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Journal of Clinical Toxicology

Case Report

Local Anesthetic Systemic Toxicity Associated with Exparel Use

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ABSTRACT

This case highlights a unique presentation of Local Anesthetic Systemic Toxicity (LAST) in a healthy young adult male following routine inguinal hernia repair surgery. Neurologic symptoms developed after the administration of both exparel and bupivacaine, albeit within their recommended safe concentrations. The symptoms occurred over an hour after administration and appeared to be more neurotoxic than cardiotoxic which is typically not what occurs with bupivacaine. Once the patient started to experience seizures after the operation was completed numerous doses of abortive IV benzodiazepines were given without successful termination of the seizures. Resolution only occurred after the patient received lipid emulsion therapy, a proposed therapy for LAST. Follow up labs and further investigation including CT and MRI of the brain did not reveal any other cause for the patient's seizure. This case demonstrates a clear-cut occurrence of LAST with a rather unique presentation. This was a much delayed presentation with neurotoxic predominance associated with bupivacaine and exparel which is not routinely used in the Emergency Department (ED). This is a diagnosis that must be on the differential for all emergency medicine physicians regarding seizure of unknown origin.

Keywords: Local Anesthetic Systemic Toxicity (LAST); Bupivacaine; Drug; Toxicity; Lidocaine

INTRODUCTION

We describe the case of an 18-year-old male who developed Local Anesthetic Systemic Toxicity (LAST) after a regional nerve block prior to inguinal hernia repair surgery. He received two doses of bupivacaine HCL 0.25% along with exparel (liposomal bupivacaine) 1.3%. The patient developed an abrupt onset of seizure activity about one hour after anesthetic administration. The seizure activity did not terminate after four doses of IV benzodiazepines. Ultimately the decision was made to administer Intravenous Fat Emulsion (IFE) which resulted in seizure termination. Symptoms of lidocaine/bupivacaine associated systemic toxicity, while well described, usually present earlier in onset after medication administration. In addition, exparel should not be used at the same site as other non-bupivacaine local anesthetics due to concern for the possibility that bupivacaine will be immediately released from exparel. This case highlights an unusual presentation of delayed central nervous system symptoms associated with exparel administered with bupivacaine HCL in an otherwise healthy young adult presenting to the hospital for a routine surgical procedure.

CASE PRESENTATION

An 18-year-old male, weighing 67.3 kg with no past medical history presented to the hospital for an uncomplicated left inguinal hernia repair. He received a Transversus Abdominis Plane (TAP) block prior to surgery, with 10 mL of exparel (molar equivalent to 150 mg of bupivacaine HCl) mixed with 30 mL of 0.25% bupivacaine. After the surgery was complete, the patient received a second direct local wound block using repeat doses from the prior TAP block. Both the TAP block and local wound block were performed by an anesthesiologist using ultrasound guided technique. There were no complications recorded during the surgical procedure or with the regional nerve block performed including significant blood loss, overdose, or intravasation. After surgery, the patient was brought to the Post-Anesthesia Care Unit (PACU). After a 1 hour observation

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Received: 26-Jul-2022, Manuscript No. JCT-22-18566; **Editor assigned:** 29-Jul-2022, PreQC No. JCT-22-18566 (PQ); **Reviewed:** 19-Aug-2022, QC No. JCT-22-18566; **Revised:** 29-Aug-2022, Manuscript No. JCT-22-18566 (R); **Published:** 05-Sep-2022, DOI: 10.35248/2161-0495.22.12.520

Citation: Hoffman S, Petrou S, Leubitz A, Schwartz A (2022) Local Anesthetic Systemic Toxicity Associated with Exparel Use. J Clin Toxicol. 12:520.

