Lipid Emulsion in Treatment of Local Anesthetic Toxicity

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Epidural, spinal, regional, local, and intravenous administration of local anesthetics (LAs) is a cornerstone of anesthetic practice. LA toxicity is a grave consequence that is of great significance to anesthesia providers. Outcomes of LA toxicity range from inconvenient symptoms such as tinnitus, twitching, and hypotension to seizures; cardiovascular or respiratory collapse; and death. Lipid emulsion has emerged as a potential "magic bullet" in treating LA toxicity. This literature review provides background information and proposed mechanisms of action for LAs and lipid emulsion as well as animal experiments and a case report that speak to the effectiveness of lipid emulsion in the face of LA toxicity.

Keywords: *local anesthetic, toxicity, lipid rescue, lipid emulsion, regional anesthesia.*

REGIONAL ANESTHESIA HAS long been an integral part of anesthetic practice. Peripheral nerve blocks, spinals, and epidurals allow patients to safely undergo a wide variety of surgical procedures with minimal side effects and pain. To accomplish a peripheral nerve block, local anesthetic (LA) solution is injected in the tissue bed of an individual peripheral nerve or nerve plexus.[1] The increased use of indwelling nerve catheters with pain pumps and ultrasound-guided techniques have decreased the risks associated with LA intravascular injection. However, regional anesthetic techniques are not without risk. Adverse effects of LAs can occur from allergic reactions, systemic toxicity, increased systemic absorption, and drug-specific effects. LA toxicity still occurs most frequently from accidental intravascular injection of a LA during performance of a peripheral nerve block. Toxic effects depend on the drug used and the amount administered. Therefore, the best method for avoiding LA toxicity is prevention.[2]

Despite efforts to prevent LA toxicity, it still occurs. A 2010 report by Corcoran et al[3] found that the rates of LA toxicity have declined over the last 25 years, but toxicity still occurs in approximately 1 in 2,500 epidurals and between 1 in 500 and 1 in 1,200 peripheral nerve blocks. Other clinical reports support that LA toxicity from regional anesthetics are uncommon. Surveys from the United States and France involving more than 280,000 regional anesthetics performed reported an incidence of seizures with epidural injection to be 1 of 10,000 and an incidence of 7 of 10,000 involving peripheral nerve blocks.

At therapeutic levels, LAs can help achieve sensory and motor blockade during surgery. Therefore, anesthesia providers must adhere to the maximum

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Conflict of interest: None to report.

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1089-9472/$36.00

http://dx.doi.org/10.1016/j.jopan.2014.03.011

safe doses for the particular LA used for the procedure. Limited high plasma concentrations from systemic absorption of LA drugs are achieved by establishing a maximum acceptable LA dose.[4] At doses higher than the therapeutic levels, LAs can produce toxic symptoms. Toxicity by highly lipophilic LAs, particularly bupivacaine, has been a major culprit of perioperative morbidity and mortality. Bupivacaine is unusual in that it exhibits high potency at cardiac sodium channels, resulting in cardiac toxicity before central nervous system (CNS) toxicity is observed.

Several animal models involving pretreatment with benzodiazepines have been effective in the prevention of LA-induced seizures. Ethical considerations make it impossible to perform such studies in humans.[2] Therefore, the medical community must rely on published case reports to educate. Recent literature, animal studies, and case reports point to the use of intralipid therapy as a treatment for LA toxicity. As more evidence emerges unveiling the potentially life-saving benefits of lipid emulsion, its place as a commonly used treatment will become more universal among perianesthesia providers.

LAs in Anesthetic Practice

Anesthesia providers have several uses for LAs. These agents are used to anesthetize nerves located in the periphery to facilitate surgery and to provide postoperative pain relief. Anesthesia providers are particularly interested in the ability of LAs to block neural impulses in the spinal cord, spinal nerve roots, and peripheral nerves. LAs are used in clinical anesthesia in various fashions. Providers use these agents for topical application, direct injection into tissues, and intravenous (IV) administration to produce desired effects at various locations including the central neuraxis, mucosa, skin, and peripheral nerves. To minimize the complications associated with LAs, the practitioner must have an intricate knowledge of the pharmacological effects of each LA that will be used in their clinical practice.[5]

Mechanism of Action of LAs

In electrically excitable tissue, LAs block the generation, propagation, and oscillation of electrical impulses. As a result, these agents prevent nerve conduction in axons by targeting and blocking voltage-gated sodium channels. Voltage-gated sodium channels are ion channels that result in rapid depolarization during the first phase of the action potential. The result is the failure of sodium ion channel permeability to increase as a result of slowing down the rate of depolarization so that the threshold potential is not reached. The net result is no propagation of an action potential.[1] The receptors near the intracellular end of the sodium channel are blocked in a time- and voltage-dependent manner by LAs. The LAs selectively bind the sodium channel in the inactivated closed state. The overall result is channel stabilization in the inactivated closed state, thus preventing change of the channel to the rested-closed and activated-open states in response to a stimulus.[1]

The minimum concentration of LAs needed to block nerve conduction is termed "Cm".[1] "Cm" varies with respect to what type of nerve fiber that is to be blocked. Clinical observation has shown that nerves functionally have different sensitivities or rates of effect when exposed to a particular LA. The concentration needed to block inner (motor) neuron fibers is approximately twice that needed to block outer (sensory) neuron fibers.[5]

Block onset can be shortened, and depth of blockade can be increased by the addition of sodium bicarbonate to the LA solution. The addition of a base increases the solubility percentage of LA in the lipid, thus making more drug available to traverse across several cellular compartments. This also explains why nerve blockade from LAs injected into acidic tissues is much less profound (ie, infected tissues).[1]

Absorption of LA at the site of administration is determined by factors such as injection site, drug dosage, drug properties, drug-tissue binding, vasoconstriction, and blood flow. Since the early 1890s, epinephrine has been added to LAs to prolong their duration of action. The reported benefits of the addition of epinephrine to LAs include increased intensity of block as well as decreased systemic absorption of the drug. Although epinephrine with longer-acting LAs does not necessarily prolong the duration of action, it does decrease the risk of rapid vascular absorption owing to vasoconstriction. Overall decreased