9-1-2009

Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals, September 2009

Medical University of South Carolina

Heather Kokko
Medical University of South Carolina

Kelli Garrison
Medical University of South Carolina

Jason Cooper
Medical University of South Carolina

Chris Wisniewski
Medical University of South Carolina

See next page for additional authors

Authors

Medical University of South Carolina, Heather Kokko, Kelli Garrison, Jason Cooper, Chris Wisniewski, and James New

MUSC Health
PHARMACY SERVICES

Drug Information Center
Department of Pharmacy Services
RT Annex, Room 604
Phone: 792-3896
E-mail: druginfo@musc.edu

Visit us on the Web!
www.formularyproductions.com/musc

Editorial Staff

In This Issue

Pharmacy & Therapeutics
Update
Drug Information for Health Care Professionals
September 2009

Lipid Rescue for Cardiotoxicity Secondary to Anesthetic Medications

By Brianne Dunn, PharmD
PGY1 Pharmacy Resident

Local anesthesia is widely used throughout MUSC. While generally safe, local anesthesia (LA) can be toxic if used in inappropriate doses or routes. Even when properly administered, patients may experience unintended reactions to LA.[1-5] Inadvertent intravascular injection is the most common cause of LA toxicity even when administered within the recommended dosage range.[1,5]

LA involves the injection of an local anesthetic agent into the skin and subcutaneous tissue, anesthetizing the skin surrounding the injection site.[1,2] These agents can be classified into 2 groups, the esters and the amides. The esters have short-acting properties and, therefore, are used for brief surgical cases. Amides are longer-acting in terms of block efficacy.[3] Onset of action, potency, and duration of action are determined by the pharmacokinetic and pharmacodynamic properties of each specific agent, such as pKa, lipid solubility, protein binding, tissue pH and vasodilatory effects.[1] Agents with greater lipid solubility generally demonstrate a greater potency while those with high protein binding show increased duration of action.[3] Toxicity is related to the structure, mechanism of action, and pharmacokinetic profile of LA agents.[2] A summary of the properties of LA agents is included in Table 1.

Systemic toxicity related to a LA overdose was first described in a 1928 report of 40 fatalities.[7] Peripheral nerve blocks carry the highest rates of systemic toxicity, which is estimated to occur in 0.1% of procedures.[5] Toxicity from epidural administration is less common with an incidence of 0.04%.[5] Changes in practice and increased attention to LA safety may help lower rates of toxicity. Safe practices include administering LA agents in divided doses, performing aspiration tests, following recommendations for dose limitations and administering test doses of epinephrine to detect inadvertent intravascular administration.[2] The maximum recommended doses of LA are listed in Table 1.

The toxicity of LA agents can be classified by manifestations at the local or systemic level. Local ad-

Table 1. Properties of Individual Local Anesthetics

Local Anesthetic	Time to Onset	Duration (min)	Half-life (hr)	Max Dose (mg)	Max Dose (mg/kg)	Min Toxic Dose (mg/kg)
Esters						
Chloroprocaine (Nesacaine®)	Short	Short (15-30)	<30 sec	800	11	22.8
Procaine (Novocain®)	Long	Short (15-60)	N/A	350-600	7	19.2
Tetracaine (Pontocaine®)	Long	Long	N/A	100	1.5	2.5
Amides						
Bupivacaine (Marcaine®)	Medium	Long (120-360)	2.7	150-175	1-2.5	1.6
Lidocaine (Xylocaine®)	Short	Medium (30-60)	1.6	300	4-5	6.4
Mepivacaine (Polocaine®, Carbocaine®)	Short	Medium (45-90)	1.9	400	7	9.8
Prilocaine (Citanest®)	Short	Medium (30-90)	1.5	500-600	5-8	N/A
Ropivacaine (Naropin®)	Medium	Long (120-360)	1.8	200	5	N/A

verse effects include neurovascular manifestations such as prolonged anesthesia and paresthesias.[1] Systemic toxicity of anesthetics involves the central nervous system (CNS), cardiovascular system, and immune system.[1-5] Allergic reactions are more common with ester LA agents as compared to amides, and may range from minor dermatitis to anaphylaxis.[2] Some anesthetics, particularly benzocaine, are associated with hematologic effects such as methemoglobinemia.[1,6] The toxicity of anesthetics may be potentiated in patients with renal or hepatic dysfunction, respiratory acidosis, preexisting heart block, or other heart conditions.[1]

After the use of LA agents, a patient should be closely observed for signs and symptoms of possible toxicity.[1] Frequent monitoring of blood pressure, heart rate and rhythm, and oxygen saturation may provide early warning signs of systemic toxicity. Table 2 provides a summary of some of the common signs and symptoms of toxicity.

