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Review article

Local anesthetic systemic toxicity (LAST) – Should we not be concerned?

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ABSTRACT

Local anesthetics are one of the most commonly used drugs in the field of medicine. Yet little is known about the systemic toxicity that can occur with their overdose. In the last few years, a lot of research has taken place understanding the etiology of the Local anesthetics systemic toxicity (LAST) and the role of lipid emulsion in treating it. There is a need to increase the awareness about LAST and establish a protocol to treat any serious neuro or cardiotoxicity.

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Introduction

Local anesthetics (LA) are one of the most commonly used drugs in the field of medicine. Anesthesiologists love them, surgeons use them and physicians like them to make some of their procedures easier. Though the recommended safe doses are always known to the users, severe neuro and cardiotoxicity consequent to unintended intravascular injection or delayed tissue uptake are not unknown in clinical practice. Are we really aware of or concerned about this systemic toxicity of local anesthetics? Are we adequately prepared to treat it? The time has come when these questions need a definite answer.

The last few years have witnessed a worldwide recognition of the existence or possibility of local anesthetics systemic

toxicity (LAST) and the acceptance of lipid emulsion as an antidote to LA poisoning. There is a non-commercial educational website dedicated to the use of intravenous (iv) lipid to treat this drug overdose <http://www.lipidrescue.org>. It was initiated by Guy Weinberg and it reports all the cases of LAST treated by lipid emulsion. Besides, there is information on the etiology of LAST, mechanism of action of lipid emulsion and various other aspects. The Council of the Association of Anaesthetists of Great Britain and Ireland was the first in the world to acknowledge and establish a guidance document on the use of lipid to treat local anesthetic intoxication in 2007 (updated in 2010).¹

American Society of Regional Anesthesia (ASRA) Practice Advisory² in 2010, also published guidelines which assimilate and summarizes current knowledge regarding the

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prevention, diagnosis, and treatment of this potentially fatal complication.

History

Mild to severe toxic effects of LA have been known since the very time cocaine, the first LA was used in 1880s.³ Since then, there have been several published reports in the literature^{4,5} which confirm their association with seizures and respiratory depression. A lot of research has taken place in the field of pharmacology with an aim to discover drugs in this category which are safer for clinical use. Bupivacaine, one of the most common long acting LA used, was introduced in the 1960s but had the most serious concerns of systemic toxicity associated with its overdose. This led to the development and marketing of its safer and less cardiotoxic enantiomers ropivacaine and levobupivacaine in the late 1980s but LAST continued to be reported even with them.⁵ It was more than ten years later that some animal studies indicated that lipid emulsion may be useful in successful resuscitation following overwhelming doses of LA.⁶ Controlled trials in humans were not possible to prove the hypothesis. However, the first case of successful use of 20% lipid emulsion in refractory cardiac toxicity was reported in 2006⁷ and since then there have been many more such reports supporting the hypothesis.^{8–12}

What is the mechanism of action of local anesthetics and how does LAST happen?

Chemically, LA have hydrophilic and hydrophobic moieties that are separated by an intermediate ester or amide linkage. The hydrophilic moiety is either a tertiary or a secondary amine and the hydrophobic moiety is aromatic. The type of linkage between the two determines many of the pharmacological properties. Hydrophobicity on one hand increases the duration and potency of the drugs while on the other hand decreases the therapeutic index making them prone to toxicity.¹³ pK_a , lipid solubility and molecular size are the other factors that also affect the pharmacological action of LA. The commonly used LA, lignocaine and bupivacaine, are both amides but differ largely in their hydrophobicity (366:3420). Lignocaine is less potent but has a faster onset though shorter duration of action than bupivacaine.

LA reversibly block the action potentials responsible for nerve conduction by binding to a specific receptor site within the pore of the Na^+ channels in nerves, thereby blocking the ion movement. They also block conduction in nerve axons in the peripheral nervous system and interfere with the function of all organs in which conduction or transmission of impulses occurs. Thus, they may also have clinical effects on the central nervous system (CNS), the autonomic ganglia, the neuromuscular junction, and all types of muscle in the event of overdose.

A variety of factors come into play when LA are injected, which is why LAST does not occur in most cases. The incidence and severity is affected by individual patient risk factors, concurrent illness and medications, site and technique of drug use, specific type of local anesthetic compound, total local anesthetic dose (concentration $\times$ volume), time of

detection of toxicity, and adequacy of treatment. In most of the cases, it is usually a combination of more than one of these factors which contributes to a severe response.

