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Case Report

Propofol Induced Bradycardia, a Manifestation of Propofol Related Infusion Syndrome

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Abstract

Propofol related infusion syndrome (PRIS) is a lethal and rare condition that affects cellular metabolism that leads to accumulation of fatty acids in the liver that can lead to arrythmias, bradycardia and cardiac arrest[1]. Since its first use 1986 its incidence has been reported around 1% of the cases worldwide but this number due to education has decreased. Despite Billions of doses sold in the world, and increasing in numbers, the incidence remains stable due to awareness of use and education. These cases show hypertriglyceridemia, fever, hepatomegaly, heart failure and arrythmias which tend to occur late. Despite this, propofol is a safe drug its wide use in chronic sedation[3]. Continuous used, increases the possibility of potential complications if we don't keep an eye and monitor for its potential side effect. We present a case report of a patient that developed PRIS, this was identified during rounds and there was a in sedation, leading to a good outcome. We will review the pathophysiology and incidence of this process and make suggestion for prevention and further decreasing its risk in the intensive care units.

Patient: Male, 50 -year-Old

Final Diagnoses: Shock, Respiratory Failure, ICU, Propofol, Anesthetic, Sedation

Symptoms: Hypotension, Tachycardia, Hypoxemia, Shock, Bradycardia

Medication: Propofol, Diprivan, bradycardia, Propofol Related Infusion Syndrome, PRIS

Specialty: Pulmonary & Critical Care Medicine

Objective: Unusual clinical course

Case Report

We report a case of a 50-year-old that presented in the intensive care unit with increased dyspnea and cardiopulmonary collapse. The patient was admitted to the ICU in hypoxic respiratory failure. He was Intubated, initiating mechanical ventilation with central venous access obtained for full cardiopulmonary support. Patient was treated with broad spectrum antibiotics and vasopressors. He received a propofol and fentanyl drip for sedation and comfort. After 2 days on the ventilator support, his oxygenation requirement improved from 100 percent to 60% and peep of 8. The patient was noted to have bradycardia, with increased lactate and CPK. The probability of Propofol-Related Infusion Syndrome (PRIS) was considered, and we stopped the propofol drip and started a Versed-Midazolam drip. The patient's overall condition continued to improve and he was extubated on day 5. An echocardiogram, cardiac enzymes, TSH and electrolytes were checked on admission and upon extubation, they were normal. Initial CPK was over 1500 and subsequently improved to less than 100. Lactic acid improved from 5 to less than 1. WBC improved from 21 to 12 and Cr was 0.9 and remained stable.

Discussion

Structural Properties, Mechanism of Action, and History of Propofol

Propofol (C12H18O) is a highly hydrophobic/lipophilic agent that is utilized in operating rooms and intensive care units throughout the world (hence, this is why it is regarded as the "milk of amnesia"). It primarily accomplishes its desired clinical uses via activation and potentiation of GABA-A receptors[3,4]. However, the precise mechanism of action on how it accomplishes this, currently remains unclear. Propofol was first introduced in London as an intravenous anesthetic induction agent in the 1980s for patients undergoing minor gynecological procedures and diagnostic bronchoscopies. It quickly became a gold standard IV anesthetic agent due to its effectiveness and relatively low side effect profile[4]. Propofol received FDA approval for the induction and maintenance of anesthesia in 1989. Since that time, the FDA has broadened the approved application of Propofol, including the sedation maintenance for patients receiving mechanical ventilation, maintenance of anesthesia in infants > 2 months old, and induction of anesthesia for children > 3 years old.

Propofol Toxicity & Propofol-related Infusion Syndrome (PRIS)

Despite its effectiveness in its clinical applications, administration of propofol can lead to life-threatening consequences[5]. While the most common side effects include pain ("burning") at infusion site, hypotension, and/or respiratory depression, prolonged infusion (especially in the ICU setting) can result in the most feared complication of Propofol-Related Infusion Syndrome (PRIS) According to a study in 2009 that observed 1017 patients from 11 different medical centers, they found that the projected incidence of PRIS is approximately 1.1 %[6]. The same study also had a mortality rate of 18%. Some available literature suggests significantly higher mortality rates, including an FDA MEDWATCH analysis report that identified 1139 PRIS patients from the years of 1985-2009 and revealed a mortality rate of 30%. With the current awareness of PRIS and knowledge of how to manage these patients, the true mortality rate today is most likely on the lower end of the spectrum. [5,6]

