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Review Article

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Intoxication Local Anaesthetics: Intravenous use of Lipid Emulsion as Antidote

Edilson Martins Rodigues Neto[1,2*], Lidia Audrey Rocha Valadas Marques[3], Francisco Josimar Girão Junior[1], Emerson Dias Ponte[4], Márcia Oliveira Coelho Campos[5], Maria Augusta Drago Ferreira[3], Patrícia Leal Dantas Lobo[6] and Marta Maria França Fonteles[3]

[1] Catholic University Center of Quixadá, Pharmacy course, Quixadá-Ce, Brazil
[2] Federal University of Ceará, Department of Physiology and Pharmacology, Fortaleza-Ce, Brazil
[3]Federal University of Ceará, Department of Pharmacy, Fortaleza-Ce, Brazil
[4]Federal University of Ceará, Department of Clinical Dentistry, Fortaleza-Ce, Brazil
[5]State University of Ceará, Fortaleza-Ce, Brazil
[6]Federal University of Ceará, Sobral Campus, Dentistry Course, Sobral-Ce, Brazil

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ABSTRACT

The local anesthetic technique when performed with a quality product results in the abolition of autonomic and sensory motors functions. The cardiotoxicity caused by local anesthetics is a hard condition to manage, given traditional therapies, which are quite limited. Thus, it is crucial to evaluate the clinical feasibility of using Lipid Emulsion (LE) intravenously in the treatment of poisoning by local anesthetics, because this may be a viable therapeutic option as rescue procedure. Currently, in the hypothetical level that the LE acts by three distinct mechanisms of action: Formation of a "Lipid Trap," transport of fatty acids to the mitochondria of the cardiac muscle tissue and a positive inotropic effect in the myocardium. One can derive that its clinical utility in cardiovascular collapse is higher in the first moments of intoxication AL, before installation of the situation of hypoxia and/or metabolic acidosis. In this context the use of LE as therapy for acute intoxication AL appears as a safe and effective alternative, with a very low risk profile and with a good degree documented evidence of benefit. Thus, it is important for the surgical team's the knowledge of this therapy in the cardiotoxicity management caused by acute intoxication for AL.

Keywords: Local anesthetics; Toxicology; Clinical pharmacology

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INTRODUCTION

Chemically, local anesthetics are molecules that can be separated into three fragments: an aminic, secondary or tertiary grouping, amine derivative ethanol or acetic acid giving water solubility properties; an aromatic grouping, benzoic acid derivative, aniline or thiophene which provides properties of lipid solubility, essential for the penetration of the local anesthetic in the nerve fiber; a chain of intermediate hydrocarbon containing an ester or amide bond, which operates in the union of the two previous groups, classified as amino esters or amino amides. The intermediate chain is of great importance, as there are large differences in the degree of allergenicity in power and metabolism, when comparing the two groups of drugs [1-3].

The local anesthetic agents are basic compounds, but their commercial preparations are slightly acidic salts dissolved in physiological saline solution or distilled water.They can be associated or not with vasoconstrictive substances. After injection into the body, these drugs cross the membrane of the axon in its non-ionized form, this way they reach the inside of the nerve cell, which its ionized by connecting to the inner portion of the sodium channel. The connection prevents the entry of sodium ion blocking membrane depolarization, required to generate a nerve impulse and conducting this to the central nervous system. Thus, thermal, barometric and

painful sensations are diminished or abolished [4].A local anesthesia performed with a quality product and proper technique results in the abolition of autonomic and sensitive motor functions. The Inhibition of transmission in peripheral fibers follows a sequence already elucidated: initial blockage of autonomic fibers, responsible for thermal sensation, tactile and painful followed by related pressure and vibration and finally proprioceptive and motor. This sequence depends on the diameter portion and myelination of nerve fibers. Recovery of nerve function occurs in reverse order [5].

