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Case Report

Opioid Toxicity, a Common Non-ACS Cause of Troponin Increase

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Introduction

The Food and Drug Administration (FDA) approved opioids for treating pain, and since then, overprescribing and the creation of synthetic opioids such as heroin led to an addiction epidemic in the United States. As a result, there are increasing amounts of drug overdose cases, and healthcare providers must recognize these and treat them appropriately. Drug overdose or toxicity is now the leading cause of injury-related mortality in the United States, but the prognostic utility of the cardiac biomarkers in these patients is unknown[4]. In this case report, we will be focusing on opioid toxicity as a common non-ACS causes of rise in cardiac biomarkers.

In this case report, as the opioid crisis increases in the state of New Jersey, we review its epidemiology, signs and symptoms, treatment, other non-ACS causes of increase in cardiac biomarkers and case presentation.

Epidemiology

The Drug Abuse Warning Network (DAWN) reported that number of emergency department (ED) visits related to non-medical use of opioids increased by 111% between 2004 and 2008[5]. The highest numbers of visits were recorded for oxycodone, hydrocodone and methadone[4]. An estimated 1.6 million ED visits were for the misuse and abuse of all drugs in 2004 compared to 2 million visits in 2008. Among these, illicit drugs such as cocaine and heroin were involved in 1 million visits in both 2004 and 2008, whereas prescription or over the counter drugs used non-medically were involved in 0.5 million visits in 2004 and 1 million visits in 2008.

New Jersey had the highest annual percentage increase in overdose deaths in the nation as of November 2017. As of January 2018, annual counts of overdose deaths increased by a projected

21.1%, compared to an overall national increase of only 6.6%[1-2]. The statistics display a two-fold rise in opioid overdose deaths from heroin, and up-to an eight-fold rise in deaths from fentanyl. Ocean Country is the epicenter of New Jersey's opioid epidemic, with 375 recorded opioid overdose deaths in 2016. Opioid abuse is most prevalent within individuals with mental health concerns. Substance Abuse and Mental Health Service Administration (SAMHSA) reports that 40% of adults with a substance use disorder have a co-occurring mental illness. Additionally, it is shown that approximately 70% of the incarcerated population is addicted, with at least 25% of this population addicted to opioids[20]. The risk of overdose death for the previously incarcerated is approximately 130 times greater than those of the general population.

Legal sales of prescription opioid painkillers may have driven the rise in opioid-related deaths, which nearly quadrupled between 1999 and 2014. New Jersey has some of the least expensive, yet highest purity street heroin in the nation, making potent opioids accessible to addicted populations.

Signs and Symptoms of Intoxication, Overdose and Withdrawal

The cardinal signs of opioid toxicity include pinpoint pupils, hallucinations, drowsiness, vomiting, respiratory depression, confusion, myoclonic jerks, and reduced level of consciousness, ranging from drowsiness, to stupor, to a coma[6]. The main cause of death is typically from respiratory depression, but in some cases may be due to hypothermia. The most commonly reported signs and symptoms of overdose morbidity are pulmonary conditions such as edema and pneumonia,[7–10] muscular complications such as rhabdomyolysis from prolonged pressure on muscles during coma, and renal failure from lysis of muscle tissue.

Opioid withdrawal occurs after sudden discontinuation of opioids following a prolonged period of use. Short-acting opioids (e.g. heroin) usually exhibit signs and symptoms of withdrawal within 8–12 hours after the last dose. If left untreated, symptoms peaks within 36–72 hours and subside substantially within 5 days. However, for long-acting opioids (e.g. methadone) withdrawal may reach a peak between 5–6 days, and the syndrome will not usually subside for 14–21 days[3]. The signs and symptoms of opioid withdrawal are categorized as objective or subjective[11]. Objective signs include vomiting, lacrimation, rhinorrhea, pupillary dilatation, piloerection, sweating, diarrhea, yawning, fever, elevated pulse and blood pressure. Subjective symptoms include dysphoric mood, insomnia, muscle aches and cramps, abdominal pain and colic. The Clinical Opiate Withdrawal Scale (COWS) is commonly used to classify the severity of opioid withdrawal based on a generated score[12].