At low drug concentrations, CNS effects may begin as a ringing in the ears. As blood levels increase further, dizziness, altered mental status, seizure activity, and coma may ensue.[3,5] Seizures that result from LA toxicity are generally self-limiting and precede signs of cardiac toxicity. Therefore, seizures may alert healthcare providers of the possibility of progression to CNS depression or impending cardiovascular collapse.[2]

The cardiovascular toxicity of LA medications is generally the most ominous presentation of toxicity.[5] When present in excess, the actions of LA agents on sodium channels contribute to cardiac tox-

Table 2. Local Anesthetic Toxicity[2-6]

Early Signs	Moderate Toxicity	Severe Toxicity
Agitation	CNS excitation	Hypotension
Lightheadedness	Cardiac arrhythmias	Bradycardia
Altered mental status	Contractile depression	Ventricular arrhythmias
Visual changes	Conduction blockade	Cardiovascular collapse
Slurred speech		Seizures
Mild hypertension		Coma
Tachycardia		

icity and may also be affected by secondary effects of LA agents on calcium and potassium channels, and the inhibition of cyclic adenosine monophosphate production.[2,5]

Cardiotoxic effects may be enhanced by pre-existing hypoxia or acidosis secondary to seizure activity.[3] These effects are first observed as hypotension and bradycardia, but rapidly progresses to arrhythmias and cardiovascular collapse.[5] The long-acting agents, such as bupivacaine, are more strongly associated with cardiovascular toxicity compared with the short-acting agents.[2] The most concerning aspect of LA-induced cardiovascular collapse is that is it is generally refractory to traditional advanced cardiac life support (ACLS) interventions. Until recently, cardiopulmonary bypass was the only method shown effective in treating refractory cardiac arrest from local anesthetic overdose.[7]

A new potential antidote for LA toxicity, intravenous lipid emulsion (IVLE), has been gaining increased attention in the literature. Both animal studies and human case reports have described successful resuscitation with IVLE in the face of presumed or documented LA toxicity.[2]

Intralipid 20% is a fat emulsion that is approved by the US Food and Drug Administration (FDA) for use as a source of calories and essential fatty acids for patients who require parenteral nutrition for extended periods of time. Additionally, it is indicated as a source of essential fatty acids for the prevention and treatment of essential fatty acid deficiency.[8,9] This product is comprised of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection.[5,9] The major fatty acid components are linoleic, oleic, palmitic, linolenic, and stearic acid.[5,9]

Despite the increasing literature on the use of IVLE in LA toxicity, its mechanism remains unknown.[2-5] One theory is that IVLE serves as a "lipid sink," providing a large lipid phase in the serum that is able to extract LA from the plasma or tissues.[2-5] The rapid binding of excess LA with lipid infusion reduces the plasma drug concentration and allows for restoration of hemodynamic stability.[3] Another theory is that IVLE has metabolic effects by inhibiting mitochondrial metabolism of lipids, reducing tissue acidosis and decreasing carbon dioxide production during times of myocardial ischemia. Also, IVLE may work to saturate the LA-impaired fatty acid delivery to the mitochondria, enabling further energy production.[2,5] An additional theory is that the fatty acids found in IVLE activate calcium and potassium channels, which have been associated with LA-induced cardiotoxicity.[2]

Based on investigational studies in rats and dogs in the late 1990s, a trial of IVLE in humans was warranted.[10,11] There have been 9 successful case reports documented in humans with the use of lipid infusion in resuscitation efforts involving suspected or documented LA toxicity to date (Table 3).[12-20]