Nowadays there is difficulty in measuring the frequency of the cardiovascular system toxicity of local anesthetics due to lack of large-scale studies, and evidence-based; however even with the lack of studies can be mentioned a theoretical rate of 0.98 per 1,000 reactions procedures [6].A complex clinical situation, in recent times, it was a cardiac arrest refractory due the classical clinical procedures such as administration of epinephrine during surgical or medical procedures. One event of this size could only be solved with the realization of a cardiopulmonary bypass [7].In this context the Lipid Emulsion (Le) appears as a promising antidote to poisoning by Local anesthetics (LA),it also provides use in poisoning by other drugs, like calcium channel blockers, β-blockers, tricyclic antidepressants and barbiturates [8]. According to published data, the toxicity systemic reactions more frequent caused by AL are: Allergic; cardiotoxicity; neurotoxicity; haematotoxicity and the mixed [6.9].It is believed by AL toxicity events in adults may be subject to sub-notifications. They can be classified as very rare, but estimates suggest approximately 20 cases per 10,000 peripheral nerve blocks and 1.2 to 10,000 epidural anesthesia. The mortality rate is around 0,023 cases per 100,000 [6].As other drugs, local anesthetics have adverse effects. The most common affect the heart and the central nervous system. It is essential the knowledge of professionals about the risks inherent in the administration of local anesthetics and the procedure to reverse its toxicity [6].The cardiotoxicity caused by local anesthetics is a hard condition to handle using just the traditional therapies, because they are quite limited [5].Thus, it is crucial to evaluate the clinical feasibility of using EL intravenously in the treatment of poisoning by local anesthetics, as this may be a viable therapeutic alternative as a salvage procedure [5]. This study aims to conduct a literature review on the use and viability of EL as antidote in poisoning situations by local anesthetics.

REVIEW

The EL has its use consolidated in the clinical practice as an energy supplier of essential fatty acids to patients on parenteral nutrition without possibility of enteral nutrition, like newborns, patients undergoing large gastrointestinal surgery and severe anorexia [10]. The EL infusion emerges as a new method for the treatment of systemic toxicity caused by AL. It is showing also be promise as an effective antidote to poisoning caused by other medicinal lipophilic drugs [11,12]. The toxicity of AL is mainly characterized by neurotoxic and cardiotoxic events. In the central nervous system level occurs a suppression of the inhibitory pathways. It leads to the feeling of metallic taste may reach a convulsive event, and the events are directly proportional to plasma concentrations of toxicant. Already in the cardiac system the toxicity culminates in a cardiovascular collapse, arrhythmias, and depression of myocardial contraction [13]. The cardiotoxicity is commonly attributed to the rapid increase in plasma concentrations or excessively high doses of AL. It happens generally by a poor anesthetic technique. It makes the drug reaches the systemic circulation. This follows a biphasic course of action: at lower concentrations is activation of the sympathetic nervous system excitatory during this phase the central nervous system (CNS) may result from hypertension and tachycardia events. This can mask the direct depressant effects on myocardium, which occurs with higher concentrations of Al, characterized by ventricular arrhythmias, myocardial conduction delays and profound contractile dysfunction leading to cardiovascular collapse [14]. The primary mechanism for cardiac toxicity refers to blockage of myocardial channels voltage-dependent sodium, which causes a decrease in the duration of the PR wave range and causes a prolonged dose-dependent, with driving the QRS; as well as a possible depression of pacemaker activity. A lock of persistent sodium channels will predispose to recurrent arrhythmias. This electrophysiological event is compounded by the direct negative inotropic effect common to the AL, which will generate bradycardia and hypotension. Blockade of potassium and calcium channels may contribute to cardiotoxicity, which means up to three sites of action for toxicity of LA [9]. Often, AL are associated in the formulation with vasoconstrictor agents, these can be sympathomimetic or analogue of vasopressin. The endogenous catecholamines and sympathomimetic synthetic agents can cause sympathetic activation in heart β1 receptors, resulting in tachycardia, palpitations, arrhythmias and increased cardiac output; and α1 receptors of the blood vessels increase blood pressure by vasoconstriction. In an ideal anesthetic technique does not occur systemic absorption of the vasoconstrictor, these effects are more common in anxious patients, in which the concentration of endogenous norepinephrine and epinephrine is increased about 20 to 40 times during the process [15]. Another worrying factor is the occurrence of lone atrial fibrillation after AL administration with vasoconstrictor. This effect occurs due to the increase in myocardial contractility because the stimulation of cardiac α receptor after the association between exogenous and endogenous catecholamines at high doses, as seen in stress situations [16]. An interesting fact is that there is a correlation between lipid solubility AL and inhibition of cardiac contractility. This clinically relevant additional

