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Use of 10% Lipid Emulsion to Reverse Ventricular Fibrillation Following Of an Iatrogenic Local Anesthetic Overdose: A Case Report

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Abstract

Local anesthetic systemic toxicity (LAST) is a potentially fatal complication. Recognition of its occurrence, appropriate treatment and post-LAST care are essential to ensure a favorable outcome. This report describes the use of a lipid emulsion therapy (10% Lipovenos® emulsion), in a 41-year old woman, who inadvertently received cardioplegia following administration of 0.5% bupivacaine directly into the coronary ostium during extracorporeal circulation for aortic valvuloplasty. Although there have been no reports recommending its use for the pharmacological treatment of LAST to reversed toxicity, 10% lipid emulsion therapy may represent a viable alternative to the use of 20% lipid emulsion.

Introduction

Moreno and Maiz first described local anesthetic systemic toxicity (LAST) in animals in 1868, even prior to the first use of local anesthetics in humans. In 1884, Karl Köller applied cocaine for the first time as an anesthetic in ophthalmology [1,2]. From then onwards, these agents have been used to perform other kinds of anesthetic techniques and the first cases of toxicity, and even death, in humans quickly began to be reported.

The severity of LAST varies in accordance with the concentration of the drug in the blood stream [1-3]. Several factors alter the degree of absorption and consequently contribute towards toxicity, including the potency and dose of the agent, the vascularization of the exposed area, the presence of local vasoconstriction and the patient's physiological characteristics (age, hemodynamic status, liver function, pregnancy and acid-base status) [2]. The principal areas affected are the brain and the heart [1]. The process begins with blockade of the inhibitory pathways, complaints of a metallic taste in the mouth, tinnitus and perioral numbness [1,4]. Gradually, peripheral muscle contractions and even convulsions develop [1,4]. When the excitatory pathways are also inhibited, apnea and coma follow [1,3].

In 1998, Weinberg et al. showed that lipid emulsion therapy, a solution used in parenteral nutrition since 1961, effectively reversed the cardio toxicity generate by local anesthetics by increasing the median lethal dose by 50% [1-6]. In 2010, 39 successful cases had already been reported in humans, [7-10] contributing towards this therapy being accepted by the medical societies of anesthesiology [1].

Due to ethical limitations, it is impossible to conduct large-scale clinical trials to clarify the exact association between cardio toxicity and local anesthetics. Therefore, case reports and series of cases constitute the principal source of data on the prognosis and frequency of these events [3,4].

Case Description

A patient, a 41-year old, female, weighing 62 kg, classified by American Society of Anesthesiology (ASA) as physical status 3, hypertensive for four years, with a double aortic lesion (severe stenosis), was admitted to the surgical theater to undergo aortic valve replacement. She was alert and oriented, with no motor deficit or arrhythmia. The laboratory tests fulfilled the minimum requisites for surgery and her echocardiogram revealed left ventricular ejection fraction of 71%. Physical examination revealed a regular heartbeat with double sound, a diminished second heart sound and a systolic murmur of moderate intensity. Monitoring consisted of cardioscopy, pulse oximetry, invasive pressure monitoring in the left radial artery, central venous access catheters inserted via the right subclavian vein, nasopharyngeal temperature, urine output by foley bladder catheter and capnography. Total intravenous anesthesia was administered with 500 mcg of fentanyl, 20 mg of etomidate, 50 mg of rocuronium and a continuous infusion of 1% propofol and remifentanil to maintain anesthesia.

Sixty minutes after the induction of anesthesia, the aorta was clamped and extracorporeal circulation initiated. After concluding the valve replacement and 20 minutes after the second infusion of the cardioplegic agent, the heart showed no electrical activity. After a few minutes of internal cardiac massage, ventricular fibrillation occurred, but was refractory to internal cardiac massage used in combination with various defibrillation attempts. This situation persisted for 20 minutes until the inadvertent substitution of lidocaine for 0.5% bupivacaine (100 mg) in the cardioplegic solution was identified as the cause. This solution had been injected directly into the coronary ostium.

An infusion of 20% lipid emulsion was requested; however, only the 10% solution was available in the hospital. After an intravenous injection of a 90 ml bolus (1.5 ml/kg) of this emulsion, approximately 40 minutes after the final dose of the cardioplegic agent, defibrillation was repeated, leading to immediate reversal of ventricular fibrillation.

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The infusion was then maintained at 0.5 ml/kg for the following thirty minutes. Extracorporeal circulation was discontinued 110 minutes after its beginning, with a total period of cardiac arrest of 75 minutes.

The patient remained hemodynamically stable, with no need for vasoactive drugs. She was extubated in the surgical theater and sent to the intensive care unit. At that time, she was responsive, with no complaints and no neurological deficit.

Discussion

Local anesthetic systemic toxicity is a severe complication that is difficult to correct, principally when bupivacaine is used. The rate of accidents is around 7.5-20/10,000 peripheral nerve blocks and 4/10,000 epidurals [1,3]. In the case described here, involving general anesthesia for heart surgery with extracorporeal circulation, the manifestations of LAST were masked until physiological circulation was restored. The habit of retaining all ampoules used during any anesthetic/surgical procedure allowed the human error (the inadvertent addition of bupivacaine to the cardioplegic solution), a common cause of LAST, to be identified.

