomized, clinical trial suggest that transdermal fentanyl is less sedative than sustained-release oral morphine (3).

Some degree of tolerance to opioids is common in cancer patients because these drugs are used over long periods of time. To achieve the same level of analgesia, very high doses may be reached causing toxicity, in particular, myoclonus.

CLINICAL STUDIES DATA

Clinical studies confirm that transdermal fentanyl is as effective as sustained-release oral morphine in the management of cancer pain (3). Some patients whose pain was previously uncontrolled

became completely pain free.

Results from clinical study in UK show that the ratings of patients and investigators are similar, 85% patients and 86% investigators rated the treatment as good or excellent (16)

In a large study, from October 1996 to February 1998 transdermal treatment was documented for 1005 patients (506 men and 499 women with a mean age of 60 years, range 20-92 years) with chronic pain in Germany. Most patients suffered from cancer pain and only 11 patients had chronic pain from non-malignant disease. Transdermal therapy with fentanyl was safe and efficient in this national survey (4).

Transdermal fentanyl is effective in the treatment of severe cancer pain, particularly when the oral route is unavailable (5,7). In addition, the vast majority of the patients found the transdermal system easy to use and reported as being satisfied or highly satisfied with it (19). Patient acceptability is high and the cost is lower than other methods required delivering parenteral opioids (10).

Some other studies showed that transdermal fentanyl provided good to excellent pain relief in the majority (about 70%) of patients (7,8,17).

Transdermal fentanyl is equally safe, effective, with a number of advantages over sustained-release oral morphine and other opioids (7,14). The transdermal system is easy to apply, generally requiring replacement every 72 hours. Advantages of transdermal fentanyl include being a non-invasive dosage form, achievement of predictable serum concentrations, high compliance, and a potential lower rate of gastrointestinal adverse effects. Studies of chronic pain comparing transdermal therapy with oral medications have shown that transdermal therapy improves sleep and most importantly, results in greater improvements in quality of life. It could be an alternative in patients who are unable to swallow and in patients with poor venous access. Preliminary data indicate that it may be useful in the management of chronic non-malignant pain (13).

Disadvantages of transdermal fentanyl are: the delay of onset of action after application of first system (it is important that rescue medication is readily available to patients receiving transdermally administered fentanyl), optimal dosing may not always be possible because patch sizes are fixed, and relatively large skin areas are required to administer higher dosages of fentanyl (3).

CONCLUSION

Transdermal administration of fentanyl offers an improvement of pain treatment. Transdermal fentanyl is a useful alternative to other opioid agents which are also recommended on the third step of the WHO analgesic ladder, in the management of cancer pain. Significantly more patients expressed a preference for transdermal fentanyl than for sustained-release oral morphine. The incidence of adverse effects was significantly lower in patients receiving transdermal fentanyl than in those receiving sustained-release oral morphine. Transdermal fentanyl is acceptable, safe and effective, and may be recommended for treatment of cancer related pain.

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