Name of Journal: World Journal of Anesthesiology

Manuscript Type: CASE REPORT

Malignant Hyperthermia and Tachyarrhythmia-A Rare Complication of Local Lidocaine Injection: A Case Report

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Author contributions: Mukosolu F. Obi contributed to manuscript writing, editing and data analysis; Vikhyath Namireddy contributed to data collection; Chelsea Noel contributed to data collection; Manveer Ubhi, Yash Garg, Manjari Sharma and Frederick N. Campos contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Supported by

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ABSTRACT

Background

Malignant Hyperthermia (MH) is a hypermetabolic disorder of the skeletal muscles triggered by exposure to volatile anesthetics and depolarizing muscular relaxants. It manifests with such clinical presentations such as tachycardia, muscle rigidity, hyperpyrexia, and rhabdomyolysis in genetically predisposed individuals with ryanodine receptor (RYR1) or calcium voltage-gated channel subunit alpha1 S (CACNA1S) mutations. Local anesthetics, such as lidocaine, are generally considered safe; however, complications can arise, albeit rarely. Lidocaine administration has been reported to induce hypermetabolic reactions resembling MH in susceptible individuals. The exact mechanism by which lidocaine might trigger MH is not fully understood. Although some mechanisms are postulated further research is needed for better understanding.

Case Report

We present a case of malignant hyperthermia (MH) in a 43-year-old male patient with an unknown genetic predisposition following a lidocaine injection during a dental procedure. This case serves as a reminder that while the occurrence of lidocaine-induced MH is rare, lidocaine can still trigger this life-threatening condition. Therefore, caution should be exercised when administering lidocaine to individuals who may be susceptible to MH. It is important to note that prompt intervention played a crucial role in managing the patient's symptoms. Upon recognizing the early signs of MH, aggressive measures were initiated, including vigorous intravenous normal saline administration and lorazepam. Due to the effectiveness of these interventions, the administration of dantrolene sodium, a specific antidote for MH, was deferred.

Conclusion

This case highlights the significance of vigilant monitoring and swift action in mitigating the detrimental effects of lidocaine-induced MH. Caution should be exercised when administering lidocaine to individuals who may be predisposed to MH and very important to be aware and vigilant of the signs and symptoms of MH as early recognition and treatment intervention are important to prevent serious complications to decrease mortality.

Keywords: Malignant Hyperthermia, Tachyarrhythmia, Lidocaine, Local Anesthesia, Dantrolene sodium, genetic mutation.

Introduction

Malignant hyperthermia (MH) is an inherited pharmacogenetic condition that affects skeletal muscles, resulting in hypermetabolism. It is an autosomal-dominant genetically heterogeneous ion channelopathy that is triggered by anesthesia. Thanks to advancements in identifying and treating MH, its incidence has decreased since it was first recognized in 1960. Currently, MH affects one in 50,000 to one in 250,000 adults and one in 15,000 children [1]. People with mutations in ryanodine receptor (RYR1) and calcium voltage-gated channel subunit alpha1 S (CACNS1S) genes (which are responsible for regulating intracellular calcium balance) are susceptible to MH. In these individuals, calcium homeostasis is disrupted. This causes hyperactivation of receptors due to an increased release of calcium from the endoplasmic

reticulum, thus leading to a hypermetabolic state. Certain medical conditions, including central core disease, multiminicore disease, King-Denborough syndrome (KDS), and MH-like syndrome with STAC3 mutations, can increase the susceptibility to malignant hyperthermia (MH). These conditions are associated with genetic mutations in the RYR1 gene, which is also implicated in most cases of MH. The RYR1 gene encodes the ryanodine receptor responsible for regulating calcium release in muscle cells. The mutations in these conditions disrupt the normal function of the ryanodine receptor, leading to abnormal calcium ion channels and muscle dysfunction. As a result, individuals with these conditions may be more prone to experiencing MH when exposed to triggers that cause hypermetabolic reactions in skeletal muscles. In the case of MH-like syndrome with STAC3 mutations, the STAC3 gene is involved in the excitation-contraction coupling process, which controls calcium release in muscle cells. Mutations in the STAC3 gene interfere with its normal function and disrupt the release of calcium ions, increasing the risk of MH-like syndrome [2] During MH crisis, oxygen consumption increases and ATP decreases, resulting in anaerobic metabolism, muscle breakdown, lactic acidosis, and an increase in body temperature and heart rate. Symptoms include rhabdomyolysis, cyanosis, muscular contracture and rigidity, arrhythmia, coagulopathy, and hyperthermia. Left untreated, MH has an 80% mortality rate. However, with effective treatment and supportive measures, the mortality rate decreases to 5%. Treatment includes stopping the use of halogenated agents, supplying 100% oxygen through hyperventilation, and administering dantrolene sodium (DS). DS is a muscle relaxant that prevents calcium release from the endoplasmic reticulum by interacting with RYR1 [1, 3]. Diagnosis is based on clinical presentation, and clinicians must act swiftly to decrease mortality in susceptible individuals. Susceptibility confirmation is based on the halothane-caffeine contracture test (HCCT), which was conducted three months after the crisis [1]. There is