period he experienced abrupt onset of confusion followed immediately by a generalized tonic-clonic seizure. Vitals at time of seizure onset were as follows: BP 140/90 mm Hg, Pulse 130 beats per minute, Respiratory rate of 20, Temperature 99.9 F, and oxygen saturation of 100% on a non-rebreather. The patient was given multiple doses of intravenous benzodiazepines with no resolution of the seizure activity. He was initially given 2 mg of midazolam followed by 3 doses of lorazepam; 2 doses of 1 mg, subsequently increased to 2 mg. The first benzodiazepine was given at 11:45, and the last dose was given at 12:08. Due to the seizure being refractory to standard treatment and the history of the recent bupivacaine injection, Intravenous Fat Emulsion (IFE) therapy was administered starting at 12:12 which resulted in seizure termination and improvement in mental status. The patient was given both 20% lipids 250 cc IVPB as well as 20% lipids 100 cc bolus. The patient was transported to the pediatric intensive care unit where he remained hemodynamically stable and had no return of Central Nervous System (CNS) symptoms. The patient was further evaluated with bloodwork and CT/MRI imaging, which were unremarkable. In addition, there were no signs of cardiotoxicity as noted by cardiac monitoring and EKG evaluation. The patient did not demonstrate interval changes including PR or QRS prolongation. The patient was presumed to have developed bupivacaine associated systemic toxicity secondary to exparel use with termination of his CNS symptoms with supportive care and IFE (Table 1).

Anesthetic	CC/CNS*
Bupivacaine	2-3
Etidocaine	4.4
Ropivacaine	5
Lidocaine	7.1
Mepivacaine	7.1

Note: *=The ratio of the dose causing cardiac collapse to the dose causing neuorologic symptoms

Table 1: A low CC/CNS ratio is associated with more cardiotoxic agents.

RESULTS AND DISCUSSION

The history of local anesthetics dates back to 1859 when cocaine was first isolated from coca leaves and first used clinically in the early 1880's [1]. Since that time, much research has gone into the development and discovery of other local anesthetics with different pharmacokinetics in order to create safer medication profiles with less adverse side effects. Nonetheless, cases of Local Anesthetic Systemic Toxicity (LAST) still exist with numerous contributing factors. LAST is not solely dependent on the amount or dose of a particular anesthetic given. Toxicity is influenced by anatomic site of administration, experience of the administrator, route of administration, the anesthetic's pharmacokinetic profile, the patient's medical comorbidities that may affect drug metabolism, as well as whether a vasoconstrictor was added to the formulation. The amide anesthetics are typically more highly protein bound and thus have a longer duration of action. Something that varies amongst these medications is their lipophilicity. A report by Albright, et al. [2], published in 1979 discusses the direct relationship between drug lipophilicity and the potential for cardiac toxicity.

Local anesthetics provide analgesia by binding voltage-gated sodium channels, blocking the excitation threshold of nociceptive afferent neurons. This blockade prevents pain transmission from peripherally located primary afferent neurons [3-5]. This same mechanism by which local anesthetics produce analgesia also contributes to one of the hypotheses for the mechanism of their toxicity. Local anesthetics binding voltage-gated sodium channels affect phase 0 of the cardiac action potential. Inhibition of these cardiac Na-channels may lead to electrophysiologic dysfunction, causing conduction disturbances and arrhythmias [3,5,6]. This effect is exacerbated by a second proposed mechanism through inhibition of fatty acid transport at the inner mitochondrial membrane. This causes decreased oxidative phosphorylation and loss of cardiac energy resulting in contractile dysfunction. The specific mechanism by which LAST occurs varies with different anesthetics due to their pharmacologic profiles, including affinity by which they bind cardiac Na-channels [3,6].

CNS symptoms, on the other hand, appear to be caused by a different mechanism altogether. Local anesthetics disrupt the transmission of GABA while also inhibiting TASK potassium channels leading to neuronal excitability and induction of seizures [7]. The ratio of cardiovascular to CNS toxicity also varies amongst local anesthetics. Within the literature is described a cardiovascular collapse/CNS (CC/CNS) ratio. This is defined as the ratio of drug dose required to cause cardiovascular collapse compared to the drug dose required to cause seizures. A low CC/CNS ratio is associated with more cardiotoxic agents while a high CC/CNS ratio is associated with a greater safety margin [8]. Bupivacaine has a CC/CNS ratio of 2.0 compared to 7.1 for lidocaine. Therefore, progression from CNS signs and symptoms to cardiovascular collapse occurs more frequently with bupivacaine than with lidocaine [9,10]. In short, bupivacaine has a higher risk/predominance of cardiovascular toxicity.