Treatment

Naloxone, a short-acting mu receptor antagonist, is the gold standard treatment for opioid overdose. Its active metabolite, 6-alpha-naloxol has a much longer half-life[3]. It is usually given intravenously (IV), subcutaneously (SC) or by intramuscular injection (IM). Some reports

indicate that the IM administration may prolong the effect of naloxone[13]. When responding to an overdose, paramedics typically administer the drug before transferring the patient to the ED.

The starting dose is usually 0.4 mg IV/SC/IM, which can be repeated until the patient responds. Some studies reported a total dose range between 2–6 mg, depending on the half-life of the opioid involved in the overdose. Other factors may explain the need for higher doses of naloxone when resuscitating overdose patients, such as concomitant use of alcohol with opioids[14].

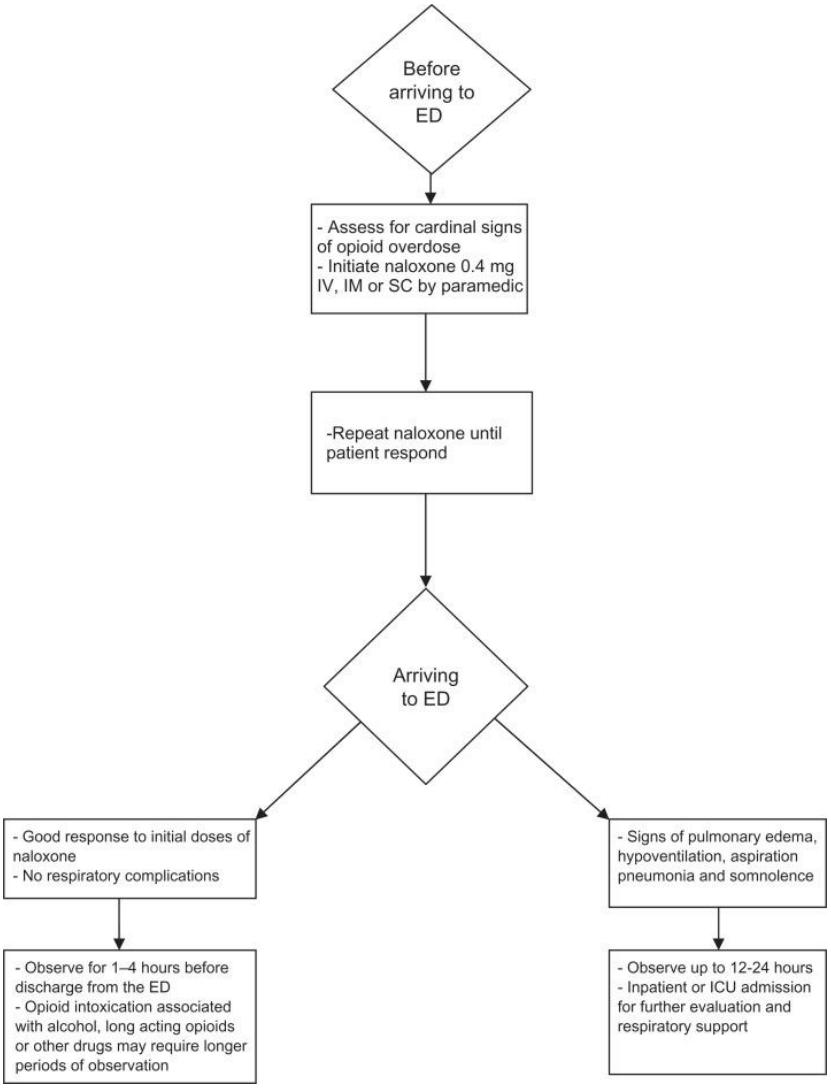

Figure 1. Management of acute opioid intoxication and overdose[3].

Common non-ACS causes of Troponin Increase

The following table (Figure 2), taken from American College of Cardiology (ACC), encompasses the known ACS and non-ACS causes of troponin increase. Healthcare providers should not immediately jump to diagnose myocardial infarction due to increased troponin levels.