some degree of controversy over whether lidocaine, a local anesthetic, causes MH. Studies indicate the incidence to be low. However, this case confirms that, while the likelihood of lidocaine causing MH is minimal, it can still trigger it.

CASE PRESENTATION

Chief complaints

A 43-year-old male arrived at the emergency department (ED) at 1:52 pm with a complaint of tooth pain. During the initial encounter, his vital signs were found to be stable. In the ED, he acknowledged that he was scheduled for a tooth extraction at approximately 2:30 pm that same afternoon. He reported that his tooth pain had started two days earlier and had become progressively worse, reaching six on a ten scale in terms of severity. The patient denied having any fever, chills, or shortness of breath. His current medication was amoxicillin (500 mg) and non-steroidal anti-inflammatory drugs [NSAID] (400mg). The dental team was consulted in the ED at 2:40pm. Following an application of 3% lidocaine (with 2 ml epinephrine), the patient's 10th tooth was extracted. His vitals at the time were stable. The patient was in no distress and was therefore discharged at 2:50 pm. Ten minutes after discharge, the patient returned to the ED with complaints of chills, trembling, shortness of breath, lower extremity rigidity and tachypnea. He also reported feeling faint but mentation was intact. The patient acknowledged that his symptoms started while he was on his way home.

History of past illness

No significant past medical history.

Family history

No significant family history was reported.

Physical examination

This patient was observed to have visible chills and facial pallor. Vital signs on presentation showed a heart rate (HR) in the 170 Beats Per minute (BPM) range, blood pressure (BP) at 107/63 mmHg, a respiratory rate (RR) of 44/min, and body temperature at 106.3 F. He was hemodynamically unstable. Muscle rigidity noted.

Laboratory examinations

The laboratory results were significant for pre-renal azotaemia, myoglobinuria, elevated CPK.

Imaging examinations

Chest X ray indicated no acute cardiopulmonary disease. No pleural effusion. No pneumothorax. Echocardiogram was significant for ejection fraction of 55-60%. No wall motion abnormalities, and no valvulopathy.

FURTHER DIAGNOSTIC WORK-UP

Prior to obtaining the electrocardiogram (EKG), there was concern of supraventricular tachycardia (SVT) as patient HR increased to 170bpm on the telemonitor. The patient received vagal maneuvers and 6mg of adenosine; subsequently, his HR dropped into the 130BPM. EKG [Figure *1*] and laboratory studies [Table *1*] were then obtained.

FINAL DIAGNOSIS

Based on the rapid onset of symptoms including increased breathing rate (tachypnea), elevated heart rate (tachycardia), muscle stiffness (rigidity), and high body temperature (hyperpyrexia) occurring within 10 minutes after the patient's last normal state, along with laboratory findings of myoglobin in the urine, elevated creatine phosphokinase (CPK) levels, acute kidney injury, and mild increase in carbon dioxide levels (hypercapnia), a diagnosis of malignant hyperthermia (MH) was made. The patient was experiencing an acute state of increased metabolism. The clinical presentation strongly supported the diagnosis, although it was classified as a mild case since the symptoms appeared within a short time frame and prompt actions were taken to address and stop this life-threatening condition. Considering the swift response, the administration of dantrolene was delayed. Given the underlying pathophysiology of MH, the use of lorazepam before dantrolene could also be justified.

TREATMENT AND OUTCOME

The patient received an immediate dose of lorazepam (2mg) and intravenous acetaminophen (1g), along with intravenous fluids. As a result, the patient's respiratory rate improved from 44 breaths per minute to 28-29 breaths per minute. Subsequently, the patient was transferred to the intensive care unit (ICU) for more thorough observation. Throughout the presentation, the patient remained conscious and aware of their surroundings. The administration of dantrolene was postponed due to the patient's clinical improvement following the administration of lorazepam and intravenous fluids.

