Transdermal Buprenorphine in the Management of Cancer Pain

a report by

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Cancer Pain

Pain is a prevalent symptom of cancer, affecting 35–45% of patients at an early stage or at the time of diagnosis, 70% of patients with advanced cancer and almost all patients with end-stage disease.[1] It not only produces considerable physical disability but also adversely affects psychological functioning and quality of life.

The treatment of cancer pain is complicated by its complex and multifactorial character. Pain may be directly related to the presence of tumour (e.g. compression or infiltration of nerve roots or visceral compression). Conditions such as lymphoedema or muscular contracture resulting from the malignancy may cause pain, as may treatment modalities such as surgery, chemotherapy and radiotherapy.[2] Cancer pain is also very complex from a pathophysiological perspective. It may incorporate a nociceptive, somatic or visceral component resulting from the activation of nociceptors, and a neuropathic component produced by damage to the central nervous system or peripheral nervous system.[3] A further consideration is the fact that patients may have to take multiple medications. This not only brings the risk of drug–drug interactions, but the inconvenience for patients may compromise their compliance with treatment.

Drug therapy is based on the three-step World Health Organization (WHO) pain ladder,[4] which advocates a sequential progression from low efficacy, non-opioid analgesics (step 1) to weak opioids for mild to moderate pain (step 2) and then strong opioids for moderate to severe pain (step 3). Adjuvant drugs and symptomatic treatment are provided as necessary, to improve the balance between analgesia and adverse effects. This approach has been validated by a number of investigators.[5–7] One 10-year prospective study reported that analgesics were constantly effective for all three steps of the WHO ladder.[5] Over the whole treatment period, good pain relief was reported by 76% of patients, satisfactory pain relief by 12% and inadequate pain relief by 12%.

Although opioids (especially morphine) play a major role in the treatment of cancer pain, in many cases their use is restricted by concern over adverse effects such as nausea, vertigo, constipation, respiratory depression, analgesic tolerance and immunosuppression.[1] Further limitations are imposed by cultural barriers, unavailability and political ideology, with the result that these agents are underprescribed.[8] However, the considerable variation between opioids in terms of their intensity and duration of action (and the adverse effects they produce) is not always fully recognised. The disparities may be explained by the many different types of opioid receptor and the differing ability of individual opioids to interact with each type.

Buprenorphine

Buprenorphine is a semi-synthetic opioid derived from thebaine. Its chemical structure is typically opioid, but a particular feature is the C-7 side-chain containing a t-butyl group, which contributes to its overall lipophilicity. It binds to μ-opioid, κ-opioid, δ-opioid and nociception (ORL-1) receptors. Although the actions at these receptors have not been fully characterised, buprenorphine is regarded as a partial agonist at the μ-opioid receptor and as an antagonist at the κ-opioid and δ-opioid receptors.[9]

The potency of buprenorphine is 25–30 times that of morphine.[10] In clinical practice it functions as a pure μ-opioid receptor agonist,[11,12] with no flattening of the dose–response curve for analgesia at less than 100% effect. Although a 'ceiling effect' for analgesia has never been demonstrated in humans, the dose–response curve for respiratory depression has been shown to be bell-shaped.[13,14] Recent animal studies have shown that buprenorphine exerts full analgesic efficacy and potent antinociceptive, antihyperalgesic and antiallodynic actions.[15]

The strong avidity of buprenorphine for opioid receptors influences the drug's pharmacological profile. The slow dissociation of opioid and receptor contributes to its long duration of action and the rarity of withdrawal symptoms. As buprenorphine produces effective analgesia at relatively low receptor occupancy (5–10%),[16] the degree of analgesia is not directly related to plasma concentration.[17] The drug is metabolised in the liver by cytochrome P450 (CYP) enzymes, mainly CYP3A4, to inactive and weakly active metabolites. However, the low plasma concentration at therapeutic doses means that clinically significant inhibition of CYP3A4 or other cytochromes in patients is unlikely.[18,19] Metabolites are excreted predominantly via the biliary system.