System	Causes of Troponin Elevation
Cardiovascular	Acute Aortic Dissection Arrhythmia Hypotension Heart Failure Apical Ballooning Syndrome Cardiac inflammation • Endocarditis, Myocarditis, Pericarditis, Hypertension, Infiltrative Disease • Amyloidosis, Sarcoidosis, Hemochromatosis, Scleroderma, Left Ventricular Hypertrophy
Myocardial Injury	Blunt Chest Trauma Cardiac Surgeries Cardiac Procedures • Ablation, cardio inversion, Percutaneous Intervention Chemotherapy Hypersensitivity drug reactions
Respiratory	Acute PE ARDS
Infectious/Immune	Sepsis/SIRS Viral Illness TTP
Gastrointestinal	Severe GI bleeding
Nervous System	Acute Stroke (Ischemic and Hemorrhagic) Head Trauma
Renal	CKD
Endocrine	Diabetes Hypothyroidism
Musculoskeletal	Rhabdomyolysis
Inherited	Neurofibromatosis Duchenne Muscular Dystrophy Klippel-Fell Syndrome
Others	Endurance Exercise Environmental Exposure (Carbon monoxide, hydrogen sulfide)

Figure 2. ACS and Non-ACS etiologies of Troponin Increase[15].

Although opioid toxicity and overdose is not directly stated under ACC's list of troponin increase, acute respiratory distress syndrome can cause elevated troponin. Opioid toxicity can cause massive respiratory depression and ARDS, which has the potential to falsely elevate cardiac biomarkers.

Case Presentation

Patient is a 42-year-old Caucasian male brought by ambulance to the ED after he was found unresponsive in his car in a parking lot. Patient was found to be blue, diaphoretic, and not breathing. Police started CPR prior to EMS arrival. Patient was intubated in the field and given two rounds of epinephrine. In the ED, routine CBC, CMP, EKG, troponin, and d-dimer were performed. EKG showed ST elevation in aVR and diffuse ST depression, suggestive of left main occlusion. Troponin was elevated at 6.21 and code heart was initiated. Cardiologist performed emergent cath which showed normal coronaries and ejection fraction. With the information provided, the cardiologist differential was left main spasm vs. severe hypoxemia secondary to brain injury. Patient was sent to ICU s/p cath with IVF and pressors to stabilize the vital signs. In addition, UDS was ordered to rule out any substance-induce hypoxemia.

On Day 1 of admission, additional imaging was performed to rule out other causative factors for this hypoxic event. CXR showed no pneumothorax, no pleural effusion, and no cardiomegaly. CT of head w/o contrast showed no acute hemorrhage. 2D ECHO showed normal EF of 65%. Duplex scan of lower extremities (due to positive d-dimer) showed no DVT and normal valve functions. CMP result showed no acute kidney injury and electrolytes within normal range, but AST and ALT were elevated in the 300s. Furthermore, UDS came out positive for opioids. Patient monitoring continued.

On Day 2, with the new results and UDS positive for opioids, further evaluations were warranted. Neurology was consulted via tele-medicine to rule out any seizure-related event, as the patient was found unconscious. The neurologist ordered another head CT w/o contrast, which showed no abnormal findings. The patient's friend reported a history of seizure-like activity, so empiric Keppra 100mg was started with EEG, which showed no seizures. Patient's family was informed and came to visit. ICU physician continued to monitor the patient; however, the patient's condition was not improving despite efforts. Patient scored 3 on the GCS, with constant sedation and intubation. WBC and liver enzymes remained elevated. Fortunately, patient's vitals were stable, afebrile, and O2 sat of 100% at 100% FIO2, RR 22 with the help of a mechanical ventilator.

On Day 3, Palliative care was consulted due to poor prognosis. The palliative care physician spoke to the family regarding the patient's situation. The cardiologist came to see the patient again with the updated reports and lab work, and concluded that the hypoxic event was most likely secondary to opioid overdose. Upon further inquiry about patient's past activities and behaviors, friends and family members reported of his use of opioids, heroin, and alcohol in the past. Based on the lab findings, we concluded that the patient drank an excessive amount of

alcohol and overdosed on opioids to precipitate his current state. Family felt unsure about discontinuing life-support, so patient monitoring continued.

