
REPORTS

Administration of Buprenorphine by Continuous Subcutaneous Infusion: Three Case Reports with Commentary

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ABSTRACT. Due to the risks associated with permanent central venous access, and disadvantages of repetitious intramuscular injections, continuous subcutaneous infusion of buprenorphine was attempted in three patients with chronic pain not responsive to more traditional medication regimens.

Buprenorphine is a highly lipophilic opioid analgesic which exhibits opioid antagonist activity. It is indicated for moderate to severe pain by intramuscular or intravenous injections administered every four to six hours. Three chronic pain patients who were unresponsive to pure opioid analgesics, administered either orally or parenterally, but who responded favorably to intramuscular injections of buprenorphine, were evaluated for administration of buprenorphine via

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continuous ambulatory infusion pump. Potential serious side effects were avoided without the complexities of chronic central venous access. Adequate pain control was achieved in patients previously unresponsive to conventional therapies. Quality of life was improved.

Continuous subcutaneous administration of buprenorphine resulted in convenient, safe, efficacious and cost-effective pain management.

KEYWORDS. Buprenorphine; Continuous subcutaneous infusion; Partial agonist opioid

INTRODUCTION

Buprenorphine is an opioid partial agonist analgesic which has high affinity and low to moderate intrinsic activity at mu and kappa opioid receptors.^{1,2} At higher doses, the drug appears to have some antagonist activity at opioid receptors. Due to high lipid solubility, the drug is unreliably absorbed from intermittently injected subcutaneous sites. The only U.S. Food and Drug Administration (FDA) approved routes of administration are intravenous and intramuscular.³

Chronic malignant pain often can be effectively managed with intermittent intravenous or intramuscular injections, or by continuous intravenous infusions.⁴⁻⁶ These routes of administration are not devoid of complications and may not be altogether convenient. Long term intermittent intravenous injections require the use of long term central venous access devices such as peripherally inserted central catheters (PICC line), right atrial catheters (Hickman,[®] Broviac,[®] etc.), or infusion port devices (Port-a-cath,[®] Infusa-port,[®] etc.), all of which require specific care protocols.⁷⁻⁹ Furthermore, peri-dose saline flushing and post-dose heparinization are required to maintain patency of the access device.¹⁰ Breaks in central line integrity through multiple intermittent injections subject the patient to potentially serious or life threatening complications such as line sepsis.⁷

Intermittent intramuscular injections may be painful and require that the patient has adequate muscle mass to withstand multiple injections. Repetitious injections over extended time periods lead to scar tissue formation and risk of sterile abscess development.¹¹

Many reports are available to support the use of opioids by continuous infusions for management of chronic pain. In view of the aforementioned disadvantages of intermittently administered parenteral agents, a methodology was developed for providing continuous subcutaneous infusions of buprenorphine to three patients utilizing ambulatory infusion pumps and Baxter #IM8463 subcutaneous infusion sets.

At the Stratton Department of Veterans Affairs Medical Center, a pharmacy-based pain management service is operated on a consult basis. Written evaluation, assessment and management recommendations are provided by a clinical pharmacist, certified in pain management by the American Academy of Pain Management. Medical, surgical, psychiatric, nursing and social work support are provided as necessary, in a multidisciplinary approach to chronic pain management.

CASE #1

T.W. is a 41 year old white male who was referred, by consult, to the clinical pharmacy section for evaluation and management of chronic pain. His surgical history included L₅S₁ laminectomy/discectomy and excision of an L₃L₄ intradural fragment. The patient was diagnosed as having chronic unrelieved lower back pain with possible arachnoiditis. His social history included possible alcohol and narcotic abuse.

Upon evaluation, the patient was found to be lying in bed in the fetal position, incapacitated and in excruciating pain. He was receiving meperidine 150 mg intramuscularly every two hours, with no pain relief. A decision was made to use a longer acting agent since meperidine has an inappropriately short duration of action for chronic pain management. Additionally, long term use of meperidine would subject the patient to accumulation of nor-meperidine, a toxic metabolite. Due to a questionable alcohol/narcotic abuse history, it was felt that an opioid analgesic with opioid antagonist activity would be most suitable, because of less potential for physical dependency.²