IVLE as rescue therapy following LA induced cardiac arrest unresponsive to conventional resuscitation is an off-label use of this treatment.[8,9] Formal dose-ranging studies have not been performed in humans and dosing information can only be extrapolated from human case reports.[12-20] While the human case reports all used IVLE 20%, the amount infused varied with each case.[2] The various dosing regimens in the published case reports are summarized in Table 3. Although there are no formal guidelines in the US, Weinberg and Picard have developed a web site that may serve as a reference site for lipid rescue (http://lipidrescue.org).[11] The authors of this web site propose a dosing regimen of IVLE 20% as a bolus of 1.5 mL/kg over 1 minute, followed by a continuous infusion of 0.25 mL/kg/min for 30 to 60 minutes. In the setting of hypotension, the infusion may be increased to 0.5 mL/kg/min. The patient may be rebolused 1 or 2 times every 3 to 5 minutes if no evidence of clinical improvement. Weinberg suggests that cumulative doses greater than 8 mL/kg are unlikely to be effective. IVLE is recommended in patients who do not respond to standard resuscitation efforts. Chest compressions still need to be performed to allow circulation of the IVLE throughout the body.[11]

In 2007, the Association of Anaesthetists of Great Britain & Ireland developed guidelines for the management of severe LA toxicity. The treatment algorithm of cardiac arrest with lipid emulsion is similar to that of Weinberg and colleagues, with the exception of

the bolus dose.[21] However, there are discrepancies between what has been suggested by these researchers and what has actually been done in the published case reports.[11-21] Therefore, the ideal dose and dosing regimen of IVLE in LA toxicity remains to be determined.

Table 3. Summary of Human Case Reports[11-21]

Reference	Local Anesthetic	Adverse Reaction	Lipid Formulation	Bolus Dose	Time Bolus Given	Infusion Rate
Lipid Rescue[11]	N/A	N/A	Intralipid 20%	1 mL/kg x 3 doses	N/A	0.25 mL/kg/min
Association of Anaesthetists of Great Britain and Ireland[21]	N/A	N/A	Intralipid 20%	1.5 mL/kg x 3 doses	N/A	0.25 mL/kg/min
Rosenblatt[12]	Bupivacaine Mepivacaine	Seizure Asystole	Intralipid 20%	1.2 mL/kg single dose	20 min	0.5 mL/kg/min
Litz[13]	Ropivacaine	Seizure Asystole	Intralipid 20%	2 mL/kg single dose	10 min	0.2 mL/kg/min
Foxall[14]	Levobupivacaine	Seizure EKG changes	Intralipid 20%	1.2 mL/kg	4 min	Not given
Spence[15]	Bupivacaine	Hypertension Tachycardia Loss of consciousness	Intralipid 20%	0.58 mL/kg x 2 doses	2 min	400 mL as infusion (rate unknown)
McCutchen[16]	Bupivacaine	Seizure Ventricular tachycardia	Intralipid 20%	100 mL + 400 mL (weight unknown)	5 min	Not given
Warren[17]	Bupivacaine Mepivacaine	Pulseless	Liposyn III 20%	unknown	10 min	0.1 mL/kg/min
Smith[18]	Bupivacaine	Seizure Asystole	Intralipid 20%	3 mL/kg	1 min	0.2 mL/kg/min
Litz[19]	Mepivacaine Prilocaine	Supraventricular extrasystoles	Intralipid 20%	1 mL/kg x 2 doses (2^{nd} dose given 3 min after 1^{st} dose)	Immediate at onset of symptoms	0.25 mL/kg/min
Ludot[20]	Ropivacaine Lidocaine	Ventricular arrhythmias	Medialipid 20%	3 mL/kg	Immediate at onset of symptoms	Not given

IVLE has a benign safety profile based on its frequent and longstanding use in parenteral nutrition. Adverse reactions are minimal, with potential complications being infectious complications, thrombophlebitis during peripheral intravenous administration and allergic reactions.[4,5,8,22] More delayed reactions occur when fat emulsions are given in excessively high doses, leading to fat accumulation. Manifestations of fat overload can include hyperlipidemia, hepatotoxicity, jaundice, seizures, thrombocytopenia and fat embolism.[5,8,9] The main safety concern for IVLE use in the acute setting is allergic reactions.[8,22] Medications formulated in lipid emulsions, like propofol, should not be considered options.[1,2,6] To date, there have been no reports of IVLE being associated with adverse side effects when used for this indication.[12-20]