Discussion:

MH is a rare, potentially life-threatening autosomal dominant hypermetabolic crisis and defective cellular membrane dysfunction that occurs in people with a genetic predisposition. MH

is caused by genetic mutations in skeletal muscle RYR1 or CACNA1S receptors; these receptors regulate intracellular calcium in muscle cells [3]. Potent volatile anesthetic agents such as halothane, desflurane, and the depolarizing muscle relaxant succinylcholine can cause MH in susceptible individuals having this skeletal muscle-cell genetic mutation. The incidence of reported MH reactions of MH ranged from 1 per 10,000 to 1 per 250,000 anesthetic administrations [3]. The use of these anesthetic agents in susceptible individuals triggers a massive release of calcium within the muscle cells, causing the MH symptoms. The influx of calcium into the cell causes sustained muscular contractions and breakdown (rhabdomyolysis), leading to clinical manifestations. They include hyperthermia, muscle rigidity, tachycardia, difficulty in breathing, metabolic acidosis, an increase in carbon dioxide production, an increase in oxygen consumption, and hyperkalemia. These symptoms are all linked to hypermetabolic crisis [3].

While there is some controversy surrounding the use of amide-type local anesthetics (such as lidocaine) due to their potential to cause MH, research has shown that lidocaine is widely used, with a low incidence of MH. However, there have been literature reviews and studies conducted to evaluate the risk of MH in patients undergoing dental procedures. These studies have given rise to some debate about the safe administration of amide-type local anesthetics for individuals who are susceptible to MH. Despite the conclusion drawn by one report that suggests there may not be a significant risk factor in the administration of such drugs to MH-susceptible individuals, our case supports the idea that caution should be exercised when administering lidocaine anesthetic, as it can indeed cause MH [4]. According to Minasian et al., members of the Malignant Hyperthermia Association of the United States (MHAUS) conducted a survey to investigate the occurrence of MH-like reactions in individuals (all of whom were MH susceptible

[MHS]) following amide local anesthesia. The survey involved 307 MHS respondents. Only one respondent reported symptoms indicative of MH after receiving amide local anesthetics. The report also highlighted that a significant proportion of the respondents (18%) had faced challenges in obtaining routine dental care due to their MHS status, with some having to undergo dental procedures without local anesthesia-or refusing treatment altogether. As a result, the members of MHAUS concluded that amide local anesthetics could be safely administered to MHS patients without major risks, and a diagnosis of MH susceptibility could negatively impact the quality of dental care provided to MHS patients. Nonetheless, while administering amide local anesthesia, caution must still be exercised toward individuals with a history of susceptibility to MH. Ignoring potential risks due to the relatively low incidence of reported symptoms could lead to poor management and increased mortality [4].

Lidocaine is an amide type of local anesthetic. Lidocaine can increase calcium release from the sarcoplasmic reticulum (SR) in muscle cells indirectly, through its effect on cyclic adenosine monophosphate (cAMP) levels. It can trigger the cAMP/ protein kinase A (PKA) signaling pathway [5]. cAMP is a signaling molecule that activates PKA, which can then phosphorylate and activate the ryanodine receptor (RYR1) in the SR. The RYR1 is the main calcium release channel in skeletal muscle cells, and its activation leads to the release of calcium from the SR into the cytosol of the muscle cell [6]. An increase in the release of calcium into the SR represents the pathophysiology behind the cause of MH. The hypermetabolic state seen in MH is due to abnormally elevated levels of calcium inside the muscle cell, which then causes rapid and sustained contraction of the muscle fibers, leading to their breakdown and rigidity. Further research has shown that lidocaine can increase intracellular calcium by enhancing the permeability of the SR membrane, which is mediated by its direct effect on SR Ca2+-dependent

ATPase enzyme [7]. Although the effect of lidocaine is not normally a concern in heathy individuals, caution should be exercised in those individuals with genetic mutations or MH susceptibility, since its use can intensify calcium release, which may, in turn, increase the risk of developing an MH reaction. Some case studies indicated that at low a concentration, lidocaine can inhibit the release of calcium from the sarcoplasmic reticulum, which is the storage site of calcium ions in muscle cells. This can lead to a reduction in muscle contraction [8]. However, at high concentrations, lidocaine can have the opposite effect leading to an increase in the efflux or release of calcium ions from the sarcoplasmic reticulum. This modulation of calcium handling by lidocaine has implications for individuals who are susceptible to malignant hyperthermia (MH). In individuals predisposed to MH, lidocaine's ability to increase calcium efflux at high concentrations can potentially trigger an MH episode. It is important to note that reports of lidocaine-induced MH are relatively rare. There have been a few documented cases where lidocaine has been associated with MH. For example, there was a case report of an MH episode occurring in a patient with underlying muscular dystrophy following extradural anesthesia with lidocaine. Another case of MH after intravenous lidocaine is administered for the treatment of ventricular arrhythmia [8]. Since there are few reported cases of lidocaine causing MH, further studies on pathophysiology of local lidocaine inducing MH are needed.

