

CASE REPORT



Use of nebulized naloxone to reverse methadone overdose – A case report and review of literature

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ABSTRACT

Opioid use is a frequent cause of morbidity and mortality in the USA. We report a case of methadone overdose reversed with naloxone nebulization. Peripheral IV access can be difficult to obtain in patients with a history of IV drug abuse making needleless routes of naloxone administration useful. When naloxone is administered as a bolus, chronically opioid dependent patients are more prone to violent withdrawal symptoms. When successful, nebulized naloxone reverses intoxication and allows the patient to self-titrate the discontinuation of naloxone when they are alert enough to remove the mask. Nebulized naloxone can provide needleless and noninvasive administration for the reversal of opioid overdose.

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KEYWORDS

Naloxone; opioid overdose; nebulized naloxone

1. Introduction

In 2017, the age-adjusted rate of drug overdose deaths in the USA was more than 3.5 times the rate in 1999, with the percentage of drug overdose deaths involving heroin triple the percentage in 2010 [1]. Naloxone a potent opioid μ -receptor antagonist can reverse opioid overdose. Traditionally, naloxone had been administered using an IV, IM or SQ route to reverse opioid toxicity. It has recently been approved for intranasal (IN) use to provide needleless, noninvasive administration for opioid overdose reversal. Patients with opioid overdose often have a history of IV drug abuse that can cause venous scarring, making IV access difficult. Also, IV, IM or SQ use of naloxone increases the risk of needle stick injury in the prehospital settings. Intranasal naloxone has been used in the prehospital settings, but its use is limited by lack of titration to patients' response, it can either precipitate withdrawals or produce an inadequate reversal response. Nebulization is a needleless, noninvasive route to administer naloxone to reverse opioid toxicity and some limited data supports its effectiveness. Here we present a case of methadone intoxication reversed with naloxone nebulization.

2. Case presentation

A 57 years old male with a past medical history significant for COPD, Hepatitis C, Opioid dependence on methadone maintenance therapy was brought to the emergency department by the emergency medical service personnel after ingesting double the quantity of

his usual methadone. Upon initial encounter, the patient was found to be lethargic, unresponsive to pain and having poor respiratory efforts (GCS 6 $E1V2M3$). He was given intra-nasal naloxone in the field leading to some improvement in his mental status (GCS 13 $E3V5M5$). He revealed that he had taken twice as much as his usual maintenance dose of methadone (70 mg was ingested, he was on 35 mg daily per the methadone maintenance program). He had been dispensed a two-day dose for the weekend and took both doses simultaneously.

Upon presentation to the Emergency Department (ED) vital signs included, pulse rate 84 beats/min, blood pressure 149/89 mmHg, respiratory rate 9 breaths/min, and SpO₂ on 6L nasal cannula 73%. Physical examination showed a pale and lethargic gentleman with shallow respirations not responding to vocal commands or pain (GCS 8 $E2V3M3$). Pupils were 2mm bilaterally and sluggishly responsive to light bilaterally. Lung auscultation revealed coarse breath sounds on the right hemithorax; cardiac auscultation was unremarkable, and there were no focal neurologic deficits. The patient was oxygenated with a non-rebreather mask, with SpO₂ only improving to 82%. An arterial blood gas sample was obtained and since opioid intoxication was evident, reversal with naloxone was attempted.

Initially, IV access was unobtainable because of venous scarring. Due to deteriorating clinical status 2mg naloxone was added to 5ml normal saline and administered using a standard nebulizer mask (the side ports were partially occluded with tape to decrease

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the escape of nebulized naloxone) while continued attempts to obtain IV access were being made in addition to preparation for endotracheal intubation. The arterial blood gas obtained upon arrival showed a pH of 7.20, pCO₂ 87 mmHg (baseline of 55 mmHg), PaO₂ 44 mmHg. After 4 minutes of the nebulization the respiratory rate improved to 22 breaths/min, SpO₂ increased to 100% on non-rebreather at 15 L/min and GCS improved to 15. After about 20 minutes of nebulization, the patient started yawning and became more alert, but no other signs of opioid withdrawal were observed. Repeat arterial blood gas showed pH 7.30, pCO₂ 60 mmHg, and PaO₂ 72 mmHg; EKG showed a QTc of 530 milliseconds, urine toxicology screen was only positive for methadone, chest X-ray, and other labs were unremarkable. After 50 minutes the SpO₂ dropped to 85% and another dose of 2mg naloxone in 5ml of saline was administered via nebulization and the patient responded well. The patient was admitted to the ICU to obtain IV access and monitor for the next 24 hours, once in the ICU a peripherally inserted central catheter (PICC) was placed under ultrasound guidance and the patient was started on a naloxone infusion at a low dose rate (2 mg/hr) without any bolus dose to avoid precipitating acute opioid withdrawal. Within 10 minutes the patient was exhibiting signs of withdrawal and was agitated. Due to concerns for continued withdrawal and pulmonary edema the infusion rate was slowed to 1 mg/hr. After a few hours on (and off) the naloxone infusion, titrated per the RASS scale, the patient was eventually downgraded to the medicine telemetry unit and later discharged from the hospital without any complications.