On Day 7, patient had a fever of 101.2 degrees, which promoted the ICU to obtain UA, UC, and blood culture. IV Vancomycin and Zosyn were initiated empirically. Within the next 12 hours, the patient became afebrile.

On Day 9, General Surgery was consulted as patient needed tracheostomy and PEG tube placement due to prolonged use of mechanical ventilator. The surgery was successful and patient management continued in the ICU, pending the family's decision to discontinue life-support. They wanted to transfer the patient to NYU hospital for further evaluation and care, but the transfer could not complete due to insurance.

On Day 16, Patient remained stable in ICU when the family requested terminal extubation. After extubation, the patient died shortly after.

Discussion

Opioid intoxication is one of the leading cause of mortality and morbidity in United States. Patients report with respiratory depression, decreased conscious level, pinpoint pupils, and hypotension. Warning signs include drowsiness, confusion, pinpoint pupils, myoclonic jerks, hallucinations (auditory and visual), vomiting, and delirium[16]. Unfortunately, these symptoms and warning signs are non-specific. It is difficult to diagnose opioid intoxication, especially if the patient is unconscious. Just like the case, ED does the initial labs and imaging to rule out any immediate life-threatening disease. In hindsight, the myoclonic jerks that patient exhibited in the ED narrowed the differential into seizure. When the UDS came for positive opioids, naloxone should have been administered immediately, if not administered beforehand. Naloxone is indicated for use in both adults and pediatrics and will reverse both natural and synthetic opioids as well as some mixed agonist-antagonist analgesics such as nalbuphine, pentazocine, and butorphanol[16]. In order to minimize mortality, a better method of differentiation is warranted to reduce the mortality of opioid toxicity.

Current research demonstrates the efficacy and beneficence of naloxone for respiratory distress[16]. We can implement new protocols that targets wide range of etiologies of respiratory distress once we rule out cardiovascular as a source. Due to its short duration of action, the observation period for the possibility of recurrence of opioid toxicity varies. In cases of short-acting opioid overdoses, patients may be discharged once respiration and mental status return to normal, and an observation period of 2 hr. can be considered after naloxone administration. For long-acting or sustained-release opioid overdoses, hospital admission with continuous infusion of naloxone may be warranted. The observation period in these cases may extend to 4–6 hr. after naloxone infusion until the patient is awake and alert with no signs of RD[17-18]. In these cases, naloxone doses should be diluted in 9 mL of normal saline and administered at 0.5 mL/min[19]. Regular and frequent assessment of toxicity is recommended for patients who are on opioids, especially in frail elderly, patients with renal impairment, and in this case, younger patient with history of substance abuse.

Conclusion

Opioid-induced toxicity should be regularly assessed and aggressively treated to improve the quality of life of the patient and to decrease distress in both patient and their caregivers. With the upcoming research centered on the efficacy and benefits of using Naloxone to manage respiratory depression, it can potentially save countless lives. As awareness of the symptoms of opioid toxicity rises, it may guide the future of medicine to reduce mortality and morbidity of opioid crisis, in state of New Jersey and the general United States.

Reflections from the Primary Author

As a third-year medical student in the midst of applying to Internal Medicine Residency in 2020, I have had the utmost pleasure and excitement writing this case report. I was on Cardiology service when this event was taking place. I had the pleasure of asking patient's friends for further inquiry about patient's history of substance and alcohol. It was an unforgettable moment for me clinically, as I felt I significantly contributed to the diagnosis. Thank you Dr. Benz at Christ Hospital for giving me the opportunity to write this paper. This case has molded me to look at the patient as a whole. There are cases where labs, or other imaging can be false positive, but if we stay true to the history and patient's presentation, we can come up with the accurate diagnosis. I hope to do this as I embark my next chapter in my medical training in residency.

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