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Opioid antidote induced pulmonary edema and lung injury

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ABSTRACT

Introduction: Opioid overdose emergencies are increasing every year, naloxone is the antidote for the treatment of opioid overdose. Naloxone is being dispensed to even lay persons through some programs to prevent opioid overdose deaths.

Case: 23 year old patient presented with naloxone treated opioid overdose complained of chest pain, pink frothy sputum production and shortness of breath. Physical exam showed tachycardia, tachypnea and coarse breath sounds. Imaging of the lungs showed diffuse pulmonary edema. Within an hour after the administration of naloxone patient developed pulmonary edema and lung injury. Patient was managed with non-invasive positive pressure ventilation which improved patient's symptoms in less than 6 hours confirmed by radiological improvement in 24–36 hrs.

Discussion: There are no specific observation guidelines post naloxone treatment in opiate overdose patients. We recommend early treatment of naloxone induced pulmonary complications during the observation period with non-invasive positive pressure ventilation to reduce the morbidity.

1. Introduction

Heroin (chemical name diacetylmorphine), a derivative of morphine, is one of the most commonly abused opioids in the United States. According to a report by SAMHSA (substance abuse and mental health services administration), heroin use in the U.S. has increased since 2000, an estimated 808,000 people (aged 12 or older) in 2018 used heroin, which corresponds to about 0.3% of the population [1]. Heroin-related overdose deaths also increased five times from 2010 to 2017, reaching 15,482 deaths in 2017, which accounts for 32.5% of opioids overdose death [2,3].

Heroin overdose is clinically diagnosed with a combination of altered level of consciousness and one of the following clinical signs: respiratory rate <12 breaths/min, mitotic pupils, or circumstantial evidence of drug use [4]. Admission diagnosis of heroin overdose has been noted to be non-cardiogenic pulmonary edema (1%–2.4% of patients), pneumonia (0.5%), possible endocarditis (0.25%), and a persistent altered mental status or respiratory depression (0.7%–4%) [5]. Pulmonary complications, of which the most widely reported is edema, are the most common adverse events after an opioid overdose [6,7].

Naloxone is an opioid antagonist used to temporarily reverse the effect of an opioid overdose such as reduced respiratory rate. Many community naloxone distribution and education programs have demonstrated significant reductions in mortality [8]. In 2018, the U.S. surgeon general issued an advisory encouraging expanded availability of naloxone for pedestrians [9]. The rate of naloxone administrated by EMS increased to 75.1% from 2012 to 2016 [10].

Reported adverse events after intramuscular or intranasal naloxone administration were agitation and/or irritation, nausea and/or vomiting, headache, tremor, sweating or convulsion [11,12]. Pulmonary edema after the use of naloxone also has been reported along with aspiration events, the most frequent complication leading to ICU admission [13,14]. In addition, there are studies that compare the effectiveness and complications of different routes of naloxone administration. One study showed patients receiving intranasal naloxone had more pulmonary complications [15].

2. Case

A 23-year-old male was brought to the Emergency Department in somnolent mental state after heroin overdose. He had received one and half dose (8mg) of Narcan (naloxone nasal spray) in the field when found to be unresponsive with a respiratory rate of 5 per minute.

The patient had consumed an unknown amount of alcohol on the same day and snorted around 3 bags of heroin (unknown quantity of pure opioid) as per the Emergency Medical Services Personnel report. He

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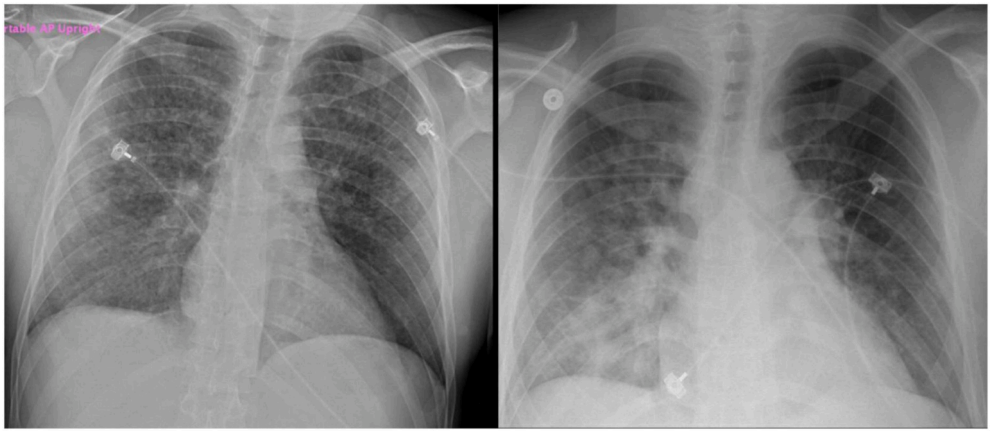

Fig. 1. (**A**) Chest X-Ray showing diffuse bilateral interstitial and alveolar density suggesting of pulmonary edema vs. multifocal infiltrative pneumonia. (**B**) Repeat chest X-Ray on day 2 showed increasing airspace opacification in the right lower lung concerning for aspiration pneumonia.

had 7 episodes of opioid overdose prior to this admission. The patient started coughing frothy pink sputum, endorsed chest tightness, shortness of breath and abdominal pain. He denied any squeezing type chest pain or palpitations.

