Intravenous Buprenorphine: A Substitute for Naloxone in Methadone-Overdosed Patients?

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Administration of naloxone is a common treatment for opioid-dependent patients who present with respiratory depression. Although safe in opioid-naive patients, naloxone may cause severe and even life-threatening complications in opioid-dependent patients, including acute respiratory distress syndrome and myocardial infarction. It has been suggested that administration of buprenorphine, a partial μ-opioid receptor agonist, to an opioid-intoxicated patient may result in reversal of respiratory depression with less severe withdrawal signs and symptoms. In addition, the longer half-life of buprenorphine compared with naloxone may reduce the need for repetitive administration of antidote. We present a 20-year-old morphine-addicted man who presented with methadone-induced respiratory depression and responded safely and effectively to intravenous administration of buprenorphine. Buprenorphine may be a useful alternative opioid reversal agent for opioid-dependent patients. [Ann Emerg Med. 2017;69:737-739.]

INTRODUCTION

Buprenorphine is a partial agonist at the μ-receptor that is commonly used in treatment of opioid dependency and as an analgesic in opioid-naive patients. Because the binding affinity of buprenorphine at the μ-receptor is higher than that of most full-agonist opioids, buprenorphine acts as an antagonist of their opioid activity.1 The current approach for the treatment of patients with opioid-induced respiratory depression is the administration of naloxone. Although safe in opioid-naive patients, naloxone and naltrexone may cause severe and even life-threatening complications in opioid-dependent patients.2,3 Opioid overdose overall is currently a major public health concern. Methadone ingestion specifically remains a substantial problem in the United States and an increasing phenomenon in Iran because of an increased number of methadone maintenance therapy programs.4,5 For patients intoxicated with a long-acting opioid such as methadone, naloxone may be suboptimal because of its short half-life, which results in the recurrence of respiratory depression after the naloxone is eliminated.6 Patients may need ICU care for close monitoring of their respiratory status, and if a naloxone infusion is used, patients risk both unintentional discontinuation and overadministration of naloxone. Buprenorphine, a partial agonist, may cause fewer withdrawal signs and symptoms in opioid-dependent patients. Experimental studies using rats have shown promising results.6 We present a patient with opioid dependence who presented with methadone overdose and responded significantly to administration of buprenorphine.

CASE REPORT

A 20-year-old man presented to the emergency department (ED) with a history of ingesting 30 mL (150 mg) of methadone syrup, ten 20-mg fluoxetine capsules, and ten 2-mg clonazepam tablets approximately 2 hours earlier. En route to the hospital, emergency medical services personnel administered 0.4 mg of naloxone for apnea. In the ED, the patient was pale and awake but agitated and sweaty. Vital signs included a blood pressure of 150/90 mm Hg, pulse rate of 113 beats/min, respiratory rate of 14 breaths/min, and oxygen saturation of 91%. A venous blood gas analysis is shown in the Table. Considering that the patient was experiencing mild withdrawal, no additional naloxone was administered.

Because of a shortage in ICU beds, the patient was admitted to the toxicology ward for close observation, with cardiac, respiratory, and pulse oximetry monitoring. Approximately 2.5 hours later, his respiratory rate decreased to 6 breaths/min and oxygen saturation was 76% (blood pressure was 110/75 mm Hg and pulse rate was 110/min), and the patient was unresponsive and cyanotic. His Clinical Opioid Withdrawal Scale score was 14. A bolus dose of 0.6 mg of buprenorphine was slowly intravenously administered, after which the patient became conscious but remained calm. Although he still had diaphoresis, no other signs or symptoms of withdrawal were detected (Clinical Opioid Withdrawal Scale score decreased to 3). Cyanosis resolved and oxygen saturation increased to 98% (blood pressure was 120/78 mm Hg, pulse rate was 96 beats/min, and respiratory rate was 18 breaths/min).
On discharge 7.46 56.2 39.5 4.5 99
During naloxone drip (with mask) 7.33 81 42 6.3 90
28 h after buprenorphine administration (second episode of apnea) 7.20 103 40.1 9.2 87
12 h after buprenorphine administration 7.36 46.7 24.8 1.3 95
Time of administration of buprenorphine (2.5 h after admission) 7.29 66.4 22.3 1.7 76
On admission 7.33 51.4 25.5

The patient remained clinically stable, with normal vital signs and 2 normal venous blood gas analysis results until approximately 24 hours later, when respiratory depression recurred (Table).

Because the patient had developed apnea after the buprenorphine administration, we switched to conventional treatment with naloxone to try to prevent further respiratory depression, with administration of a standard therapy. An initial intravenous dose of 0.4 mg of naloxone was followed by a naloxone infusion at 0.2 mg/hour. However, he experienced moderate to severe withdrawal (Clinical Opioid Withdrawal Scale score of 26), mandating discontinuation of the naloxone drip. An hour later, a venous blood gas result showed respiratory acidosis, prompting reinitiation of the naloxone infusion at 0.1 mg/hour. This was continued for approximately 3 days, during which time the patient was minimally conscious and had mild respiratory acidosis. The dose of the naloxone infusion was titrated carefully, but the patient was either experiencing opioid withdrawal or worsening respiratory acidosis and hypoxemia. Finally, 3 days after initiation of naloxone therapy, the naloxone infusion was discontinued and near-normal vital signs and venous blood gas results were observed for at least 30 hours. A urine sample was positive for methadone and serum was positive for benzodiazepines. He was discharged home 5 days after admission, in normal condition.

DISCUSSION

Unlike naloxone, which is a full antagonist at opioid receptors, buprenorphine is a partial agonist. It can cause respiratory depression in opioid-naive patients, but can also cause a withdrawal syndrome in opioid-dependent patients.8 Our patient experienced reversal of respiratory depression without withdrawal. This may have occurred because in overdose, the opioid receptors are occupied and buprenorphine displaces the full agonist activity, preventing respiratory depression, with partial agonist activity while providing sufficient agonism to prevent withdrawal.7 The first report of using a partial agonist for reversing apnea was by sublingual administration of buprenorphine and naloxone to a patient with a heroin overdose.8 Subsequently, a patient with a heroin overdose survived after intravenous administration of a crushed sublingual tablet of buprenorphine and naloxone.9 Confirmatory drug tests were not available in these case reports.

Our case is an example of moderate to severe methadone poisoning. Buprenorphine was administered on the basis of these previous reports to a patient who developed recurrent opioid toxicity after the antagonist effects of naloxone waned. Buprenorphine proved useful initially to reverse the respiratory and mental status depression while limiting the development of opioid withdrawal. However, overdose signs and symptoms recurred after approximately 24 hours, which is expected, considering the 4- to 10-hour half-life of buprenorphine.10 A naloxone infusion was subsequently used, but the patient never tolerated the naloxone infusion well: he was either in withdrawal or had respiratory depression. This created a substantial management problem for our patient and it limited the treatment results with naloxone. Perhaps repetitive doses of buprenorphine would have been preferable and avoided the cyclic withdrawal and intoxication caused by the naloxone infusion.

We believe that buprenorphine may offer an alternative treatment for opioid-dependent patients who are sufficiently opioid intoxicated to require an antidotal therapy. Moreover, it may assist linking acute treatment of overdose with long-term treatment with buprenorphine and recovery from opioid addiction. The role of transmucosal buprenorphine, which is more readily available and easier to administer, requires additional consideration. Additional study to elucidate the possible role of buprenorphine in opioid-intoxicated and opioid-dependent patients is warranted.

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