Drug doses have to be reduced in the neonates and young infants because of their immature liver and renal function and decreased plasma protein concentration. The elderly may have poor organ function affecting the metabolism of LA. There may also be a need to alter LA doses in epidural infusions in obstetric cases because of several hormonal and mechanical factors.¹⁴

It is a common practice to combine one long acting LA with another LA with faster onset like bupivacaine with lignocaine. However, it should be strictly noted that their toxicity is additive and therefore, the individual recommended doses (usually 2–3 mg/kg, 5 mg/kg and 7 mg/kg for bupivacaine, lignocaine and lignocaine with adrenaline respectively for most peripheral nerve blocks) are no longer safe.¹⁵

The site of injection of LA plays a major role in the incidence of LAST. Some of the regional nerve blocks are vulnerable to iv injection of the drug because of their close proximity to blood vessels. The commonest are intercostal blocks followed by epidural and brachial blocks. The incidence is approximately 1:10,000 for epidurals and 1:1000 for peripheral nerve blocks (www.lipidrescue.org). Considering how common and frequent these blocks are, it is very important that care should be taken while performing them, and adequate monitoring and resuscitation measures should be available to treat any untoward toxicity.¹⁶ It is best not to administer more than one block in order to avoid any overdose.

Features of LAST

With absorption of LA and their increasing plasma concentration, there is stimulation of the central nervous system (CNS) followed by depression. As the LA is absorbed further, there may be tremors, restlessness followed by tonic-clonic convulsions due to selective depression of inhibitory neurons. With faster and greater absorption, it may directly cause loss of consciousness with respiratory depression following sudden depression of all neuronal activity.¹³

LA may target the myocardium where it may decrease the electrical excitability, conduction rate, and force of contraction resulting in severe ventricular arrhythmias and myocardial depression. There may be a sudden cardiovascular collapse with sinus bradycardia, conduction blocks, asystole or ventricular tachyarrhythmias (mainly re-entry type). Bupivacaine is more cardiotoxic than equi-effective doses of lignocaine. Although both the drugs block sodium channels rapidly during systole, it is bupivacaine which dissociates more slowly during diastole. Therefore, at the end of diastole there are still a large number of these channels which are blocked making the cardiotoxicity more cumulative and more potent. The dose of bupivacaine required for irreversible cardiovascular collapse compared to that required for CNS toxicity is lower than that of lignocaine (CC:CNS ratio 2.0:7.1 for the two LA).¹⁷ Moreover, bupivacaine cardiotoxicity may be difficult to treat and may worsen in the presence of hypoxemia, hypercarbia or acidosis.¹³ Commercially available

bupivacaine is a racemic mixture of (R)- and (S)-stereoisomers. Ropivacaine and levobupivacaine are single (S)-stereoisomers formulated with an aim to decrease the cardiotoxicity (former has a propyl group compared to a butyl group on the piperidine ring in the latter). The reversal of Na^+ channel blockade appears to be faster and negative inotropy lesser with ropivacaine.^{18–20} Groban et al has shown that the doses required to induce cardiovascular collapse were greater for lignocaine than ropivacaine, levobupivacaine and bupivacaine in that order.²¹

Guidelines for the Management of Severe Local Anesthetic Toxicity based on the 2010 update by the Association of Anaesthetists of Great Britain and Ireland¹ are as follows-

For the immediate management

Recognize symptoms of severe toxicity and stop the LA injection immediately. Maintain airway (if required with a tracheal tube) and administer 100% oxygen. Confirm intravenous access and control seizures with either

a benzodiazepine, thiopental or propofol in small incremental doses. It is recommended to monitor the cardiovascular status throughout the resuscitation and take blood samples for analysis, if feasible.

Treatment of cardiac arrest – Cardiopulmonary resuscitation (CPR) should be started and arrhythmias should be managed using standard protocols (they may be very refractory to treatment and lignocaine should not be used to treat them) in cases of circulatory arrest. Conventional therapies may be used to treat hypotension, bradycardia or tachyarrhythmia in patients without circulatory arrest.

Treatment with lipid emulsion should be started simultaneously with an intravenous bolus injection of 20% lipid emulsion 1.5 ml/kg over 1 min followed by an infusion at 15 ml/kg/h. A maximum of three repeat boluses (in not less than 5 min interval) can also be given 5 min later if the cardiovascular stability has not been restored or has deteriorated further. The infusion dose may also be doubled after 5 min if required, and the infusion should be continued till the stabilization of circulation or maximum lipid emulsion dose

LOCAL ANESTHETIC SYSTEMIC TOXICITY (LAST)

MANAGEMENT GUIDELINES

Initial Management

RECOGNITION OF SIGNS OF LAST
CALL FOR HELP
STOP LA IMMEDIATELY
MAINTAIN AIRWAY
IV ACCESS
CONTROL SEIZURES

Treatment

Your nearest lipid emulsion(20% Intralipid) is kept here.....

