Transdermal opioids for cancer pain management

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SUMMARY POINTS

- The prevalence of pain in cancer is up to 90%, more than 45% of this can be adequately managed using the World Health Organisation three step analgesic ladder.
- Transdermal opioids are safe, effective, and produce significantly fewer side effects than oral morphine when used for moderate to severe cancer pain.
- Transdermal buprenorphine has a lower incidence of systemic side effects than transdermal fentanyl and it is indicated for use in cancer patients with neuropathic pain and renal dysfunction.
- Transdermal opioids require a long lag period for dose stabilisation and elimination, hence are unsuitable for acute or unstable pain, and may result in prolonged side effects.
- Transdermal analgesics reduce the need for frequent dosing, clock watching and are more convenient for patients, physicians and carers, hence increasing treatment compliance.

Introduction

The prevalence of pain in cancer patients is between 30-50% with pain becoming much more common as the cancer advances. 70-90% of patients with advanced staged cancer are reported to suffer from cancer pain.¹ Pain due to cancer is often multidimensional with physical, psychological, social, cultural and spiritual components

each contributing uniquely to an individual patient's pain. Cancer pain can be described as acute or chronic, background or breakthrough, somatic or visceral, nociceptive or neuropathic and direct or referred. The three main causes of pain in cancer patients are shown in Table 1.

In 1986 the World Health Organization (WHO) recognised the global need to establish guidelines for basic pain control in cancer patients, hence developed the three step analgesic ladder, as shown in Figure 1.² Transdermal opioids such as fentanyl and buprenorphine provide systemic analgesia and are often placed on the third step of the WHO analgesic ladder to treat moderate to severe pain associated with cancer. The WHO estimates that 80–90% of cancer pain can be relieved by appropriate use of the analgesic ladder. Although several studies have demonstrated the effectiveness of this tool in managing cancer pain,³⁻⁵ recent research shows that as many as 50% of cancer patients with pain may remain under treated.⁶ Very few controlled clinical trials have been performed to validate the effectiveness of the WHO three-step analgesic ladder. Until effective analgesic strategies are validated, healthcare professionals must use clinical judgment and a holistic approach to manage cancer pain adequately.

The aim of managing cancer pain is to relieve pain to an acceptable level, enabling the patient to function effectively in their daily routine. Pain relief can be achieved by a variety of means. However, the treatment of cancer pain must be tailored to the individual, with pharmacological, surgical, psychological, physical and behavioral approaches geared specifically to the patient's needs.

Table 1. Aetiology of Pain in Cancer Patients

Direct or metastatic invasion of cancer	Bone
	Soft Tissue
	Nerves
	Viscera
	Muscle
Related to treatment	Surgery
	Radiotherapy
	Chemotherapy
	Hormonal therapy
	Immunotherapy
Co-morbid medical disorders	Rheumatoid or Osteoarthritis
	Osteoporosis
	Diabetic neuropathy
	Ischaemic heart disease
	Various other medical causes of pain

Transdermal opioids

Transdermal opioid delivery avoids first pass metabolism and limits variation in plasma concentration. Its greatest barrier is the stratum corneum, a 10–20 µm thick layer of highly lipophilic epidermis. Transdermal opioids must cross this layer in order to be absorbed by the capillaries in the dermis, thus enabling action on the opioid receptors in the central nervous system (CNS) via the systemic circulation. In order for good penetration through the stratum corneum, transdermal opioids must have a low molecular mass (<500 Da), high lipid solubility, and high potency (daily required dose <2mg).⁷ Fentanyl and buprenorphine combine these three qualities, as opposed to morphine, which is very lipophobic, hence it is unsuitable for use via the transdermal route.

