

Treatment with lipid therapy to resuscitate a patient suffering from toxicity due to local anesthetics

Manuel Monti,¹ Alessio Monti,²
 Francesco Borgognoni,¹
 Giovanni Maria Vincentelli,³
 Federico Paoletti¹

¹Emergency Department, Local Health Unit UMBRIA1, Assisi; ²Department of Engineering, Roma Tre University, Rome; ³Emergency Department, Fatebenefratelli Hospital, Rome, Italy

Abstract

Recently, although without a universal recognition, the use of lipid emulsions as a rescue therapy for the bupivacaine cardiac toxicity has been proposed. In this article we report a successful resuscitation of a patient after the injection of bupivacaine in emergency room and a commented review of the related literature. The patient is a 73 years old man that, after a subcutaneous injection of bupivacaine (0.5%, *i.e.* 0.5 mL/h), developed circulatory arrest. After the failure of the initial treatment based on the advanced life support protocol, we have successfully performed a therapy with lipid emulsion. The bupivacaine intravascular injection, together with its interaction with amitriptyline and carbamazepine, could lead to cardiac depression, severe arrhythmias, hypotension, and/or cardiac arrest. In the case of failure of traditional life support treatment, intravenous lipid emulsion proves to be the best therapy to treat bupivacaine systemic toxicity.

Introduction

Local anesthetics (LAs) are frequently used in emergency therapy.^{1,2} They generally exhibit a low incidence of adverse events, but they have a very high mortality rate.^{3,4} Local anesthetics have common features: they are all composed of three chemical groups and produce a reversible inhibition of the sensory conduction of the nerve impulse at the regional level by selectively blocking sodium channels in the membrane (Figure 1). In particular, local anesthetics hinder the propagation of the action potential along the axon. This effect provokes the inhibition of the sodium channels by acting on specific receptors. Under quiescent condition, LA has a reduced functionality but, during depolarization, LA binds to the

sodium receptor and it further decreases the sodium stream.⁵ This indicates that LA has different binding affinities depending on the conformation of the channel and, in particular, LAs are greater when the channel is depolarized. The first studies about the systemic toxicity of local anesthetics were done by Murloy.³ More recently, Lee,⁶ performing a study named *Closed Claims Database* for the American Society of Anaesthesiology and using data from 1980 to 2000, pointed out that the toxicity of LA is the main cause of brain damage or death. Although it is difficult to calculate the precise impact of LA systemic toxicity, many studies on animals have established the direct effect of LAs on the systemic reaction.^{3,4,6,7} The organs mainly affected by LA toxicity are the central nervous and the cardiovascular system. Toxicity depends on many factors, among which the most important ones are the plasma concentration, the time required to reach the peak concentration, the drug type, the characteristics and the co-morbidities of the patient, apart from the way of administration.⁸

Between the main manifestations of neurotoxicity, it is possible to include partial seizures and fasciculations and, with an increasing dose, a generalized tonic-clonic seizures until reaching a central nervous system (CNS) depression state.^{9,10} The cardiovascular system is less resistant to bupivacaine if compared to other anesthetics,¹¹ and the toxic manifestations include deep sinus bradycardia, elongation of the PQ interval, QT and QRS complex to atrioventricular block and, finally, asystole and hypotension.¹² Recent studies indicate that, beside the blockage of sodium the channel, LAs also act in the mechanisms of potassium and calcium channels and they are responsible of some alterations in the mitochondrial metabolism as well as in the ATP production.¹³

In 1998, in an experiment on animal *in vivo*, Weinberg was the first to demonstrate the efficacy of the intravenous lipid emulsion (ILE) in the treatment of cardiac arrest induced by a bolus of bupivacaine.¹ Subsequent case reports¹⁴⁻²¹ have validated the clinical use of ILE in the treatment of severe systemic toxicity due to local anesthetics.

The effectiveness mechanisms of the ILE treatment against the toxicity of local anesthetics have not been yet clarified, but, probably, one of the dominant effects of the emulsion is the lipid intravascular expansion that is able to absorb the offending circulating lipophilic toxin and to reduce, in this way, their concentration in the sites of action (lipid sink theory).²²⁻²⁶ The hypothesized mechanism is schematized in Figure 2. At this regard, we observe that Mazoit *et al.*²⁷ have studied the different formulations of fat emulsion used in the treatment of the local anesthetics toxicity and they have concluded that the formulations

Correspondence: Manuel Monti, Emergency Department, Local Health Unit UMBRIA1, Via V. Muller 1, Assisi (PG), Italy.
 Tel. +39.334.6617176 - Fax: +39.075.5412205.
 E-mail: montimanuel@tiscali.it

Key words: local anesthetics, cardiac toxicity, resuscitation, lipid therapy.