The physicochemical properties of buprenorphine (high lipid and water solubility, low molecular weight [467] and low melting point) make it an excellent candidate for transdermal administration.[12] Patches that incorporate buprenorphine into the adhesive polymer matrix are widely available with release rates of 35, 52.5 and 70μg/h (equivalent to total daily dosages of 0.8, 1.2 and 1.6mg, respectively). These need to be replaced after 72 hours. A low-dose product with release rates of 5, 10 and 20μg/h and an extended application period of seven days has recently been

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introduced, but is currently available in only a few countries. All of these patches can theoretically be divided in order to reduce the continuously released dose and allow precise titration. The simple self-application process can be managed even by patients whose manual dexterity is limited.

Benefits of Transdermal Buprenorphine in Treating Cancer Pain

The transdermal formulation offers several advantages over traditional routes of administration. These include non-invasive delivery and rate-controlled release, ensuring constant and predictable plasma levels over a prolonged period and eliminating the need for more frequent dosing.[20] Stable plasma concentrations avoid the 'saw-tooth' effect of intermittent dosing with its attendant risks of adverse effects from the plasma peaks and inadequate analgesia from the plasma troughs. The transdermal approach is particularly useful when oral administration is difficult or precluded, for example, in patients experiencing nausea and vomiting, mucositis or tumours of the head and neck. The ease of use and greater convenience of this route, even for elderly and infirm patients, also means that compliance is significantly better than with oral, intramuscular or intravenous medication.[21,22]

Transdermal buprenorphine therefore complies with WHO requirements for non-invasive administration, avoidance of analgesic peaks and troughs, consistent pain relief and improved quality of life.[4] It fits well on the WHO pain ladder, notably on step 2 (20–30mg of oral morphine equivalents) and, in its medium dose range, on step 3 (60–180mg of oral morphine equivalents). Indicated for moderate to severe cancer pain, it demonstrates a full analgesic effect over the complete pain continuum in patients with malignancy. Treatment can be started at a very low dose and titrated upward, even for very severe pain. In a study to evaluate the efficacy and safety of buprenorphine, a large proportion of patients with severe, chronic cancer pain who had been receiving 90–150mg of oral morphine per day were effectively treated with a 70µg/h patch during the run-in phase.[23]

Cancer pain has a significant neuropathic element in more than 30% of cases, the dominant feature of which is central sensitisation of the pain pathway. Studies have indicated that neuropathic pain is relatively insensitive to typical µ-opioid analgesics such as morphine.[24] In contrast, buprenorphine has demonstrated efficacy in treating neuropathic pain and pain with a substantial neuropathic component, resulting from various conditions,[25–27] sometimes when other opioids proved ineffective.[28] One possible explanation is that buprenorphine, unlike other µ-opioid agonists, induces lasting antihyperalgesic effects.[29]

Long-term treatment with opioids can induce tolerance, so that higher doses are necessary over time to achieve the same level of analgesia.[8] With buprenorphine, the risk of tolerance is low. Prolonged administration of sublingual buprenorphine (0.4–3.2mg per day) has been shown to provide effective analgesia with a relatively slow escalation in dosage,[30,31] and 134 cancer patients in three clinical trials of transdermal buprenorphine extended their treatment for up to six years in an open-label study that demonstrated continuing efficacy and safety.[32–34] A post-marketing surveillance study involving 13,179 patients (of whom 3,690 were suffering from cancer) found no indication of tolerance over a 10-week period.[35]

The risk of drug–drug interactions with transdermal buprenorphine is also low. This is an important factor when treating cancer patients, who may be receiving many different medications. In particular, no problems have been encountered in clinical trials when switching to and from buprenorphine patches and other opioids, allowing opioid rotation in order to improve pain management. It is also possible to combine buprenorphine with other analgesics, such as morphine, fentanyl or tramadol, to control breakthrough pain.

Transdermal buprenorphine is well tolerated and the incidence of constipation, in particular, is very low. The post-marketing surveillance study reported a constipation rate of 0.97%,[35] whereas another study on long-term performance in chronic pain recorded a rate of 3.8%.[36] This contrasts with studies on transdermal fentanyl[37] and morphine,[38] in which constipation rates were markedly higher and constipation was the most frequent persistent adverse effect.