Vitals were significant with a heart rate of 109 beats per minute, blood pressure 121/93 mm of Hg, respiratory rate of 22 per minute and oxygen saturation of 89% on room air. On exam, he appeared to have respiratory distress, pupils were small but reactive to light and nystagmus was observed. Heart rhythm was regular without murmurs or rubs. Lung sounds were coarse with rhonchi and rales. The abdomen was tender to palpation with normal bowel sounds. No extremity swelling was noted.

Electrocardiogram showed sinus tachycardia and troponin level was within normal limits. On further workup, labs showed elevated white blood cell count of 14.9K/μL, hemoglobin of 16.3g/dL, platelet count of 281,000/μL. Basic metabolic profile showed sodium of 134 mmol/L, potassium of 5.6mmol/L, creatinine of 1.74 mg/dL, glucose of 364mg/dL. Arterial blood gas showed respiratory acidosis with pH 7.2, pCO2 59.8 mm of Hg, pO2 92 mm of Hg. Prothrombin time with International Normalized Ratio, Brain Natriuretic Peptide (16 pg/ml), and liver function tests were within normal range. Serum alcohol level was below 10mg/dL and initial urine drug screening including opiate was negative. HIV panel was also negative. Fecal occult blood test was positive which was secondary to the hemoptysis (probably swallowing of bloody sputum). However, his hemoglobin was stable.

Chest X-Ray revealed diffuse bilateral interstitial and alveolar density with concerns of asymmetric pulmonary edema or multifocal infiltrative pneumonia (Fig. 1A).

The patient was initially admitted to the ICU, started on BiPAP with minimal settings which was uptitrated to FiO2 of 60% (IPAP 12cm H2O, EPAP 8cm H2O) depending on patients clinical response. Then eventually weaned off Positive pressure ventilation and transitioned in couple of hours to Hi-flow oxygen support (vapotherm) for acute respiratory failure with hypoxia. Creatinine level was trended down to normal with intravenous fluid support.

On day two, patient was transferred to regular floor on 3 L of oxygen support and eventually weaned off to room air. Patient remained hemodynamically stable, however, he had a fever spike with a temperature of 38.3 °C. Repeat chest X-Ray showed no pulmonary edema but worsening of pneumonia on right lower lobe (Fig. 1B). Patient completed regular course antibiotic therapy with ampicillin-sulbactam, ceftriaxone and oral azithromycin for community aquired pneumonia with aspiration.

3. Discussion

There are multiple studies and Case reports in literature about lung complications like non cardiogenic pulmonary edema, bronchiectasis, pulmonary fibrosis, ARDS, diffuse alveolar hemorrhage secondary to both intravenous and inhaled opiate overdose [16–19,25]. Although the pathogenesis for Non Cardiogenic Pulmonary Edema is unknown, it was probably due to hypoxia induced altered alveolar capillary membrane permeability and defects in basal lamina seen in post mortem pathological specimens examined in Germany [20,21]. However there are also few case reports/studies which showed a temporal association between intranasal naloxone administration and lung injuries [22]. An observational study showed naloxone had a dose dependent increase in pulmonary complications in heroin overdose patients [23]. A small retrospective chart review suggested that patients need to be observed for at least a minimum of 2 hour post administration of naloxone in an overdose patient [24]. There are two very recently reported cases of naloxone reversal induced pulmonary edema and hemorrhage who were treated with positive pressure noninvasive ventilation along with other modalities like diuretics, antibiotics.

In our patient the symptoms followed administration of naloxone. Patient's hemoptysis and pulmonary edema were probably due to naloxone administration itself causing lung injury. We strongly recommend close monitoring of the patient post administration of naloxone for signs of respiratory failure. If pulmonary complications were to occur, we recommend treating with noninvasive positive pressure ventilation as long as the patient qualifies this modality of treatment.

Naloxone is the drug of choice for opiate overdose. However in literature there is limited evidence of naloxone treated opiate overdose induced lung complications. Therefore we strongly recommend monitoring these patients post treatment for these complications with early initiation of noninvasive ventilation whenever possible to reduce the morbidity in these patients. Moreover studies need to be done in this perspective for establishing standardized post naloxone treatment protocols in opiate overdose patients.

Declaration of competing interest

All authors have no conflict of financial interest to disclose.

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