evidence supports the conclusion that ropivacaine is less toxic than levobupivacaine. And levobupivacaine is less toxic than bupivacaine [9]. Currently it is believed that the EL acts on three different action mechanisms: Formation of a "trap Lipid", transporting fatty acids to the mitochondria of the cardiac muscle tissue and positive inotropic effect on infarction [8]. In the case of lipid trap is believed that the infusion of intravenous EL will generate the creation and / or expansion of a highly lipophilic phase in the plasma. This results in the "trapping" of drugs with lipophilic characteristics. And the local anesthetics (due to the aromatic groups present in its structure to ensure a high degree of apolaridade), reflecting, in a biological availability of the drug to exert its toxicity in its site of action. This theory presents three fundamental points: the important how quickly the myocardial tissue recovers from AL toxicity after infusion of EL and may be related to a physical-chemical phenomenon; AL may be set in vitro with the use of lipids, such fixing increasing according to the increase of character nonpolar its chemical and finally structure, it was found that in experimental preparations isolated heart exposed to toxic doses AL was further removing the toxicant after the introduction of the EL system [17,18]. In a second EL mechanism of action, the supply of fatty acids to the mitochondria can be related particularly to the toxic action of bupivacaine, which leads to a blockade of this pathway. Thus, infusion of EL become an exogenous source of fatty acids into the mitochondria of the cardiac tissue carrying an opposing action in this toxic effect, thereby preventing a cardiovascular collapse [19,20]. In addition to these other mechanisms EL also features as pharmacological action the modulation of the cardiac contractility with the positive inotropic effect. This action antagonize the depressor effect of LA, being very effective. It occurs at lower concentrations than those required to lower the concentration of Al in the aqueous phase of the system, thus, can not be attributed to the action of "Trap Lipid". This response is due to the increased concentration of intracellular calcium [8,21-23]. In the market there is currently a range of pharmaceutical products that deliver fatty acids in the form of EL. All of them with the main purpose to provide fatty acids to patients on total parenteral nutrition (TPN). The differences between the products are made from a composition. The EL can be classified into four generations, according to their chronological order of development (Table 01) [10].

Table 1: Classification of Laws according to their chronological order of development (Waitzberg; Torrinhas; Jacintho, 2006)

First generation	Second generation	Third generation	Fourth Generation
EL rich in omega-6 to establish safe EL. We chose to product rich in long-chain triglycerides (LCT), mainly from soybean oil and less frequently, the corn and sunflower oils. In the 70s it was noticed that the EL seemed modular negatively the immune system, which encouraged the development of new products.	EL mixed presenting medium chain triglycerides (MCT) and soybean oil. In order to reduce the amount of omega-6. This EL consists in a mix of 50% MCT (derived from coconut oil) and 50% soybean oil (LCT). By not relying on cotransporters, as carnitine, which carries long-chain fatty acids into the cells. The MCT metabolism is rapid energy source.	EL animal. This is formulated with fish oil rich in omega-3s, particularly EPA - eicosapentaenoic acid and DHA - docosahexaenoic acid.Studies suggest that inflammatory nature of diseases can be sensitive and that an increase in these fatty acids can improve the treatment of patients with respiratory disorders, cystic fibrosis, rheumatoid arthritis, arteriosclerosis, acute heart disease, sepsis, and cancer associated cachexia in use NPT.	EL composed of mixed fatty acids of animal and vegetable origin with soy oil, olive oil and fish. This formulation contains small amounts of omega-6 (30%), TCM (30%), olive oil (24%) and fish oil, rich in omega-3 (15%), in addition, it is supplemented with appropriate amounts alpha-tocopherol antioxidant. This new pharmaceutical product showed good tolerance and metabolism in clinical trial with healthy volunteers. There was also less associated liver dysfunction.This contributs also to preserve the antioxidant activity in-patient intensive care unit and a favorable effect on the length of stay of surgical patients.