At toxic doses, local anesthetics may inhibit sinoatrial and atrioventricular nodal conduction, prolonging the PR interval, widening the QRS complex, generating atrioventricular blocks of various degrees and arrhythmias, including both bradycardia and tachyarrhythmia, reentering as ventricular tachycardia or fibrillation.[1] A blockade of the Na+, K+ and Ca+++ channels occurs. Bupivacaine binds predominantly to the Na+ channels in the open and inactive states [1,2]. Myocardial depression occurs for various reasons: inhibition of Ca++ release from the sarcoplasmic reticulum, blockade of the beta adrenergic receptors, and a reduction in adenylate cyclase activity, in cyclic adenosine monophosphate synthesis and in the conversion of ADP into ATP [1,2]. In the present case, the absence of electrical activity even 40 minutes after the final dose of the cardioplegic agent and following the conventional resuscitation maneuvers led to the hypothesis of LAST.

Evidence shows that local anesthetics exert different effects on mitochondrial oxidative phosphorylation and that these effects are largely dependent on their chemical structure [2,4]. Liposolubility, rather than stereospecificity, determines their effects on this bioenergetic function [4]. A study showed that bupivacaine, but not lidocaine, interacts avidly and selectively with small unilamellar, biomimetic liposomes containing cardiolipin, which alters their integrity, suggesting that this interaction is partially responsible for the cardiotoxicity of bupivacaine [4]. Mitochondrial dysfunction results in the depletion of ATP with an impact on intracellular calcium (Ca++) homeostasis, which in vivo, also contributes to toxicity [4]. Long-acting local anesthetics induce negative inotropic and lusitropic effects on the cardiac myocytes and this effect is mainly caused by a deficiency in calcium [4]. Bupivacaine, in vivo, reduces cardiac output, both because it is a negative inotropic drug and because it increases ventricular afterload [1,2].

Until recently, cardiopulmonary bypass was the only method recognized as effective for the treatment of refractory cardiac arrest due to LAST [1,9]. Currently, lipid emulsion therapy represents an effective option, with various reports of success. Three non-exclusive mechanisms may explain the effect of lipid emulsions [1]. The most generally accepted hypothesis, referred to as lipid sink, assumes that the lipid emulsion creates/expands a plasma lipid phase capable of chelating the liposoluble molecules of the local anesthetics, reducing their free fraction [1,9]. Three findings support this mechanism: the first one refers to the rapid functional recovery of the cardiac tissue (physical phenomenon) when these solution is administered. Thus, in vitro, the greater the lipid solubility of the lipids, the more they bind to the local anesthetics. Moreover, in the isolated intoxicated heart, the lipids hasten the process of eliminating these agents [1-23]. The second hypothesis refers to an effect involving inhibition of the reduction of fatty acid transport provoked by bupivacaine. Finally, the third hypothesis concerns an increase in intracellular Ca++ levels, with a positive inotropic effect on lipid levels below those required to reduce the aqueous level of bupivacaine [1].

In the current case, extracorporeal circulation, implemented to permit surgery to take place, may have contributed towards the success of resuscitation, even with a bolus of 1.5 ml/kg of 10% Lipovenos® MCT, half the concentration recommended in the literature (1.5 ml/kg of 20% emulsion).

In fact, for LAST therapy, even in the case of pregnant women, [13] the Association of Anaesthetists of Great Britain and Ireland (AAGBI) [14] and the American Society of Regional Anesthesia and Pain Medicine (ASRA) [15] recommend the following process: (1) Airway management and ventilation with 100% oxygen. (2) Suppression of seizures with benzodiazepines. (3) Lipid emulsion (20%) therapy: 1.5 ml/kg in 1 minute. (4) Continuous infusion of 20% lipid emulsion at 0.25 $ml/kg^{-1}.min^{-1}$. (5) Repeat the bolus twice with a five-minute interval between the two if satisfactory circulation is not reestablished (a maximum of three times, including the initial bolus). (6) After another five minutes, increase the infusion to 0.5 $ml/kg^{-1}.min^{-1}$. (7) Respect the upper limit of lipid emulsion recommended, which is 10 ml/kg (ASRA, 2010) or 12 ml/kg (AAGBI, 2007) over the first 30 minutes [16,18]. ASRA also differs in some other points: they recommend only one additional bolus and advocate maintenance of the emulsion therapy infusion for ten minutes after hemodynamic stability is achieved [15].

Few studies have evaluated the most effective dose, the ideal duration and the most opportune moment at which to initiate therapy [3]. There is also a need to understand the side effects and long-term effects of LAST [3,9-25]. Cardiovascular instability may also return, even after reversal of the bupivacaine-induced cardiotoxicity with lipid emulsion therapy [25].

In the case described here, since the 20% lipid emulsion was unavailable, LAST was reversed in an alternative, unusual way. A 1.5 ml/kg bolus of the emulsion with half the recommended dose was used, followed by a continuous infusion as recommended. Noteworthy that the propofol used in intravenous anesthesia is also a lipid emulsion; however, no data in the literature justify any possible benefit and it did not indeed substitute the 20% lipid emulsion [9]. Although unusual, 10% lipid therapy proved effective. The patient remained hemodynamically stable throughout her hospital stay. Therefore, this dose may represent an alternative treatment option.

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