There are two types of transdermal patches available: reservoir or matrix drug delivery system. The reservoir patch holds the drug in a gel solution and delivers it to the skin via a rate-controlling membrane. Whereas the matrix patch incorporates the drug into an adhesive polymer matrix, enabling continuous release into the skin. The dose of drug delivered by matrix patches is proportional to the area of the patch applied to the skin.⁷ Both types of patches are equally effective and well tolerated,^{8–10} however matrix patches are

much more robust in terms of handling. Cutting matrix patches to titrate doses for patients sensitive to opioids, such as the elderly and paediatric population, does not interfere with the controlled release of the drug. Whereas damaging reservoir patches may result in 'dose dumping' and potentially overdosing the patient.¹¹

Fentanyl

Fentanyl is a synthetic opioid agonist, which acts primarily at the µ-opioid receptor.¹² It is 100 times more potent than morphine resulting in an estimated conversion ratio of 1:100, in order to provide an equal degree of analgesia.^{13,14} Its low molecular weight, high potency and lipid solubility make it ideal for delivery via the transdermal route. Matrix patches (e.g. Durogesic®) are designed to deliver fentanyl at a constant rate and are available in various doses: 12, 25, 50, 75 and 100 µg/hour, requiring replacement every 72 hours. It may take 12–24 hours for plasma levels of fentanyl to stabilise after starting patch therapy or changing the dose.¹² The transdermal route eliminates first-pass metabolism of fentanyl by the liver, increasing bioavailability to 90%, making it possible to use lower doses of the drug, thus reducing the incidence of adverse effects.^{11,12} Fentanyl is metabolised by cytochrome P450 enzymes into inactive metabolites, hence drugs that enhance or inhibit cytochrome P450 will affect its metabolism. The elimination half-life

after patch removal is 13–22 hours. This is due to the slow release of fentanyl from the skin depot. Several studies have shown that when compared to sustained-release oral morphine (SROM), transdermal fentanyl has a 30% lower incidence of adverse effects such as constipation and sedation ($p < 0.05$).^{15,16} Furthermore randomised, controlled, open-label trials suggest that transdermal fentanyl is safe and as effective as SROM in the treatment of chronic cancer pain.^{15–17} Hence significantly more patients expressed a preference for transdermal fentanyl at the end of a randomised controlled, open-label crossover trial.¹⁸

Buprenorphine

Buprenorphine is a semi-synthetic compound derived from thebaine, a natural opium alkaloid.¹⁹ It is 25–100 times more potent than morphine, resulting in an estimated conversion ratio of 1:110–1:115, in order to provide an equal degree of analgesia.^{14,20} Buprenorphine acts as a partial μ -opioid receptor agonist as well as a κ and δ opioid receptor antagonist. It binds to the receptors with high affinity and its slow dissociation, results in slow onset, but relatively long duration of analgesic action.²¹ Steady state plasma levels are achieved after application of the third consecutive patch (>200 hours), and the elimination half-life is up to 27 hours.²¹ Transdermal buprenorphine also bypasses first-pass metabolism, yielding bioavailability of 50%.²² The liver metabolises buprenorphine to norbuprenorphine, its major, mildly active, metabolite that is excreted with bile, preventing opioid accumulation. This enables the use of buprenorphine for patients with renal dysfunction; such as diabetics, the elderly and those patients requiring haemodialysis.²³ Transdermal buprenorphine (Transtec®) is available in three matrix patch strengths: 35, 52.5 and 70 $\mu\text{g}/\text{hour}$. Each patch continuously delivers buprenorphine for up to 96 hours across the skin and into the systemic circulation. The release of buprenorphine from the matrix patch is regulated by the concentration gradient between the skin and patch. The recent introduction of low-dose patches (Norspan®, BuTrans®), in strengths of 5, 10 and 20 $\mu\text{g}/\text{hour}$ released over seven days, can be used to better treat chronic cancer pain in opioid naïve patients.²¹