Fig. 1 – Guidelines for the management of Local Anesthetic Systemic Toxicity (LAST).

given (12 ml/kg cumulative dose). It should be noted that prolonged resuscitation may be required in these cases and CPR should be continued along with lipid emulsion.

It is most important to emphasize the need for awareness of the antidote so that its immediate availability could be made. All the members of the medical and paramedical staff must be aware of clinical presentation of LAST and the exact place where lipid emulsion (commonly 20% Intralipid™) is available in their set up. A copy of the institutional guideline to treat LAST should be displayed in common treating areas of the hospital. Fig. 1 shows a prototype of guidelines which may be used for the armed forces medical units.

Once signs of local anesthetic toxicity are manifest, the accumulating evidence supports early use of lipid infusion to attenuate progression of the local anesthetic toxic syndrome contrary to the earlier practice of trying lipids only after an unsuccessful cardiopulmonary resuscitation. The therapeutic potential of lipids has also been highlighted by the National Patient Safety Agency of UK.²²

How does lipid emulsion help in treating LAST?

The exact mechanism of how lipid emulsion works is yet not clearly established despite several animal trials and convincing reports of its clinical success.^{23,24} Among the various theories proposed, the 'lipid sink' theory²⁵ is widely accepted. It suggests that lipophilic LA molecules partition into a lipid phase created by the lipid emulsion within the plasma. The lipid thus acts as a 'sink' by binding and extracting LA, reducing free LA in the aqueous plasma phase and making it unavailable to the cardiac tissue. Bupivacaine being more lipophilic than others in the group, explains this effect in refractory cardiotoxicity.

The other theory proposes the direct effect of lipid emulsion on inotropy of the heart.²⁶ It improves cardiac contractility and restores ventricular systolic pressure, thereby playing a significant role in treating myocardial depression due to LA.

Last but not the least is the theory by Weinberg et al suggesting a salutary effect of lipid emulsion on oxidative metabolism in cardiac myocyte. Bupivacaine inhibits acyl-carnitine exchange in cardiac mitochondria and potentially inhibits mitochondrial function by affecting the fatty acid transport at its inner membrane. Lipid emulsion improves mitochondrial fatty acid uptake by providing a high plasma triglyceride concentration or more specifically by acting on the flux of acylcarnitine.²⁷

Lipid emulsion should be immediately available in all areas where potentially cardiotoxic doses of LA are given, along with guidelines for its use. However, future laboratory and clinical experiences are likely to bring refinement to the method.

LAST does happen and we should be prepared to detect it in time and take all necessary measures to prevent any morbidity or mortality.

Conflicts of interest

All authors have none to declare.

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Book review

P. Ganjei-Azar, M. Jorda, A. Krishna, *Effusion Cytology – A Practical Guide to Cancer Diagnosis 2011*, Demos Medical Publishing LLC, 11W, 42nd Street, 15th Floor, New York, NY10036, USA (2011). pp. 192, Paperback, Price-\$5\$, ISBN: 13 9781933864655

The presence of malignant cells in body cavity fluids commonly indicates an advanced cancer stage associated with poor prognosis. The detection in effusions is extremely important and presents a challenging task. There is an urgent need to reduce the high false negative rates of conventional cytology by using a simple systematic approach to the diagnosis of malignancy, the potential subclassification of the neoplastic process and by determining the site of origin whenever possible. The authors have used a practical and simple approach for the diagnosis of malignancy in effusions including a primer on the most effective use of immunocytochemistry (ICC) with small panels of antibodies for select cases.

This book emphasizes on easily accessible diagnostic clues. Initial chapters offer an introduction and discussion on cellular content of pleural, peritoneal, and pericardial effusions. General diagnostic criteria used to differentiate benign from malignant cells are discussed along with detailed list of the types of malignancies found in effusions. Major differential diagnoses such as adenocarcinoma versus reactive mesothelium and malignant mesothelioma are covered. Next few chapters explain the detection of primary tumor site based on morphology, site of sample and patients' gender. Chapter 6 is dedicated to cerebrospinal fluid cytology. Sample collection, fixation, and preparation of slides for ICC are

discussed. Illustrated examples and the basic cytodiagnostic criteria of malignant cells and their markers as well as pointing out the pitfalls in the use of ICC have been covered lucidly. Tables listing the differential expression of specific markers for the diagnosis of various types of tumors are shown. Last chapter briefly discusses flow cytometry as a diagnostic tool for detection of malignant cells in body cavity fluids. Examples of flow cytometric data used to identify malignant cells on the basis of their DNA aneuploidy and tumor cell associated markers' expression are discussed.

This book will serve as a practical text for the budding and practicing pathologists, who face daily diagnostic dilemmas in effusions cytology, requiring the use of ICC. Cross-references are extensive and are intended to help the reader without having to read preceding chapters. A short list of suggested readings complement each chapter for further information.

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