Research Letter

Low Doses of Transdermal Buprenorphine in Opioid-Naive Patients With Cancer Pain: A 4-Week, Nonrandomized, Open-Label, Uncontrolled Observational Study

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ABSTRACT

Objective: The aim of this study was to evaluate the effect and tolerability of low doses of transdermal (TD) buprenorphine patches in opioid-naive patients with cancer pain.

Methods: This was a nonrandomized, open-label, uncontrolled study in consecutive opioid-naive patients with advanced cancer and moderate pain. TD buprenorphine was initiated at a dose of 17.5 μg/h (0.4 mg/d), with patch changes every 3 days. Doses were then adjusted according to the clinical response. Pain intensity, opioid-related adverse effects, TD buprenorphine doses, and quality of life were monitored over 4 weeks. The time to dose stabilization and indexes of dose escalation were also calculated.

Results: Thirty-nine consecutive patients completed all 4 weeks of the study. Low doses of TD buprenorphine were well tolerated and effective in these opioid-naive patients with cancer pain. Pain control was achieved within a mean of 1.5 days after the start of TD buprenorphine therapy. The mean TD buprenorphine dose was significantly increased from baseline beginning at 2 weeks after the start of therapy and had doubled by 4 weeks ($P < 0.05$). Pain intensity was significantly decreased from baseline beginning at 1 week and continuing through the remaining weekly evaluations ($P < 0.05$). The mean buprenorphine escalation index, calculated as a percentage and in milligrams, was 41.2% and 0.2 mg, respectively. Quality of life improved significantly over the study period ($P = 0.007$). There were no significant changes in opioid-related symptoms between weekly evaluations.

Conclusion: Observations from this study suggest that randomized, controlled, double-blind studies of TD buprenorphine 17.5 μg/h in opioid-naive patients with cancer pain may be warranted. (*Clin Ther.* 2009; 31:2134–2138) © 2009 Excerpta Medica Inc.

Key words: cancer pain, opioids, buprenorphine, morphine.

INTRODUCTION

Management of cancer pain is based on the World Health Organization (WHO) analgesic ladder, which consists of 3 steps that correspond to drugs with increasing potencies—nonopioids (aspirin and paracetamol [acetaminophen]), mild opioids (codeine), and strong opioids (eg, morphine).[1] Some have questioned the role of mild opioids in the management of moderate cancer pain, hypothesizing that step 2 of the analgesic ladder might be bypassed.[2] Low doses of morphine and oxycodone have been reported to be effective and well tolerated in opioid-naive cancer patients with moderate pain.[3–5]

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Use of transdermal (TD) buprenorphine has been studied as a replacement for both weak and strong opioids.[6] This research letter provides some observations from a nonrandomized, open-label, uncontrolled study of TD buprenorphine patches 17.5 μg/h in opioid-naive patients with cancer pain.

PATIENTS AND METHODS

A nonrandomized, open-label, uncontrolled observational study was conducted in a sample of consecutive opioid-naive patients with advanced cancer, moderate cancer pain (score >4 on a scale from 0 to 10), and a Karnofsky score ≥50. Written informed consent and institutional approval were obtained. Exclusion criteria were poor renal or hepatic function, a history of drug abuse, cognitive impairment, and expected survival of <3 months.

The initial dose of TD buprenorphine was 17.5 μg/h (0.4 mg/d), with patch changes every 3 days. Oral morphine doses of 5 mg were allowed for breakthrough pain. The TD buprenorphine dose was adjusted every 2 to 3 days—first to 35 μg/h, then to 52.5 and 70 μg/h. Adjuvant symptomatic drugs were used according to clinical need and department policy. Patients were visited or contacted at least weekly for adjustment of therapy based on the clinical response.

Study measures were recorded at baseline (T0) and at 1 week (T1) and 4 weeks (T4) after the start of therapy. Pain intensity was rated by patients on a numerical scale from 0 = no pain to 10 = worst pain imaginable. The presence of opioid-related adverse effects or symptoms associated with advanced cancer (ie, nausea and vomiting, drowsiness, confusion, and dry mouth) were rated by patients using the following scale: 0 = not at all, 1 = slight, 2 = a lot, and 3 = severe. Constipation was rated by physicians using the following scale: 0 = stool in the previous 24 hours, 1 = stool in the previous 2 days, 2 = stool in the previous 3 days, and 3 = stool in the previous ≥4 days or need for an enema. Quality of life was measured using the validated Spitzer score,[7] which includes 5 items (activity, daily living, health, support, and outlook), each rated from 0 to 2, for a maximum score of 10.

The time to dose stabilization was calculated as the number of days to achievement of pain control (pain intensity score <4) with acceptable tolerability. The buprenorphine escalation index (EI) was calculated at T4, both as the mean percent increase in the TD buprenorphine dose from the starting dose and as the mean milligram increase in the TD buprenorphine dose. The EI for the mean percent increase was calculated using the following formula: ([buprenorphine maximal dose – buprenorphine starting dose]/buprenorphine starting dose)/days × 100. The EI for the mean increase in milligrams was calculated using the following formula: (buprenorphine maximal dose – buprenorphine starting dose)/days. The latter formula has been used in a previous study of low doses of morphine in opioid-naive cancer patients.[3]

The presence of pain syndromes (nociceptive, neuropathic, or mixed mechanism) was evaluated based on the clinical history, anatomic sites of the primary tumor and distant metastases, physical examinations, and investigations such as computed tomography and nuclear magnetic resonance imaging, when necessary.

Statistical Analysis

Frequency analysis was performed using the χ^2 test. The Wilcoxon signed rank test was used to compare scores for pain intensity and symptom intensity in the 4 weekly periods, and the paired *t* test was used to compare mean opioid doses in the 4 weekly periods. One-way ANOVA was used to evaluate differences in pain mechanisms and buprenorphine EI (as a percentage and in milligrams) between primary cancers. *P* values <0.05 were considered statistically significant.[8]

RESULTS

Of the 40 patients originally included in the study, 1 was excluded from the analysis due to incomplete data. The mean (SD) age of the remaining 39 patients was 67.2 (11.9) years. Twenty-two patients were males and 16 were aged >70 years. The primary cancers were gastrointestinal (12 [31%]), breast (8 [21%]), lung (6 [15%]), genitourinary (4 [10%]), and other (9 [23%]).

Twenty-four patients were followed for all 4 weeks of the study. Two patients required alternative treatment (other opioids and/or routes of administration) because of an unfavorable balance between analgesia and adverse effects (vomiting and uncontrolled pain), and 4 were poorly compliant with TD buprenorphine therapy. The remaining 9 patients were lost to follow-up.