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CASE REPORT

Lidocaine-induced central nervous system toxicity during implantable cardioverter defibrillator placement – A case report and literature review

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KEYWORDS
Lidocaine;
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Abstract Lidocaine, a local anesthetic, is commonly used in various medical procedures. Despite its widespread use, most physicians are not familiar with the life threatening presentation of lidocaine toxicity and its treatment. Our case demonstrates successful management of local lidocaine-induced systemic toxicity in a 53-year-old female during insertion of an implantable cardioverter defibrillator. Our goal was to raise awareness of the risks and symptoms of local anesthetic toxicity, educate regarding the site of administration and dose of anesthetic delivery as independent risk factors for systemic toxicity and highlight the use of intravenous lipid emulsion as an antidote.
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PALAVRAS-CHAVE
Lidocaína;
Emulsão lipídica;
Anestético local;
Toxicidade

Intoxicação do sistema nervoso central durante a implantação de um cardioversor desfibrilhador implantável – Um caso clínico e revisão da literatura

Resumo A lidocaína é um anestético local vulgarmente usado em vários procedimentos médicos. Apesar do seu uso abrangente, a maioria dos clínicos não está familiarizada com os sinais e sintomas de toxicidade e o seu tratamento. O nosso caso demonstra o tratamento bem-sucedido de uma intoxicação sistémica de lidocaína numa mulher de 53 anos durante a implantação de um cardioversor desfibrilhador implantável (CDI). O nosso objetivo é consciencializar para os

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riscos, sinais e sintomas da intoxicação de anestésicos locais, informar sobre o local e dose de administração como fatores de risco independentes para a toxicidade sistémica e enfatizar o uso de emulsão lipídica como antídoto.
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Introduction

Lidocaine-induced systemic toxicity can occur after administration of an excessive dose, rapid absorption or accidental intravenous injection. Managing local anesthetic (LA) toxicity is challenging, therefore understanding the circumstances and being prepared for treatment is essential to optimize patient outcomes.

We present a case of lidocaine-induced systemic toxicity in a 53-year-old female with congestive heart failure (HF), who underwent an elective insertion of an implantable cardioverter defibrillator (ICD) as an outpatient. Our aim was to raise awareness among cardiologists of the warning signs of LA toxicity and create an understanding of the pathophysiology behind its various clinical manifestations and the use of intravenous lipid infusion as the treatment of choice to reverse symptoms.

Case report

A 53-year-old female patient with congestive HF, whose pre-procedural echocardiogram revealed an ejection fraction of 23% presented for an elective ICD at an outpatient hemodynamic center. She had a history of dilated cardiomyopathy post myocarditis, chronic obstructive pulmonary disease, hypercholesterolemia, peripheral artery disease and anxiety. Her outpatient medication was loop diuretics, angiotensin-receptor blockers and a benzodiazepine.

She had received fully optimized medical therapy but had sustained HF with reduced ejection fraction (HFrEF), and thus was referred for elective ICD insertion for the prevention of sudden cardiac death.[1] At the pre-procedure assessment, her body weight was 37 kg, her blood pressure (BP) was 85/40 mmHg, heart rate (HR) 76 beats per minute, respiratory rate (RR) 12 per minute and temperature 36.6 °C.

For the procedure, the patient was monitored with non-invasive blood pressure, pulse oximetry and electrocardiography. She received 2 mg midazolam prior to the procedure and had a Glasgow coma scale of 14. Lidocaine 1% subcutaneous infiltration was used for LA. Initially one ampoule 20 ml of lidocaine 1% (total 200 mg) was administered subcutaneously to enable dissection to create the pocket. Due to sustained patient discomfort during the procedure, additional lidocaine was given, total dose of 60 ml of lidocaine at 1% (3 lidocaine 20 ml ampoules, giving a total of 600 mg). There was a sudden loss of patient response to verbal and painful stimulus; an anaphylactic reaction was suspected, and an anesthesiologist was called for patient evaluation.

In the initial evaluation the patient was breathing at room air, with O_2 saturation of 99%, with oxygen at 3 L/min, bradypnea with resting rate of 9, normal chest expansion, no audible respiratory signs on auscultation, BP of 70/40 HR 69 and GCS of 3. Initially a bolus of 50 micrograms of adrenaline was given in order to increase cerebral perfusion pressure with increase of BP to 90/40 HR 97 with no neurological improvement. Local anesthetic toxicity was suspected and intralipid 20% 1.5 ml/kg bolus was given over the course of one minute. The patient became responsive with improvement of neurological status to GCS 10 to (O2M5V3). Continuous infusion of 0.25 mg/kg/min was given until complete neurological recovery. The patient was then transferred to an intensive care unit for 24 hours for surveillance and was discharged at 48 hours.