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The safety profile of transdermal buprenorphine is advantageous. A ceiling effect for respiratory depression has been demonstrated at ~50% of baseline with doses >2mg/kg, and this response can be fully reversed by naloxone infusion.[39] Morphine, fentanyl and other opioids suppress the immune system, modulating both innate and acquired immune responses and altering resistance to infectious agents.[40] This is particularly important in cancer patients, whose immune systems may already be depressed by malignancy and/or cytotoxic therapy, and because it may also hasten metastatic spread. Opioids differ in their immunomodulatory effects, however. Recent research indicates that buprenorphine is devoid of any immunosuppressive effects and may be protective of immune responses.[41] Biliary excretion means that the pharmacokinetics of buprenorphine, unlike opioids such as morphine and codeine, change little in renal failure. Patients with renal impairment may therefore safely receive it.[42]

Clinical Trials of Buprenorphine for Cancer Pain

Before the introduction of the transdermal formulation, the benefits of sublingual and transdermal buprenorphine in treating cancer pain had been demonstrated in many cohort studies and small randomised trials. Pain relief was achieved by doses of 0.15–3.2mg, with most patients receiving between 0.8 and 1.6mg/day.[43] Adverse events were similar to those produced by other opioids. Tolerance to these adverse effects developed with prolonged use.

In a study comparing five different opioids in the treatment of moderate cancer pain, 245 patients were started on a dosage of sublingual buprenorphine 0.2mg/day.[44] Pain relief in this group rose to 50% by the final week of the four-week study. Over the same period, pain intensity was significantly reduced at a mean maximum dosage of 0.6mg/day. Adverse events and dosing trends were similar for all five opioids. Two small-scale studies found that sublingual buprenorphine produced

better relief from cancer pain and fewer adverse effects than pentazocine.[45,46] When a multicentre trial compared sublingual buprenorphine 0.2mg every six hours with sustained release tramadol 100mg every eight hours in 131 cancer patients whose pain could no longer be controlled by non-steroidal anti-inflammatory drugs, both drugs rapidly reduced the severity of pain and produced a similar incidence of adverse events.[47]

In three randomised, double-blind, placebo-controlled trials, transdermal buprenorphine was shown to be an effective analgesic against severe to very severe chronic pain, reducing pain intensity and increasing the duration of pain-free sleep.[32–34] The incidence of adverse events was similar in the placebo and active treatment groups. No problems were encountered in switching to buprenorphine from other opioids, including morphine and tramadol. Of the 134 cancer patients in these trials, 86.6% rated their pain relief as complete, good or satisfactory. A Spanish study investigated the efficacy of transdermal buprenorphine in 164 patients suffering from various types of malignancy including lung, colon, breast and laryngeal cancer.[48] The dosage was titrated against pain, and stable doses were achieved after four weeks, when the mean score on a visual analogue scale (0–10) had dropped from higher than seven to lower than four. Initially, adverse events were relatively frequent, but the number gradually decreased to a level found with other opioids, and the incidence of constipation was less than 10% over the entire study period.

The efficacy and safety of transdermal buprenorphine (70µg/h) in 289 opioid-tolerant patients with severe cancer pain was investigated in a randomised, multicentre, double-blind, placebo-controlled study.[23] Patients who were successfully treated with buprenorphine during a 14-day run-in phase were randomised to receive either active medication or placebo patches during the 14-day double-blind phase. Rescue medication (sublingual buprenorphine 0.2mg) was allowed throughout the study. The superior efficacy of buprenorphine during the double-blind phase was statistically significant, despite the high placebo effect of the patch, and was confirmed by secondary parameters such as pain intensity and consumption of rescue medication. Adverse events were comparable in the two groups (30.9 versus 25.3%), but nausea and vomiting were more common in the placebo group, and the incidence of constipation in the buprenorphine group was low (9.6%).