Buprenorphine 0.3 mg IV push was administered as a STAT dose, followed by intravenous hydrocortisone sodium succinate 100 mg in 50 mL dextrose 5% injection, administered over twenty minutes. Pain was assessed based upon visual analogue scores with "10" representing the worst imaginable pain, and "1" representing no pain. Prior to receiving the initial doses, the patient rated his pain as "10." Within ten minutes of administration of the buprenorphine, significant pain relief was evidenced by a pain score of "2." We suspect that pain relief was primarily in response to buprenorphine since pain relief occurred prior to completion of hydrocortisone infusion and peak serum levels of buprenorphine occur within two minutes after intravenous administration.² Suppression of inflammation with intravenous corticosteroids usually occurs within twenty-four hours of infusion.¹² Subsequent therapy was begun with intravenous buprenorphine 0.45 mg in 50 mL dextrose 5% injection, every six hours and intravenous hydrocortisone sodium succinate 100 mg in 50 mL dextrose 5% injection, twice

daily. Since the patient was relatively young and significant toxicities are associated with chronic steroid use,¹³ hydrocortisone was tapered over seven days and discontinued. Oral tolmetin sodium 400 mg every eight hours was started to maintain anti-inflammatory effect. Physical therapy was initiated through Rehabilitative Medicine Service to enhance back muscle strength. Although the patient continued to experience some pain or discomfort, it was felt that this was due to physical exertion during therapy, of which he was previously incapable. After one week, the patient was discharged home with buprenorphine 0.45 mg intramuscularly every six hours, with follow-up care scheduled through Rehabilitative Medicine. Cranio-sacral therapy was initiated. After approximately one month of intermittent intramuscular injections, an attempt was made to convert the regimen to oral propoxyphene, with no success. To reduce the number of required injections, continuous subcutaneous buprenorphine in non-preserved normal saline, 0.15 mg/mL infused at 0.25 mL/hr was started in lieu of intramuscular injections. Verbal communication with the manufacturer of buprenorphine indicated a stability of the admixture of at least fourteen days. Infusion was provided via Parker Micropump® and subsequently changed to the Pharmacia-Deltec CADD PCA 5800® pump due to inability to procure micropump disposables. Subcutaneous sites were rotated every three days to reduce irritation. Cassette changes were initially made during clinic visits. Cassette changes were subsequently performed by the patient when it was apparent that no abuse attempts occurred. Visual analogue pain scores after one week were "5-6." Due to increased pain, the infusion rate was increased to 0.5 mL/hr with complete resolution of pain. Aggressive physical therapy was continued to strengthen back and leg muscles. The infusion rate and concentration of buprenorphine remained at these levels for seven months. A ten percent reduction in concentration was then instituted, while the infusion rate remained constant. The concentration was decreased by twenty percent every two weeks, and subcutaneous therapy was discontinued when the admixture contained only saline. No breakthrough pain occurred. The patient then was taking only oral tolmetin sodium 400 mg every eight hours, without significant pain. Initial adequate pain control allowed intensive physical therapy to strengthen muscles, and subsequent buprenorphine dosage reductions.

CASE #2

C.F. is a 51 year old white male with a complicated medical history which includes chronic pancreatitis secondary to cobalt radiation therapy for testicular carcinoma. Due to exocrine pancreatic insufficiency, minimally

managed with enzyme replacement therapy, and associated malabsorption with consequent weight loss, an Infus-a-port® was inserted for the purpose of home parenteral nutrition. He was admitted four times in a two month period for recurrent episodes of Staphylococcal septicemia. The venous access device was replaced because of inability to maintain sterility of the device. A decision was made to once again perform enteral alimentation, to avoid utilization of the central line if possible, and subsequent septic episodes. His first admission to the Stratton VA Medical Center occurred five months later after complaints of chronic incapacitating pain, which was unresponsive to either morphine or methadone. He also complained of increasing nausea and vomiting as doses were increased to achieve better pain control. A clinical pharmacy consult was requested for evaluation and management of chronic pain. Upon evaluation, the patient described pain consistent with chronic pancreatitis; however, he did not appear to be in significant discomfort. All previously ordered opioids were discontinued and buprenorphine 0.3-0.45 mg by deep intramuscular injection every six hours was ordered. The patient complained of inadequate pain control and the dose was increased to 0.45 mg intramuscularly, every four hours, with adequate pain control. Since maintaining chronic repetitious intramuscular injections in a patient with little muscle mass is difficult, a decision to change to continuous subcutaneous administration was made. Buprenorphine 0.3 mg/mL, infused at 0.3mL/hr was begun via Pharmacia-Deltec CADD-PCA 5800® pump after pain was controlled with repeated intramuscular injections. The patient was discharged two days later with adequate pain control. Upon follow-up in Nutrition clinic, the buprenorphine infusion rate was increased to 0.4 mL/hr due to increasing breakthrough pain. Episodic nausea and vomiting associated with chronic pancreatitis precluded rapid conversion to an oral agent. Continuous subcutaneous buprenorphine was continued for five months with no episodes of increased pain, nausea or vomiting. Subcutaneous infusion was subsequently converted to oral oxycodone/acetaminophen for maintenance pain control once episodes of nausea and vomiting subsided.