Discussion

Local anesthetics are widely used in daily medical practice. Their mechanism of action is through binding voltage-gated sodium channels, through which they inhibit the propagation of action potential, therefore enabling anesthesia. The main target organs are the central nervous system (CNS) and the cardiovascular system (CVS). Since the CNS is more sensitive to electrophysiological changes than the CVS, the dose that causes CNS symptoms is typically lower than the dose and concentration that results in cardiovascular toxicity.

Practitioners who use LA need to be aware of which patients at high risk of toxicity, the early symptoms and signs of LA systemic toxicity, in order to implement preventative measures when using local anesthetics, and the initial management of systemic toxicity with intravenous lipid emulsion.

The most critical aspect of LA is appropriate dosing. The lowest effective dose should be used and patient weight and comorbidities need to be considered when calculating the dose. The maximum recommended dose for subcutaneous lidocaine without epinephrine is 4.5 mg per kilogram (mg/kg) and for lidocaine with epinephrine, it is 7 mg/kg[2] as epinephrine acts by vasoconstricting the vessels at the administration site, thus reducing the absorption rate.[3,4] A suitable adrenaline concentration is 5 μg/ml (1:200 000), which reduces the peak plasma concentration of the LA by 30–60%.

The choice of the LA is a critical step. Lidocaine has the safest profile and offers the fastest onset but the lowest duration of action. The available preparations are lidocaine

1% (10 mg/ml), lidocaine 2% (20 mg/ml). Lidocaine 2% has, therefore, a lower safety margin when used subcutaneously in highly vascularized areas, such as the anterior thorax. Other available LAs are ropivacaine, levobupivacaine and bupivacaine. These have a slower onset of action but are longer in duration. Awareness of the cardiovascular collapse/CNS (CC/CNS) ratio is important. This is the ratio of the LA dose to cause cardiovascular collapse in relation to the drug dose required to produce seizures.[5] The lower the ratio, the more potentially hazardous the drug is. Among the commonly used LAs, bupivacaine has the lowest CC/CNS ratio, followed by levobupivacaine, ropivacaine, and lidocaine.[6] LA with a higher CC/CNS ratios has a greater safety margin, as the earlier occurrence of convulsions facilitates recognition of LA systemic toxicity and early intervention to prevent progression.[7]

Although local anesthetics are remarkably safe at therapeutic doses, practitioners treating medically complex patients must address the existing systemic diseases that may exacerbate the risk of toxicity from the anesthetic agent, as well as the technique. Any factors that alter LA pharmacodynamics contribute to increasing its plasma concentration and toxicity. Regarding absorption, an injection site close to a highly vascularized area and the use of high pressure while injecting contributes to intravascular installation. It is advisable that when using a subcutaneous infiltration injection technique, frequent aspiration is used prior to injection to ensure there is no intra-vessel administration as coupled with slow injection rate, it decreases the toxicity risk.

Lidocaine is a weak base and is distributed in blood bound by α1-acid glycoprotein (AAG). Any condition that leads to low AAG titer results in a higher concentration of free LA. Reduced hepatic and renal function and thus clearance leads to accumulation with repeated doses and infusions.

Special care is needed for patients with severe cardiac failure as they are particularly susceptible to LA-induced myocardial depression and arrhythmias. Characteristically systemic low perfusion leaves these patients with slower renal and liver clearance, slowing LA metabolism and elimination, thus posing the risk of drug accumulation. The use of LA with epinephrine needs be handled with care in patient with ischemic heart disease and arrhythmia.

In renal dysfunction, AAG is increased in patients with uremia and offers protection against systemic toxicity. Nevertheless, LA clearance is lower therefore the LA dose should be reduced by 10–20%.[8]

Patients with severe liver dysfunction often have other concomitant diseases such as renal and cardiac. Single-dose LA can be administered without dose reduction in liver dysfunction. However, in repeat blocks, it needs to be reduced by 10–50%. Elderly patients frequently have multiple co-morbidities altering LA pharmacokinetics and pharmacodynamics and there is a reduction in nerve morphology. In combination, all these factors suggest there is a benefit, in terms of safety, of dose reduction without reducing clinical efficacy.