Evidence from randomised controlled, double-blind, multicenter clinical trials, demonstrates that patients receiving transdermal buprenorphine experienced significantly greater pain relief, better sleep, and a reduced need for rescue therapy, when compared to SROM.^{9,24,25} Various post marketing studies and randomised controlled double blind trials show good pain relief in up to 89% of patients using transdermal buprenorphine when compared with placebo, proving it to be safe and effective for the management of chronic cancer pain.^{24,26,27} Previous concerns over the analgesic potency and clinical safety of buprenorphine have been consistently disproved. Several studies have shown buprenorphine to have a dose–linear response curve within the therapeutic dose range with *no analgesic ceiling effect*.^{19,28} Furthermore no antagonism of pain relief, or opioid withdrawal has been reported when buprenorphine is combined with pure μ -opioid receptor agonists. In fact several studies have shown that combining buprenorphine with μ -opioid receptor agonists such as morphine or fentanyl, actually synergises their analgesic and anti-hyperalgesic effects, resulting in effective pain management.^{19,28}

Buprenorphine also shows promise in treating neuropathic pain, which can often manifest in cancer pain conditions. The use of transdermal buprenorphine in cancer related neuropathic pain resulted in a significant decrease in the number of patients reporting moderate to severe pain.²¹ It has been suggested that buprenorphine's anti-hyperalgesic effect might contribute to its efficacy in neuropathic pain, however the mechanism for this is not well understood. It may be associated with buprenorphine's receptor subtype selectivity, binding characteristics and coupling to opioid receptor G-protein, which is distinctly different from the typical characteristics of pure μ -opioid receptor agonists.²¹

Advantages of the transdermal route

Transdermal patches considerably reduce pill burden for cancer patients, preventing 'clock watching' and alleviate the burden of breakthrough pain, resulting in increased compliance and therefore more effective pain relief.²⁹

Transdermal opioids are more effective than SROM for the management of moderate to severe cancer pain and produce significantly less side effects. This is because of their inherent lipophilic nature, low molecular weight and high potency, enabling rapid uptake into the CNS.

Transdermal analgesics provide a simpler and more convenient treatment route especially for those patients with gastrointestinal problems such as intestinal hurry and malabsorption, severe nausea and vomiting or dysphagia. They provide slow, rate-controlled delivery of analgesia and stable plasma concentrations.

The transdermal route eliminates first-pass metabolism by the liver, increasing bioavailability of analgesics, making it possible to use lower doses of the drug.

Disadvantages of the transdermal route

It often takes more than 24 hours for plasma levels of transdermal opioids to stabilise after starting patch therapy or changing the dose, often resulting in significant under-treatment of cancer pain during the transition period.

Elimination half-life of transdermal opioids can be up to 27 hours, thus patients who experience side effects, especially respiratory depression, need to be monitored and supported for a full day after discontinuing therapy. Systemic and local side effects of transdermal analgesics and their incidence are shown in Table 2.

Reservoir patches, when damaged, often result in 'dose dumping' and potentially overdosing the patient. Patients should always be advised not to cut or damage reservoir patches and all effort must be made to prescribe matrix patches whenever possible. Although matrix patches are more expensive, they are invaluable especially for those patients who are sensitive to opioids and require specific intermediary doses.

Table 2. Incidence of side effects using transdermal analgesics

Side effect	Transdermal Fentanyl ^{12,30}	Sustained-release Oral Morphine ³⁰	Transdermal Buprenorphine ^{22,27}
General			
Fatigue	6%	3%	2.9%
Central and peripheral nervous system			
Dizziness	11%	4%	4.6%
Headache	9%	6%	<1%
Somnolence	18%	14%	-
Gastrointestinal system			
Constipation	29%	48%	3.8%
Nausea	26%	18%	9.2%
Vomiting	10%	10%	4.2%
Skin			
Pruritus	33%	8%	10.5%
Increased sweating	9%	5%	3.8%
Erythema	41%	-	12.1%
Oedema	6%	-	1.3%
Papules or pustules	12%	-	8.8%

Some patients cannot tolerate patches either due to skin irritation or annoyance at poor adhesiveness to their skin type. Additional dressings can be used to ensure good patch contact, however this reduces the ease of use and simplicity of the transdermal approach.