Local Anesthetic Systemic Toxicity (LAST) should be suspected whenever physiologic changes occur after administration of local anesthetics. It is classically described as the onset of both cardiovascular and central nervous system symptoms within 5 minutes of administration of local anesthetic [10]. However, in a review of 93 reported cases of LAST that occurred over 30 years until 2009, only 60% of cases followed this classic presentation [10]. The remaining cases either had delayed onset or solely involved cardiovascular effects. LAST has a variety of presentations, ranging from cardiovascular to neurologic. Neurologic complications include agitation, confusion, and loss of consciousness with seizures being the most severe [10].

Treatment of LAST includes supportive care and airway management, as prevention of hypoxia and acidosis may

eliminate the potential cardiovascular collapse and/or seizures [11]. Benzodiazepines can be used for seizure termination but should theoretically not prevent seizure recurrence. Benzodiazepines will exert their effect on GABA but will not alter the amount of local anesthetic in circulation, which is where Intravenous Fat Emulsion (IFE) exerts its benefit. The lipid sink theory proposes that highly lipid-soluble drugs, including local anesthetics, are absorbed into the lipid emulsion of the plasma and removed from tissues affected by toxicity [12]. Multiple studies have examined this theory including a study that showed lipid emulsion enhanced bupivacaine removal from cardiac tissues following bupivacaine induced asystole in isolated rat hearts. The increased removal also caused an improvement in hemodynamics [13]. Another proposed mechanism focuses on decreased fatty acid transportation in the cardiac mitochondria due to local anesthetic inhibition of carnitine-acylcarnitine translocase. Fatty acid oxidation provided by lipid emulsion contributed to the recovery from bupivacaine induced cardiac depression in rats [14]. Combined, these theories propose that lipid emulsion therapy not only removes local anesthetic from affected tissues, but also aids cells in oxygen phosphorylation and energy production. Lipid emulsion therapy has now been added to resuscitation guidelines internationally.

There are numerous formulations of local anesthetics that we as providers must be aware of. This includes liposomal bupivacaine-exparel, which was administered to the patient in this case. Pharmacokinetically, the delayed and sustained release of the bupivacaine results in continuous analgesic serum concentrations with attenuated peak concentration. Co-administration of non-liposomal anesthetics can cause an undesired more rapid release of bupivacaine molecules, resulting in an increased potential toxicity. Thus, it is recommended not to give a local anesthetic other than bupivacaine at the same time, as this will result in an immediate release of bupivacaine from the liposomal formulation. There is also a suggested maximum dose of exparel, just like with all local anesthetic formulations. This recommended maximum dose is 266 mg. If also administering bupivacaine, it is recommended not to exceed a ratio of milligram dose of bupivacaine to exparel of 1:2 [15]. The occurrence of LAST, when administering doses within these guidelines is extremely rare, however can still occur as was seen in this patient, which further demonstrates the uniqueness of this case.

This case demonstrates the development of LAST in an otherwise healthy 18-year-old male with no significant past medical history or predisposing risk factors for LAST including cardiac disease, liver dysfunction, or concomitant use of other medications [9]. It occurred after a non-emergent surgical procedure where all precautions were taken to ensure anesthesia efficacy and safety, including use of ultrasound guided technique and use of recommended doses for co-administration of exparel and bupivacaine. Nonetheless, the patient experienced an unusual presentation of bupivacaine toxicity, with onset of symptoms 1 hour after anesthetic administration with a predominance of CNS symptoms.

CONCLUSION

This case highlights an unusual presentation of bupivacaine associated systemic toxicity with delayed symptoms that were predominantly Central Nervous System (CNS) in nature. Regardless of doses given, providers must keep Local Anesthetic Systemic Toxicity (LAST) on their differential diagnosis as a cause of potential CNS toxicity, which may not always follow the typical trend occurring rapidly after medication administration. Bupivacaine is highly lipophilic and more classically associated with cardiovascular toxicity when compared to other local anesthetics such as lidocaine. Resolution of the CNS dysfunction only terminated after administration of IFE, the suggested antidote for LAST. Providers must also be aware of the different formulations of anesthetics, including exparel which is becoming more routinely used during surgery.

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