Pathophysiology of PRIS

The pathophysiology of PRIS is complex and multifaceted. At its foundation, it is thought to be caused by propofol-induced uncoupling of mitochondrial oxidative phosphorylation, inhibition of electron transport required for ATP production, and disruption of free fatty acid metabolism via increased activity of Malonyl CoA[7]. These mechanisms ultimately lead to the development lactic acidosis and myocyte necrosis (in both cardiac and skeletal muscle). Furthermore, propofol antagonizes beta-adrenergic receptors and calcium-channel binding, thus further contributing to the cumulative negative impact on myocardial function[8]. The arrhythmias associated with PRIS (i.e., bradycardia, RBB, asystole, etc.) are thought to be secondary to the increased concentration of free fatty acids secondary to propofol-induced defects in metabolism. Patients with low carbohydrate/glycogen stores (critically ill, children) are at increased risk due to their enhanced reliance on fat metabolism for energy preservation. High levels of non-esterified free fatty acids are represented by elevated triglycerides, which can assist in the diagnosis and management of PRIS.[7]

Clinical Manifestations and Risk Factors of PRIS

PRIS can be defined as acute refractory bradycardia, which inevitably can lead to asystole, plus one or more of the following: metabolic acidosis, rhabdomyolysis/hyperkalemia, acute renal failure, acute liver toxicity.[8]

and/or hyperlipidemia.[1,7,8] It is important to note that there is not a universally agreed upon definition of PRIS in the literature, but the two most commonly reported clinical presentations include metabolic acidosis and ECG changes (i.e. bradycardia, QRS complex widening, asystole). Risk factors of PRIS include prolonged infusion > 48 hours, high propofol dosage (> recommended infusion protocols), children, severe head injuries, sepsis, high catecholamine or glucocorticoid concentrations, low carbohydrate intake/storage, inborn errors of fatty acid oxidation, hyperglycemia, use of vasopressors, and obesity.[9,10]

Improving Outcomes: Management and Prevention of PRIS

Initial management of PRIS should include immediate recognition of clinical and metabolic signs of the syndrome and cessation of propofol infusion.[11] Alternative sedation can be obtained via the use of dexmedetomidine, alfentanil, or midazolam.[12] Hemodynamic stability should be the foundation of treatment, followed by targeting the various clinical manifestations PRIS accordingly.[1,7,9] If hyperkalemia, sepsis, or fever remains refractory after initial measures, hemofiltration or hemodialysis should be initiated to remove propofol and PRIS-associated metabolites.[9] Limited studies suggest that extracorporeal membrane oxygenation (ECMO) has been effective in patients with PRIS that is refractory to vasopressors or inotropic agents. Some studies also report that transcutaneous electrical pacing can be beneficial in treating associated bradycardia.

Preventive measures of PRIS and propofol-induced toxicity should include enhanced caution when using propofol in the critically ill and in children, a dose limit of 4mg/kg/hr and restricting the infusion period to less than seven days. Laboratory monitoring could include checking CK and triglyceride levels daily after 48 hours of propofol infusion, which could aid in promptly recognizing the consequential clinical manifestations of PRIS.

Conclusion

Propofol will continue to be utilized in clinical settings throughout the world due to its effectiveness, accessibility, and relatively favorable side effect profile[3,11,12]. In this case, we report the vital importance of the awareness of PRIS in patients receiving prolonged propofol infusion who are clinically deteriorating.[1,7] In any patient receiving prolonged propofol infusion (or requiring doses exceeding the recommended dosing limits) that are experiencing refractory bradycardia and/or metabolic acidosis, PRIS should be included on

the list of differential diagnoses and an appropriate work-up should be conducted (i.e., triglycerides, CK, lactate, electrolytes). Quickly being able to recognize patients experiencing PRIS is critical and doing so will undoubtedly save lives. Adhering to the recommended propofol infusion protocols when able reduces the risk of developing PRIS. While there are no studies currently available, routine monitoring of triglycerides and CK every 48 hours after initiating propofol sedation could be beneficial in earlier recognition and decreasing overall mortality in patients suffering from PRIS.

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