Contributions: MM is the main author and conceived the paper and drafted its first version; FP provided a critical revision of the paper in some important intellectual aspects; GMV contributed with literature review and pictures design; AM contributed in data analysis of the study and, in the final version of the paper, improved technical aspects and English-written; FB, as Emergency Department director, made the overall revision of the paper and guaranteed the integrity of the entire study. All the authors read and approved the manuscript.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 4 July 2013.
 Revision received: 16 December 2013.
 Accepted for publication: 20 December 2013.

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 Emergency Care Journal 2014; 10:1820
 doi:10.4081/ecj.2014.1820

consisting of long-chain fatty acids are about 2.5 times more effective compared to that consisting of a mixture of fatty acids 50/50 long and media chain.

Case Report

The patient was a 73-year-old, 75 kg, 176 cm, male, that arrived at the emergency department for a major wound involving the skin and subcutaneous tissue (width 10 cm, length 5 cm) on the left leg. After his arrival in the emergency area, the patient shown the following clinical conditions: heart rate (HR) of 80/min, sinus rhythm, SpO₂ 100, noninvasive blood pressure (NIBP) 128/82 mmHg, peripheral pulse was palpable, capillary refilling time was normal. Regarding his medical history, the patient did not report significant events except for a previous diagnosis of fatty liver, arterial hypertension treated with angiotensin-converting-enzyme inhibitors and a chronic neuropathic pain treated with amitriptyline and carbamazepine. We performed therapy with local anesthetic (bupivacaine 0.5%, *i.e.* 0.4 mL/kg) and we began the wound suturing.

Approximately 30 seconds after anaesthesia, the patient has abruptly lost consciousness and has developed a tonic-clonic seizure. An oxygen treatment was immediately started using a facemask attached to a self-inflating resuscitation bag. About 90 seconds later, the tonic-clonic seizure was interrupted and the patient remained unconscious.

Immediately, we have applied to the patient the patches of a Zoll biphasic defibrillator that have shown an asystolic cardiac rhythm. Moreover, it was not possible to detect blood pressure. Advanced cardiac life support (ACLS[®]) was immediately started by performing chest compressions. The patient was intubated and the tube position was confirmed by auscultation. During the first 20 minutes of the ACLS, a total of 3 mg epinephrine, given in three doses, was administrated to the patient without noticing an improvement of the clinical situation.

Since there was no response with the normal protocol of cardiac advanced support, we have used an initial intravenous bolus injection of 20% lipid emulsion 1.5 mL/kg⁻¹ over 1 min (Intralipid[®]; Fresenius Kabi, Bad Homburg, Germany) followed by administra-

tion of 100 mL/h of lipid emulsion, while continuing cardiopulmonary resuscitation. After 5 minutes of lipid administration, the electrocardiogram tracing was reassessed and it showed a shockable rhythm (Figure 3), which was converted through the technique of biphasic defibrillation (200 J). After 2 minutes of reevaluation, we have noticed the presence of a sinus rhythm and of the carotid pulse. After the described emulsion lipid therapy, vital parameters were: HR 158/min, sinus rhythm NIBP 120/68 mmHg, SpO₂ 100 on O₂, RR- 24/min. Blood tests are shown in Table 1. Thereafter, the patient remained hemodynamically stable. He has not required further inotropic/vasoactive medications during his persistence in the emergency department. An infusion of lipid emulsion was started and continued at 0.5 mL×kg⁻¹×min⁻¹ over the following 2 h and then discontinued. He was weaned from mechanical ventilation and extubated approximately 2.5 h later.

Then, the patient was transferred to the intensive care unit in stable conditions with a normal sinus rhythm (Figure 4) and, after one month, he was discharged with no neurologic abnormalities.

Discussion

Bupivacaine was first synthesized in 1963 and, since then, it have been used in many applications including local anaesthesia. In addition to its local anesthetic effect, it is a strong depressant of electric conduction which predisposes the heart to arrhythmias.²⁸

The toxic dose of bupivacaine is generally 1.5 mL/kg. In our case, it is a very unusual that a low dosage of bupivacaine 0.5% (0.5 mL/kg) has given such dramatic effects. In our opinion, there are several causes that could explain these tragic consequences. In particular, the local anesthetics toxicity probably has depended on the unintentional fast intravenous injection (considering the emergency department where we have operated) that, as already described in other studies,²⁸ and is responsible of toxicity effects on the cardiac function (hypotension, aritmia, *etc.*²⁹) and on the CNS.⁹⁻³⁰ Moreover, we noted that the rapid appearance of cardiovascular depressant effect of the LA agent affects, as a probably contributory cause, the association among bupivacaine, carbamazepine and amitriptyline.

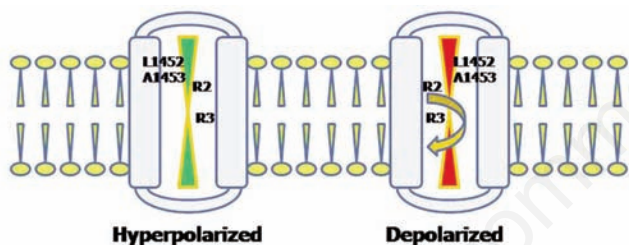


Figure 1. Model of the fourth homologous domain (D4) of the human skeletal muscle sodium channel (hNaV1.4) with the S4 segment depicted as a rotating cylinder.



