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The Use of High Dosages of Transdermal Buprenorphine for Pain Management in Palliative Cancer Patients: A Case Study

Paul M.J. Clement[a, b] Benoit Beuselinck[b] Karen Van Beek[a, b]
P. Georgette Mertens[b] Paul Cornelissen[b] Johan Menten[a, b]

[a]Department of Oncology, KU Leuven, and [b]Leuven Cancer Institute, Leuven, Belgium

Key Words
Cancer pain · Palliative cancer · Transdermal buprenorphine

Abstract
Pain is a prevalent condition in patients with cancer, particularly in advanced stages of cancer. Although strong opioids are the mainstay of cancer pain management protocols, patients are often undertreated. Transdermal buprenorphine is currently available for the treatment of moderate to severe cancer pain and severe pain which does not respond to nonopioid analgesics; patch doses of 35, 52.5 and 70 μg/h are available (applied for up to 96 h), with no more than 2 transdermal patches at the same time, regardless of the strength. To date, there are no published reports in the literature of the use of high-dose transdermal buprenorphine (>140 μg/h). Herein, we present 2 cases of palliative cancer patients who received transdermal buprenorphine at doses titrated up to 210 and 175 μg/h, respectively, for the management of pain. Transdermal buprenorphine titrated to doses >140 μg/h provided adequate pain control and was well tolerated. Future studies to confirm these initial observations are warranted.

Introduction

Pain is a common and clinically relevant symptom of cancer, particularly with advanced stage cancer [1–3]. According to the WHO three-step approach to the management of cancer pain, administration of the right drug in the right dose at the right time should be 80–90%

Paul M.J. Clement, MD, PhD
Department of Oncology
KU Leuven, Herestraat, 49
BE–3000 Leuven (Belgium)
E-Mail paul.clement@uzleuven.be

effective [4]; however, it is widely accepted that pain control in palliative cancer patients is often inadequate [1].

The use of strong opioids is recommended for the management of pain in palliative cancer patients [4]. Buprenorphine, a μ-opioid receptor agonist and κ-opioid receptor antagonist, binds with high affinity to both receptors [5]. Previous concerns about a possible analgesic 'ceiling effect' with buprenorphine have since been questioned. In fact, buprenorphine displays a ceiling effect for respiratory depression, which is a positive safety characteristic [5]. A transdermal buprenorphine patch (Transtec®) is available in three patch strengths: 35, 52.5 and 70 μg/h, corresponding to buprenorphine 0.8, 1.2 and 1.6 mg/day, respectively [6, 7]. The drug is released from the patch for up to 96 h [6].

The efficacy and tolerability of transdermal buprenorphine are well established in patients with chronic cancer pain [8–10]. The results of these trials have been confirmed in large postmarketing surveillance studies in a clinical practice setting [11, 12] and retrospective pharmacoepidemiological studies [13, 14]. Transdermal buprenorphine is currently approved for the treatment of moderate to severe cancer pain and severe pain which does not respond to nonopioid analgesics, at patch strengths (no more than 2 transdermal patches, regardless of the strength, should be applied at the same time) of 35, 52.5 and 70 μg/h, for up to 96 h [7].

The current case study presents data for 2 palliative cancer patients who received transdermal buprenorphine at doses >140 μg/h, in excess of currently recommended dosages, for the management of cancer-related pain.

Case Study

Individual data for the 2 patients are presented in table 1.

Case 1

A 77-year-old female (height: 161 cm; weight: 31 kg; body mass index: 14.66) was hospitalized in the Department of Oncology and Palliative Care, University Hospital Leuven, in November 2008. The patient had bladder cancer with retroperitoneal lymph node metastases.

Pain management initially consisted of paracetamol 1 g four times daily and transdermal fentanyl 150 μg/h. The patient was also receiving laxatives. Pain relief was unsatisfactory with a numerical rating scale (NRS) score of 8 (on a 0–10 scale, where 0 = no pain, 10 = worst imaginable pain). She was subsequently switched to transdermal buprenorphine 140 μg/h (day 1). The next day, after switching to buprenorphine, the NRS score remained at 8 and the transdermal buprenorphine dose was increased to 210 μg/h (day 2). The NRS score decreased to 2.

The patient started treatment with as-needed subcutaneous morphine 30 mg for breakthrough pain. This dose was gradually increased to 120 mg. Over a period of 18 days, the mean daily dose of morphine as rescue medication was <100 mg. The patient was then switched to the subcutaneous administration of morphine 260 mg/day by means of an automated pump. The patient died 9 days later.

Case 2

A 72-year-old male patient (height: 173 cm; weight: 73 kg; body mass index: 24.39) was hospitalized in the Department of Oncology and Palliative Care, University Hospital Leuven, in November 2008. The patient had a neuroendocrine tumor and metastases in the liver and

bone. He initially reported an NRS score of 2, but clinical observation indicated considerable pain-related discomfort. During hospitalization the patient was observed continuously by the nursing staff and, although he did not report a high NRS score during the course of treatment, at several time points his behavior indicated a high degree of pain-related discomfort, which was the basis for the decision to increase the dose of analgesics.

