INTRODUCTION

Analgesics have consistently remained the most common substance involved in human poisonings in the United States, with immediate action opioid analgesics associated with the greatest percent of fatalities per exposure. [1] Often current practice dictates that patients with presumed opioid overdose can be safely discharged one hour after naloxone administration if they meet certain criteria: 1) ambulate as usual; 2) have oxygen saturation on room air of >92%; 3) have a respiratory rate >10 breaths/min and <20 breaths/min; 4) have a temperature of >35.0°C and <37.5°C; 5) have a heart rate >50 beats/min and <100 beats/min; and 6) have a Glasgow Coma Scale score of 15. [2]

However, use of modified-release (MR) opioid products can lead to delayed toxicity following intentional overdose of MR opioid preparations. Protracted symptom onset and resultant clinical consequences have not been well described in the existing literature. The following two illustrative cases recently seen in our emergency department (ED) demonstrate that the early recognition and treatment of patients who have abused modified-release (MR) opioid products can be life-saving.

CASE REPORT

Case-1: A 20-year-old man with a medical history of drug and alcohol abuse came to the ED stating he ingested ten-100 mg tablets of morphine one-hour previously in a suicide attempt. It was not known at the time that the product was a modified-release opiate. On arrival the patient was sleepy but arousable and maintaining his airway. His vital signs: blood pressure 129/76 mmHg, heart rate 89 beats per minute, temperature 37.3°C, respiratory rate 16 breaths per minute, oxygen saturation of 96% on room air. Serum chemistries were within normal limits, ethanol, acetaminophen and aspirin concentrations were all negative. A urine drug screen was positive for cocaine and opioids. Throughout his six-hour observation period his vital signs were normal, he maintained good oxygen saturation, and did not require naloxone. Prior to transfer to a psychiatric ward, he was sitting up in bed talking and eating. Approximately six hours following ED discharge and subsequent admission to an inpatient psychiatry unit, the patient was found apneic and pulseless. Despite resuscitation attempts by the hospital staff, the patient died on hospital day 14 because of complications of prolonged hypoxia. Quantitative analysis of opiates in the urine by liquid chromatography-mass spectrometry revealed a free morphine concentration >5000 ng/ml, free codeine concentration 9.9 ng/ml, and free hydromorphone concentration 105 ng/ml.

Case-2: A 16, year-old-boy recently released from a psychiatric facility for a previous overdose attempt, was brought to the ED after ingesting an unknown amount of his father’s morphine. The patient was lethargic, oriented and had slurred speech. Vital signs: blood pressure 123/78 mmHg, heart rate 60 beats per minute, temperature 36.7°C, and respiratory rate 15 breaths per minute. His oxygen saturation was 99% on room air. The patient was given 2 mg of naloxone. This caused minimal improvement in mental status. Serum chemistries were within normal limits, ethanol, acetaminophen and aspirin concentrations were all negative. Approximately two hours later the patient’s systolic blood pressure had dropped into the 90’s with a heart rate of 50 beats per minute. He remained lethargic but was able to maintain
his airway. The patient was given a fluid bolus and transferred to a pediatric intensive care unit (PICU). Approximately nine hours following presentation the patient was awake, alert and oriented, with no evidence of respiratory insufficiency, normal vital signs, and had not required any naloxone since admission. The patient was medically cleared and awaiting admission to a psychiatric ward in the PICU under one-on-one observation. During that time, approximately six hours later, the patient had an apenic episode with his oxygen saturations dropping to 83%. The patient received 1 mg of naloxone and had an immediate improvement in his mental and respiratory status. Over the ensuing 15 hours, the patient required an additional three doses of naloxone. Later it was determined that the patient had ingested 15 tablets, 15 mg each, of a MR morphine preparation.

DISCUSSION

MR opioids, including MS Contin, Oramorph, Kadian, Avinza, Opana, Nucynta, Embeda and Oxycontin CR, have become an increasingly popular therapeutic option as they can minimize wide variations in analgesic plasma concentrations in patients with chronic pain. However the MR preparations have greater potential for delayed toxicity. Collins et al[3] observed that the mean time to peak plasma concentrations with once-daily morphine formulations was 8.5 hours (range: 4.0-11.4 hours). Contributing to this variability are the individualized immediate release opioid concentrations of various preparations, as well as the varying hydrophilic polymer, the type of hydrophobic matrix, and/ or their ratio.[4] Not all MR preparations have an immediate release component, and delayed toxicity may be particularly concerning with these formulations. The most common preparations with an immediate release component include Avinza and Oxycontin, and the early resolution of initial symptoms with those formulations may be misleading.

Because delayed toxicity is a reality, the decision making process regarding a patient care plan where MR opioid preparations are involved should include a prolonged observation period in a monitored unit even if there is apparent lack of symptoms of early clinical toxicity. We urge physicians to consider the possibility of these preparations being used in an overdose, particularly in patients with chronic pain and evidence of an intentional ingestion. Early identification of these patients and provision of extended observation may be life-saving.

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