3. Discussion

Naloxone is a competitive inhibitor of the μ receptor and is indicated for the reversal of opioid anesthesia and known or suspected opioid overdose. It follows first order kinetics and is highly lipophilic so enters the CNS [2–4]. The ideal route of administration for naloxone is IV and this route is the most studied in terms of duration of drug effect and kinetics. The time of onset is within one minute, and 1 mg naloxone is enough to counteract 25 mg of heroin for about 60 minutes. In addition to the IV route, IM, SC, intralingual, endotracheal and IN routes have been described for the administration of naloxone. IM, SC, and intralingual routes all require the use of a needle and the bioavailability of naloxone through these routes is highly variable; with IM administration the bioavailability is around 35% and time of onset is 12 minutes [5,6]. Our case highlights special circumstances where a nebulized route of administration can be useful over other routes.

Patients with a history of intravenous opioid abuse can have peripheral venous scarring that makes obtaining venous access difficult. The delay in obtaining intravenous access may result in the loss of valuable time as the patient becomes hypoxic. Also, trying to gain IV access in the field possesses a potential for accidental needle stick injury. This may put the healthcare workers at risk of exposure to Hepatitis B and C, and human immunodeficiency virus (HIV) [7]. A study comparing IV and SC naloxone in pre-hospital settings showed that the delay time of onset from the SC route was balanced by the delay in obtaining functional intravenous access for the IV route thus making the mean time of onset of reversal for both routes 9 minutes, however, both routes require the use of needles [8,9] increasing risk to the provider. After the reversal of opioid intoxication with naloxone, the patient can become agitated and aggressive, which raises the risk for provider exposure to blood borne pathogens [10]. In our patient, use of nebulized naloxone had a time of onset of 2–4 minutes with a needleless and noninvasive approach.

Chronically opioid-dependent patients, especially those who use methadone and other synthetic opioids, are more prone to violent withdrawal symptoms from naloxone administration, especially when naloxone is administered as a bolus dose. Not only is this withdrawal painful for the patient, but also places the healthcare personnel at risk after giving the naloxone [10]. If nebulized naloxone effectively reverses the intoxication from opioids, the patient can self-titrate the administration and take off the mask when they are awake and alert [11]. Also, nebulization provides a sustained dose of naloxone without a bolus so there is a lesser chance of precipitating a violent withdrawal response. Although intranasal administration is needleless, it is administered as a bolus dose and cannot be titrated by the patient; higher doses if given might precipitate a violent response.

Naloxone, when administered by nebulized route, acts both at the pulmonary opioid receptors [12] and has systemic absorption, both these pharmacodynamic properties play a role in reversing intoxication from opioids. A 2 mg dose of naloxone administered by nebulization will result in a serum concentration of 0.54 ng/mL, 15 minutes after the administration [13]. Hence nebulization provides an alternative needleless route for naloxone administration. It is yet to be determined what minimum respiratory rate will still allow for successful resuscitation with nebulized naloxone administration or what the optimal dose of naloxone should be for administration by nebulization. A recent meta-analysis [5] reviewed the mean time of onset for naloxone when administered through various routes, the mean time of onset

when naloxone is administered through the inhaled route was 5 minutes based on the data from poled studies. Naloxone administered as nebulized therapy in the prehospital setting [14] appears to be safe and effective. A prospective observation study [15] done in the emergency department has provided further evidence for the effectiveness of the nebulized route.

4. Conclusion

The nebulization of naloxone provides a unique and effective way to reverse opioid intoxication by a needleless and noninvasive approach.

5. Patient perspective

Unfortunately, the patient was lost to follow up as outpatient, his perspective could not be obtained afterwards.

Author Contribution

M.Sameed is primary author for the case, who drafted the manuscript and had full access to all the patient related data

H. Teague supervised the project and was the attending of record for the case, she proof read the manuscript and formatted the final article.

Disclosure statement

No potential conflict of interest was reported by the authors.

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