CASE #3

H.Z. is a 67 year old white male with a medical history significant for chronic back pain, non-insulin dependent diabetes mellitus, congestive heart failure, pulmonary embolus and multiple gastrointestinal and genitourinary disorders. His surgical history includes multiple T₃T₄ laminectomies. The onset of back pain was secondary to sustaining a gunshot wound to the dorsal thoracic region in 1944. In 1971, complications of

surgical laminectomy for intractable pain resulted in paraplegia. A cordotomy was performed in 1979, with several subsequent years of pain relief. Severe pain returned in 1988 in the thigh and buttock regions. Ibuprofen and oxycodone/acetaminophen therapy was initiated with moderate success and continued until September, 1989. Alternative therapy with intramuscular injections of 0.3 mg buprenorphine every six hours was started and the dose was titrated over the next several months until a dose of 0.3 mg every four hours maintained pain relief. In February, 1991, a clinical pharmacy consult was requested for evaluation and management of chronic pain. Continuous subcutaneous infusion of buprenorphine 0.3 mg/mL, infused at 0.4 mL/hr via Pharmacia-Deltec CADD-PCA 5800® pump was started due to breakthrough pain associated with intermittent intramuscular injections. The infusion rate was decreased to 0.3 mL/hr on May 21, 1991 due to tremulousness, probably unrelated to buprenorphine. Adequate pain relief was achieved. The patient was admitted in June, 1991 complaining of severe knee pain after falling from a wheelchair. A diagnosis of patellar fracture was made. One day after admission, the buprenorphine infusion was increased to the original rate of 0.4 mL/hr. Intramuscular ketorolac, 30 mg every six hours was started on the next day to treat inflammation secondary to fracture. Ketorolac was discontinued after several days. Chronic non-steroidal anti-inflammatory therapy was not pursued due to worsening renal function. The patient is currently maintained on buprenorphine 0.2 mg/mL at an infusion rate of 0.4 mL/hr by continuous subcutaneous infusion, with no complaints of pain. This regimen has been in effect for approximately two years with no complications.

DISCUSSION

Many factors must be considered when evaluating a chronic pain patient for continuous opioid infusion. Opioid partial agonists with opioid antagonist activity such as buprenorphine may be particularly suitable for the young chronic pain patient suffering from other than a terminal disease state, due to a lower potential for development of tolerance to these agents.² Buprenorphine has a low potential to induce drowsiness, respiratory depression, or euphoric effects.¹ Long-term peripheral venous access is difficult, if not impossible to maintain, and is not ideal for continuous infusions. Permanent central venous access is suitable for continuous infusion; however, placement of the catheter requires a surgical procedure. Dressing changes, catheter care supplies, nursing care and patient teaching

time add to the expense and complexity of providing continuous analgesic infusions, especially in the ambulatory outpatient.⁹

Buprenorphine is an opioid partial agonist indicated for moderate to severe pain administered by intermittent intramuscular or intravenous injections up to every six hours. While intermittent subcutaneous buprenorphine is ineffective for chronic pain management due to high lipid solubility,¹ continuous subcutaneous infusions may be an effective means of chronic pain management. Several authors have described continuous subcutaneous infusions with opioid/opioid agents other than buprenorphine.¹⁴⁻¹⁷ Buprenorphine was selected due to the previously mentioned advantages. Some chronic pain patients may be effectively managed with intermittent injections of buprenorphine; however, there are associated risks which may be minimized with continuous subcutaneous administration. Subcutaneous infusion poses no risk of central line sepsis, is more cost effective due to fewer necessary ancillary supplies such as heparin and saline flush solutions, and no surgical procedure is required. Ambulatory infusion devices are required to deliver drug continuously, regardless of route, i.e., intravenous vs. subcutaneous. Devices such as the Pharmacia-Deltec CADD-PCA 5800® pump are suitable for either type of delivery, and were used for all of these patients. The pumps have proven to be reliable and durable. Appropriately selected patients can be easily instructed in self-management of the infusion. The patients treated with continuous subcutaneous buprenorphine were selected on the basis of failure to achieve adequate pain control using conventional modes of opioid/opioid administration, i.e., intermittent injection or oral ingestion. Adequate pain control was achieved in these cases, with corresponding subjective improvement in quality of life. Few or no adverse effects were noted.

CONCLUSIONS

Continuous subcutaneous infusion of buprenorphine appears to be efficacious, convenient, safe and cost-effective for chronic pain management, based upon these limited experiences. The Pharmacia-Deltec CADD-PCA 5800® pump is reliable for this means of administration. Potentially serious complications of more invasive therapy may be minimized through subcutaneous administration. It appears that continuous subcutaneous buprenorphine is a useful alternative parenteral analgesic modality for both institutionalized patients and outpatients. Controlled studies comparing continuous subcutaneous buprenorphine to other standard therapeutic modalities would be beneficial.

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