Initial subjective symptoms of CNS toxicity include signs of excitation, such as lightheadedness and dizziness, tinnitus, confusion, and peri oral numbness. The objective signs of LA toxicity are excitatory, including shivering, myoclonus, tremors, and sudden muscular contractions. As the LA level rises, tonic-clonic convulsions occur. Symptoms of CNS excitation typically are followed by signs of CNS depression and ultimately respiratory depression and respiratory arrest. In the concomitant presence of other CNS depressant drugs, such as benzodiazepines, CNS depression can develop without the preceding excitatory symptoms.

Where there are higher plasmatic doses, CVS manifestations can occur such as rhythm changes, including a variety of arrhythmia presentations and negative inotropic effects and vasodilatation leading to a cardiovascular collapse.

LA-induced cardiac toxicity is particularly resistant to treatment, and advance life support (ALS) efforts should be prolonged up to one hour.[9,10]

A diagnosis of LA systemic toxicity is usually clinical as serum levels are not readily available and they do not guide or change treatment.

Once a patient develops symptoms of systemic toxicity, the only therapy that prevents death is lipid infusion. 20% lipid infusion is the first safe intravenous lipid emulsion used in medicine and was primarily use in parenteral nutrition. Intravenous lipid emulsion has been incorporated into safety guidelines over the last decade by anesthetic organizations all over the globe.[11,12]

The current agreed hypothesis for the efficacy of intravenous lipid emulsion in treating LA systemic toxicity, supported by in vitro studies, is the formation of an expanded intravascular lipid phase that absorbs the circulating lipophilic LA, hence reducing the unbound free LA available to bind to the myocardium.[13]

The recommended approach from the Association of Anesthetists of Great Britain & Ireland[14] for the management of severe LA toxicity involves four steps:

(1) Recognition of the CNS symptoms such as sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions as well as signs of cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias.
(2) Immediate management by stopping the injection of LA, calling for help, maintenance of a permeable airway, giving 100% oxygen and ensuring adequate ventilation, confirmation of a patent intravenous access, assessment cardiovascular status, and if present, seizure control with a benzodiazepine or propofol in small incremental doses. If cardiac arrest, start ALS.
(3) Treatment of the cause with an initial intravenous bolus injection of 20% lipid emulsion 1.5 ml/kg over 1 min and start an intravenous infusion of 20% lipid emulsion at 0.25 ml/kg/min associated with ALS. If cardiovascular stability has not been restored, a maximum of three boluses can be given (including the initial bolus) with 5 minutes interval. The infusion can be increased up to 0.5 ml/kg/min. Infusion should be continued until patient is stable and adequate circulation is restored.
(4) Follow-up in a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved. Exclusion of pancreatitis by regular clinical review, including daily amylase or lipase assays for 48 hours.

When there is sudden altered mental status (AMS) during a medical procedure under LA, the physician should evaluate

the patient in a systemic ''ABCDE'' approach to check for quickly reversible causes of AMS. Ideally this should happen as the patient is being placed on a monitor and intravenous access is being established. Rapidly reversible causes should be suspected and the patient checked for any causes for the hypoventilation and hypoxic state (hypercapnia, narcotic or benzodiazepine overdose), hypoperfusion state (cardiogenic, hypovolemic, allergic, hemorrhagic), or neurological depressant factors (hypoglycemia, electrolyte disturbances, stroke, toxic effects of medication).

Our patient weighed 37 kg and she received 60 ml of 1% solution. This totals 600 mg which is 3.6 times the amount of a recommended dose of 166 mg in her case. The anterior thorax is an area richly vascularized coupled with her low body weight and low ejection fraction caused her to be a high-risk patient for LA systemic toxicity.

When such challenging patients for LA infiltration are identified and it is likely to be difficult for them to tolerate the procedure, one of the most effective preventive measure is to refer them to an anesthesiologist for the procedure to be done under sedation or even general anesthesia.

Conclusion

Systemic lidocaine-induced toxicity can be life threatening. Rapid identification of the clinical symptoms is key to preventing death. For safer practice, it is advisable to calculate the highest tolerated patient-tailored dose prior to administration, opting for conservative conduct with LA doses in patients of an advanced age and those with poor cardiac function; to monitor BP HR and neurological status and to communicate with the patient, if feasible.

A plan for managing systemic LA-induced toxicity should be established and 20% lipid emulsion should be stocked close to facilities where LA is used for an early infusion and prevention of cardiac toxicity.

Conflicts of interest

The authors have no conflicts of interest to declare.

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