An open-label study of patients who had suffered from chronic cancer pain for at least one year compared the analgesic activity of transdermal buprenorphine 35µg/h with that of sustained-release morphine 60mg/day.[1] In the event of inadequate pain control, patients in both groups could take oral tramadol as necessary, up to a maximum of 200mg per day. Patients receiving buprenorphine reported significantly better scores for physical pain (p=0.01), mental health (p=0.001), vitality (p=0.001) and interference with sleep (p=0.001) than those in the morphine group. The incidence of adverse events was also lower in the buprenorphine group, and in the case of nausea, vertigo and constipation the difference was statistically significant. These data indicate that buprenorphine was more effective in controlling cancer pain and produced a greater improvement in quality of life.

Two recent trials have confirmed that no conflicts exist between morphine and buprenorphine. In the first study, patients (21% with cancer) receiving high-dose morphine (>120mg/day) were switched to transdermal buprenorphine because of inadequate analgesia and severe adverse effects.[49] This resulted in better pain relief and high dose stability. In the second study, intravenous boluses of morphine were highly effective (a reduction of >33% within 15 minutes) in combating breakthrough pain in 29 cancer patients whose basic analgesic regimen was transdermal buprenorphine.[50]

Conclusion

Transdermal buprenorphine can be used successfully in the management of cancer pain. The German post-marketing surveillance survey clearly demonstrated that doctors already use this modality in cancer patients. In this study it provided effective, sustained and dose-dependent analgesia (irrespective of age) in 3,690 cancer patients (28% of the study population). Most of the patients were elderly (44% were aged >70 years), reflecting the general population of chronic pain patients. Increasing experience should firmly establish this valuable analgesic option and help to counter the current underprescription of opioids for cancer pain. ■

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European Oncology Nursing Society (EONS)

INTRODUCTION

The European Oncology Nursing Society (EONS) has provided support to cancer nurses across Europe since 1984. The mission of EONS is to add value to the work of its individual members and national societies in delivering care to patients with cancer. It aims to assist in the promotion of healthy communities through influencing, research and education.

The changing landscape of cancer management in relation to cancer treatments, new technologies, psychosocial care and health care provision has meant a significant shift in the way nurses apply their clinical skills and knowledge in the workplace. However, the professional development and status of cancer nurses across Europe is not uniform and EONS strategic agenda (CARE) aims to address this inequality by working with oncology nurses through their national societies.

CARE encompasses four bodies of work:

C Communication
A Activities for the Political agenda
R Research
E Education

STRATEGIC PRIORITIES

Communication

Communicating with and to oncology nurses across Europe remains a challenge. Developing diverse communication pathways is complex and EONS is committed to doing this by continuing to produce and distribute (through the national societies) a newsletter four times a year. The EONS website (part of Cancerworld) is an established forum for cancer nurses and EONS will be developing multi-language sections within the site as well as options for interactive forums to promote professional discussion, information and networking. The European Journal of Oncology Nursing continues to be one of the leading cancer journals and celebrated 10 years of publication in 2006.

Political Agenda

EONS is one of the professional cancer societies that form part of the umbrella organisation renamed ECCO in 2007 (European CanCer Organisation) previously known as FECS – Federation of European Cancer Societies. The organisation provides a collective political voice in Europe. EONS is also a member of the European Specialist Nurses Organisation (ESNO) which consists of associations from both European Nursing Specialist and Nursing Interest Groups. The organisation acts as a platform to represent nursing in the wider political forum.

Research

Promoting evidence based clinical practice through research has always been a core function of EONS. Various grants are distributed through EONS to promote and facilitate research initiatives. One of the priorities is to develop a European cancer nursing research network which will enable wider collaboration, participation and sharing of research evidence as well as build a body of research and development expertise.

Education

The themes as priorities in education are to develop cancer nurse educators to develop and accredit teaching programmes which have education quality standards as part of the review process. Inequality in accessing post-registration cancer nursing education exists across Europe. Alongside this work is the commitment to develop specialist education and leadership programmes which can be viewed in **www.cancerworld.org/eons**

Notwithstanding the busy agenda the patient experience lies at the heart of the CARE Strategy. By utilising and working in collaboration with patients, EONS will continue to provide a unique contribution to the agenda of cancer care in Europe, whilst promoting the unique contribution of cancer nursing in this processs.

For more information on EONS, please contact the secretariat at

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