Transdermal opioids are of limited use in patients with unstable pain. The European Association for Palliative Care recommends that transdermal opioids be reserved for patients who require stable opioids doses.³¹ The relatively long induction period of transdermal opioids also makes them unsuitable for use in acute postoperative pain, as they often provide inadequate pain relief and result in a high incidence of respiratory depression.¹² Although transdermal opioids are generally safer for use in renal failure, patients should still be monitored for evidence of gradual opioid accumulation.³²

The limitations of transdermal drug delivery have led to physical and chemical advances in delivering transdermal drugs. Chemical methods include adding ethanol or propylene glycol to drugs to enhance their lipid solubility. Physical methods include iontophoresis, where an electrical field is used to drive small, charged, lipophilic particles across the skin.^{7,33} Iontophoresis can be used to deliver drug boluses and has been shown to be safe and effective in treating acute postoperative pain and breakthrough pain among chronic cancer pain sufferers.³⁴⁻³⁶

Practical information

Tips to ensure good patch adhesion

Patients should be advised to place patches on glabrous skin, avoiding oily, irritated or damaged skin. If this is not possible patients should be advised to clip hair and not shave.

Prior to patch application, it is important to clean the skin area with clean water, avoiding use of soaps, oils or lotions. The skin must be patted down until completely dry. After peeling the protective liner patients should press the patch onto the skin and hold it there for at least 30 seconds ensuring good adhesion at the edges. If the patch does not stick or loses adhesiveness, patients should tape the edges down with first aid tape. If the patch falls off, patients should be advised to throw it away and place a new one at a different skin site. Extra dressings such as plasters or see-through dressings should be used, in the event of increased perspiration. Patients should be informed that they can bathe, swim or shower while they are wearing patches. If the patch falls off, they should put on a new patch, ensuring that the new skin area chosen is dry before putting it on.³⁷

Tips on managing skin reactions

Some patients cannot tolerate patches due to skin irritation. Rotating patch sites and using local steroids can manage the issues of local sensitivity. Steroid creams should be used the day before patch adhesion, but not immediately prior to application as this will compromise good patch adhesion.

Conclusion

Transdermal fentanyl and buprenorphine are extremely effective for the management of cancer patients experiencing moderate to severe pain. They provide slow, rate-controlled delivery of analgesia and stable plasma concentrations, resulting in more effective analgesia and fewer adverse effects. Transdermal opioids reduce the need for frequent dosing, and are more convenient for healthcare professionals, patients and their carers hence increasing rates of treatment compliance. However clinicians need to be aware of the indications, contra-indications and opioid conversion ratios to make effective, patient specific, pain management plans. Generally, a more aggressive approach to converting patients to transdermal opioids, may be warranted, considering its superiority in treating background cancer pain. Care must be taken to ensure adequate pain relief during the transition period, preventing opioid withdrawal or toxicity by close monitoring.

Cancer pain remains inadequately controlled despite advancing diagnostic and therapeutic means of pain management. Further educational tools are necessary to deconstruct the barriers to providing effective pain management in cancer patients; and overcome the patterns of ignorance, which result in the unnecessary suffering of cancer patients. Economically the multimillion pound healthcare costs for treating chronic pain are superseded by the multibillion pound socioeconomic costs due to inadequate pain relief resulting in work loss, disability, and social welfare benefits.

The WHO guidelines provide explicit treatment protocols for the management of cancer pain, which can be clinically useful, however these have not been established as evidence based. Hence it is important to use clinical judgment and a holistic approach to maximise analgesia and minimise adverse effects. Randomised controlled clinical trials must be conducted in order to validate the effectiveness of the WHO three-step analgesic ladder, or determine other more effective analgesic strategies for cancer pain.

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