Pain management was initiated with transdermal buprenorphine 35 μg/h, which provided satisfactory pain relief for 21 days (days 1–21). At the start of buprenorphine treatment, the patient reported nausea and constipation. He received laxatives for the entire treatment period.

After 3 weeks, the patient demonstrated increased pain and the transdermal buprenorphine dose was increased to 70 μg/h (days 22–26). Four days later the buprenorphine dose was increased further to 105 μg/h (days 27–34) and, 2 weeks later, to 140 μg/h (days 35–55). At this time, the patient also received sublingual buprenorphine for breakthrough pain at a progressively increasing frequency over a 20-day period. Following this time period, transdermal buprenorphine was increased to 175 μg/h (days 56–123). Subcutaneous morphine was used for the control of breakthrough pain; over a 68-day period the patient required rescue analgesia at a dose of 20 mg on average once every 3 days. In the terminal phase, a continuous subcutaneous infusion of morphine at 80 mg/24 h (days 123–125) was administered in addition to buprenorphine.

Discussion

In advanced cancer, up to about half of all patients undergoing palliative anticancer treatment experience pain [1]. Yet, for many patients, cancer-related pain is often undertreated [15].

This case study presents data relating to 2 cancer patients undergoing palliative care who successfully received higher than currently recommended maximum dosages of transdermal buprenorphine for pain management. The highest dosage of transdermal buprenorphine used in these 2 patients was 210 and 175 μg/h, respectively. The observation that adequate pain control, with minimal adverse effects, was achieved in these 2 patients, who received transdermal buprenorphine up to 210 μg/h, supports the hypothesis that dose titration of transdermal buprenorphine above 140 μg/h can be clinically effective and well tolerated.

The observation of pain control with transdermal buprenorphine up to 210 μg/h also challenges the assumption of a buprenorphine ceiling effect in the clinical setting, in line with an expert panel opinion relating to the analgesic action of transdermal buprenorphine [5, 15]. Indeed, despite the fact that a ceiling effect was reported in several preclinical animal models with buprenorphine [5], a consensus group agreed that buprenorphine behaves as a full μ-opioid agonist for analgesia and that a ceiling effect is only clinically relevant for respiratory depression (thus reducing the likelihood of this potentially fatal adverse event) [5]. However, as the current anecdotal evidence is only based on experience obtained with 2 patients in a non-interventional setting, it would benefit from confirmation in an interventional clinical trial setting (large prospective cohort studies, for example), with a larger sample size. Moreover, another potential limitation of the current case study is the fact that, in the absence of an objective way of assessing pain, treatment success was assessed through subjective evaluation by the healthcare practitioner and patient.

Consensus criteria for selecting analgesics for the treatment of cancer pain were recently reviewed by an expert panel and, although efficacy (which is dependent on whether the

pain is of nociceptive, neuropathic or mixed origin) is the most important factor, other aspects include individualized treatment to suit the patient, cultural influences (e.g. fear of opioid use), pain intensity, comorbidities, ease of titration and dose flexibility, and knowledge of pretreatment [15]. The general failure to control cancer pain can possibly be attributed to poor control of the neuropathic component. Transdermal buprenorphine has demonstrated a beneficial analgesic effect in patients with chronic neuropathic, nociceptive and cancer-related pain [13, 14].

In summary, we describe 2 patients undergoing palliative cancer treatment who received successful analgesic medication with transdermal buprenorphine at doses up to 210 μg/h. Whilst we acknowledge that these clinical observations are based on only 2 patients and, therefore, should not be overstated, these findings provide initial evidence that transdermal buprenorphine >140 μg/h could provide effective pain relief and is well tolerated. A clinical study to confirm these initial observations is warranted.

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Table 1. Individual data for 2 patients who received transdermal buprenorphine >140 µg/h

Patient	Gender/ age	Body mass index	Cancer diagnosis	Initial pain medication	Initial pain score (NRS)	Maximum transdermal buprenorphine dose (duration)	Rescue medication	Post-treatment NRS score	Adverse effects
1	Female/ 77 years	14.66	Bladder cancer with retroperitoneal lymph node metastases	Paracetamol ≤1 g 4 times daily, transdermal fentanyl 150 µg/h	8	210 µg/h (18 days)	Morphine s.c. (mean daily dose: <100 mg)	2	None
2	Male/ 72 years	24.39	Neuroendocrine pancreatic cancer with liver and bone metastases	Transdermal buprenorphine 35 µg/h	2*	175 µg/h (68 days)	Morphine s.c. (mean dose frequency: 20 mg once every 3 days)	NA	None

NA = Not available; s.c. = subcutaneous. * Clinical observation indicated considerable pain-related discomfort.