Lorazepam increases the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), thereby causing skeletal muscle relaxation. In this case report, lorazepam was given with IV fluids, which improved patient symptoms and as a result, dantrolene administration was altered. The mechanism behind the patient’s improvement was due to an increase in GABA, which can inhibit Ca influx inside the cell, leading to hyperpolarization and relaxation of muscle cells [9]. Based on the hypermetabolic state observed in MH, the tachyarrhythmias associated

with MH were, likely, a result of elevated calcium levels within the cardiac myocytes, which disrupts the normal electrical activity by affecting the pacemaker cells and conduction system. Additionally, the acidotic state in MH can trigger premature excitability of the pacemaker cells and conduction system, resulting in tachyarrhythmia.

Conclusion:

MH is a life-threatening hypermetabolic condition that occurs in people who are genetically predisposed to it. This genetic mutation is often seen in RYR1 or CANCA1S receptors, leading to an increase in intracellular calcium. This causes sustained muscle contractions and rigidity, leading to muscle breakdown and metabolic acidosis. Our case reported a patient with unknown MHS, who experienced MH symptoms after a lidocaine injection during a dental procedure- indicating that lidocaine can cause MH. Although the prevalence of lidocaine induced MH is low, it is essential to understand that certain individuals with genetic susceptibility can still be vulnerable to MH from lidocaine use. It can affect the SR either directly through an increase in its membrane permeability (causing calcium influx) or indirectly through the cAMP/PKA signaling pathway. As such, caution should always be exercised prior to administration of lidocaine as it is the most used local anesthesia.

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Footnotes

Informed consent statement: Informed verbal consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016)

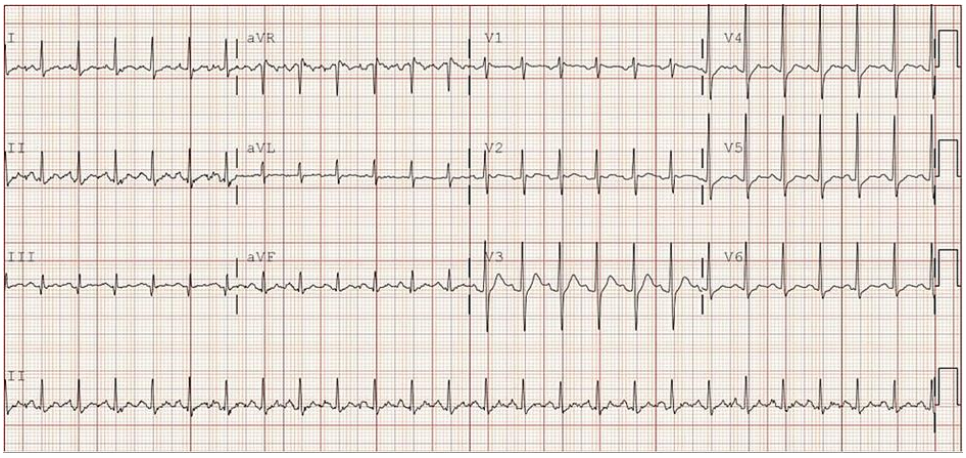

Figure 1: Electrocardiogram indicative of sinus tachycardia with heart rate of 150bpm and prolonged QT Interval of 520

Chemistry	**Results**
Urine toxicology	Negative

High-sensitive troponin	6.6 (3.0–58.9 ng/mL)
Myoglobin	197 (25–72 ng/mL)
Creatinine Phosphokinase	499 (10 - 120 mcg/L)
Calcium	7.5 (8.6–10.3 mg/dL)
Sodium	144 (136–145 mEq/L)
Potassium	3.7 (3.5–5.2 mEq/L)
Chloride	114 (96–106 mmol/L)
CO_2	21 (23–29 mEq/L)
Blood urea nitrogen	15 (7–20 mg/dL)
GFR	>60 (>60 ml/min/1.73m2)
Creatinine	1.63 (0.7–1.3 mg/dL)
Basic Coagulation	**Results**
International Normalized Ratio (INR)	1.17 (0.88 - 1.13 Ratio)
Partial Thromboplastin Time (PTT)	32.7 (27 – 37 Sec)
Prothrombin Time	13.7 (10.2– 13.3 NL)
Venous Blood Gas	**Results**
pH venous	7.37 (7.31- 7.41)
PCO2 venous	36 (41-51mmHg) Arterial conversion 41mmHg
HCO3 venous	20.8 (21-28mmol/L)
PO2 venous	78 (30-40mmHg)

Table 1: Laboratory Studies—Indicating Acute Renal Injury and Elevated CPK and Myoglobin