In urgent toxicology the treatment of poisonings still not having a consensus about the usefulness of the various formulations. Some studies have suggested that pharmaceutical preparations have equivalent effectiveness. However, other authors suggest greater efficiency EL containing LCT, this earning a power 2.5 times larger than the other. The EL animal and mixed are still little used in clinical toxicology [13,24,25]. Despite the increasing interest in clinical toxicology for the use of EL as a pharmaceutical for the treatment of poisoning by AL and other chemical structure of drugs predominantly nonpolar and physicochemical character lipophilic the use of EL also has limitations . One difficulty of its clinical use is the safety of the rapid infusion of a considerable amount of EL, considering that his classic clinical use in TPN occurs with slow administration and diluted [13].

Studies show that in case of hypoxia the infusion of EL could generate a negative effect for the loss generated by the situation in the main metabolic pathway of fatty acids. In addition, metabolic acidosis in situations would be a decrease of the therapeutic effect of EL in the capture of the LA, which would make it less effective. Thus, you can earn your clinical utility in cardiovascular collapse is higher in the first moments of intoxication AL before installing the hypoxic situation and / or metabolic acidosis [8,13,24].

Like other pharmaceutical products the EL present risks in their therapeutic use. Studies have associated with its use with a range of adverse events, even in a nutritional requirement, as: allergic reactions, fever, thrombocytopenia, coagulatórios disorders, decreased neutrophil activity, pancreatitis and transient elevation of liver enzymes. Although not documented adverse events in the use of EL as an antidote in doses not usais nutritional therapy [8,26].

An important factor in the clinical use of EL is that the size of lipid droplets have an impact on the occurrence of adverse effects. Thereby, theoretically the rapid infusion EL could contribute to the coalescence of the system leading to an increased risk of embolism lesion vascular [8].
Some information about the treatment of poisoning with AL infusion EL are interesting. Unlike the NPT, the EL do no need administration in a central venous catheter. This may be infused EL in peripheral veins. This occours because its low osmolarity which at 20% solutions is 270-345 mosm / L-1. In TPN the recommendation of dosage is 0.7 to 1.3 g of triglycerides / kg-1 / day and monitoring triglyceride levels; If Chegem 400 mg / dL-1 or 1000 mg / dL-1 infusion should be decreased or stopped, respectively. Given another reality in clinical toxicology the EL doses needed to be adapted for acute cases of serious poisoning AL. The Association of Anaesthetists of Great Britain and Ireland in 2007 released guidelines currently accepted for the management of poisonings AL, being followed by other companies such as the American Society of Regional Anesthesia and Pain Medicine, cited in Table 02 [5,13,27,28]

Table 2: Guidelines of the association of anaesthetists of Great Britain and Ireland for the management of poisoning (Neal; Bernards; Butterworth, 2010)

1. Maintenance of the airways and oxygenation;
2. Treatment of convulsions with intravenous diazepam, EL 20% 1,5mLl / kg-1 in 1 minute bolus;
3. EL Infusion 20% 0.25 ml / kg-1 / min;
4. Repeat bolus twice with five minutes interval was satisfactory circulation is not restored;
5. After another five minutes, increasing infusion to 0.50 ml / kg, 1 / min
6. Respecting the upper limit of 20% lipid emulsion is recommended that 10 ml / Kg-1 in 3 minutes.

CONCLUSION

Local anesthesia is essential to carry out a range of invasive procedures. So it is extremely important that the professional is familiar with the anesthetic solution to be injected, especially in relation to their actions and contraindications. All these factors contribute to the prevention of systemic adverse effects.
In this context the use of EL as therapy for acute intoxication by AL is an alternative safe and effective. This has a very low risk profile and documented benefits with a good degree of evidence. It is therefore important for the surgical team knowledge of this therapy in the management of cardiotoxicity caused by acute intoxication AL.

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