Figure 3. Ventricular fibrillation.

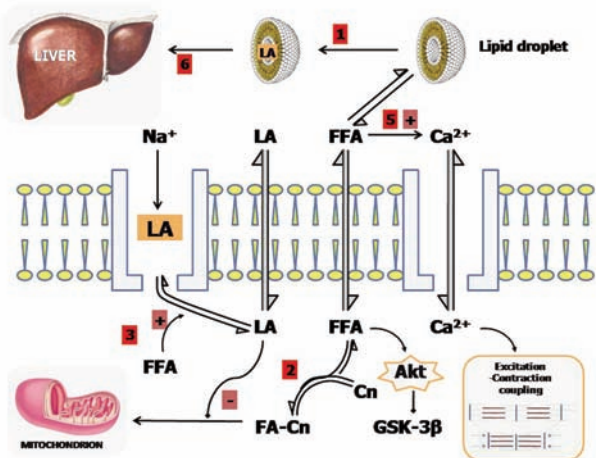


Figure 2. The theoretical mechanisms of lipid rescue.

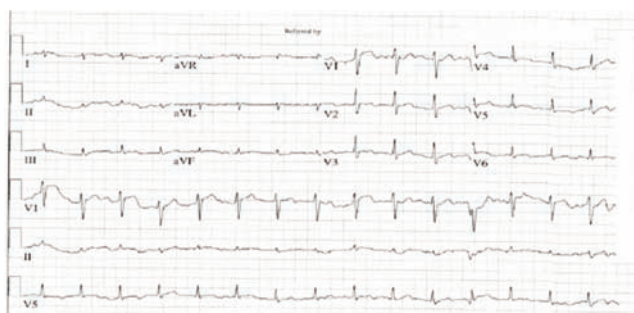


Figure 4. Sinus rhythm after defibrillation.

Table 1. Blood test results.

Parameter	Value	Normal range
pH	7.35	7.35-7.45
pCO ₂ (mmHg)	37	35.00-45.00
pO ₂ (mmHg)	75	80-100
Na ⁺ (mEq/L)	135	136-145
K ⁺ (mEq/L)	3.6	3.5-5.1
Glucose (mg/dL)	157	60-110
HCO ₃ (mmol/L)	24.3	21-28
SO ₂ (%)	98	75-99
Hct (%)	41	40-50
Hb (g/100 mL)	14.1	13-17
Lactate (mg/dL)	13	13-15
Albumin (μmol/L)	25	35-50

pCO₂, plasma carbon dioxide; pO₂, pressure of oxygen in the blood; HCO₃, bicarbonate; SO₂, sulfur dioxide; Hct, hematocrit; Hb, hemoglobin.

In fact, the unusual combination of the amitriptyline and carbamazepine,^{31,32} used for chronic neuropathic pain, can exacerbate bupivacaine toxicity. As it is well known, amitriptyline is a pharmacologically weak base capable of accepting protons to become cationic, thus generating an acidic environment. This effect may induce a reduction of the bupivacaine lipophilicity with a consequent increase in the active bupivacaine concentration. This phenomenon has been first observed by Strichartz, who demonstrated an increase of the aqueous:octanol partitioning of bupivacaine in case of pH reduction,³³ and confirmed by Mazoit *et al.*³⁴

Moreover, carbamazepine is able to reduce the propagation of abnormal impulses in the brain, by blocking sodium channels, and to interfere with the action potential of the Purkinje fibers and of the bundle of His, leading, finally, to atrioventricular blocks and arrhythmias.³⁵ In our case, characterized by an high-level of active bupivacaine concentration, the carbamazepine could have facilitated the appearance of tonic-clonic seizure and ventricular fibrillation.

Finally, our patient had an undiagnosed severe hypoalbuminemia (2.5 g/dL) that could have definitely increased the toxic effect of the anesthetic.³²

Conclusions

The experience provided by this case report suggests to make immediately available in all areas of our emergency department a proper number of 100 mL of 20% lipid emulsion. Since 2006, the Association of Anaesthesiology of Britain recommends that intralipid 1000 mL of 20% should be immediately available in all areas where potentially cardiotoxic doses

could be administered through local anesthetics. Intravenous lipid emulsion is also recommended in the guidelines of Australian and New Zealand College of Anaesthetists for cardiac arrest due to lipophilic molecules responsible for blocking and calcium channel beta, when conventional therapies fail resuscitation.^{36,37}

The expected benefits of ILE are difficult to quantify, but on the basis of limited animal and human data, it can be classified as life-preserving. However, human cases of LA poisoning are infrequent and a systemic evaluation is not yet possible. We agree with Picard³⁸ when he states that fat emulsion is a *crucial antidote* to the toxicity of local anesthetics.

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