In conclusion, the available cases demonstrate that LA toxicity occurs as a result of different regional techniques and with a variety of agents.[12-20] Lipid emulsion has been successful in the reversal of LA cardiac toxicity, not just bupivacaine-induced toxicity.[22] Although doses of LA used were within recommended dosing guidelines and steps were taken to minimize the risk of intravascular administration, toxicity still occurred.

The clinical presentation of the toxic reactions and the timing of their onset varied, thus emphasizing the diversity of the clinical circumstances in which LA toxicity may occur and in which lipid emulsion therapy may show its benefit.[10] Warren et al and Ludot et al demonstrated that the beneficial effect occurs irrespective of the brand of lipid emulsion.[17,20] To date, there have been no case reports of lipid rescue failing; however, there have been only a small number of published case reports over the past three years.[12-20] Additional advantages of IVLE include low cost and accessibility.[5]

There remain many details unknown despite the documented successes in the case reports. Guidelines have yet to be published in the US and the literature supporting IVLE safety and efficacy is still lacking. It is also unclear how resuscitation with fat emulsion will affect other lipophilic drugs used during advanced cardiac life support (ACLS), such as amiodarone.[5] The most appropriate timing of initiation is still unknown as well as the optimal and maximal doses to be given. From the available literature, the appropriate rate of administration and duration of therapy cannot be established, but the beneficial trend of using early therapy is evident.[11-21] Although the adverse effects of this therapy are not known, for a patient in the desperate circumstance of LA toxicity who is receiving supportive care, conventional treatment and resuscitation efforts, lipid emulsion therapy seems to be a viable and effective consideration.[5,10] *References available upon request*

New Vancomycin Monitoring Protocol

The Anti-infective Subcommittee recently approved a protocol for vancomycin dosing recommendations, monitoring parameters, and laboratory monitoring in light of the recently published recommendations and guidelines from the Infectious Diseases Society of America[1,2]. In addition, the microbiology and clinical laboratories will also change the reporting of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates obtained from various cultured specimens and the reporting of range values for vancomycin levels. The following are a summary of the recommendations:

- MRSA vancomycin minimum inhibitory concentrations (MICs) will be released automatically by the microbiology laboratory on the following specimen types:
  - Blood cultures
  - Respiratory cultures including sputum, endotracheal aspirates, bronchoalveolar lavage (BAL), mini-BAL, transbronchial lung biopsy, and lung biopsy
  - Cerebrospinal fluid cultures
- The microbiology laboratory will enter the following disclaimer when a vancomycin MIC result is released: *Vancomycin efficacy may be compromised with MRSA isolates with MICs of 2 micrograms/mL or greater. Please contact Infectious Diseases or the Antimicrobial Stewardship Team for guidance in dosing or therapeutic alternatives.*
- Alternative antibiotic agents, linezolid and daptomycin, indicated to treat serious MRSA infections will remain under the restricted antibiotics list and will have the same current approval mechanism to be dispensed by the pharmacy.
- The microbiology laboratory will keep the same policies in effect in regards to reporting linezolid and daptomycin susceptibilities.
- The clinical laboratory will change the currently used vancomycin normal range when reporting trough concentrations to 10 to 20 micrograms/mL. Test results with a value below 10 micrograms/mL will include a comment stating "Subtherapeutic for MRSA infections".
- It is recommended that a vancomycin loading dose of 25 to 30 mg/kg be administered to critically ill patients.
  - Vancomycin infusion times should be adjusted accordingly: approximately 30 minutes for every 500 mg infused.

On October 1st, the microbiology and clinical laboratories will be instituting these changes and they should appear in eCareNet Viewer. The Infectious Diseases consult service as well as the Antimicrobial Stewardship Team welcome any questions regarding vancomycin MICs, vancomycin dosing, or appropriate therapy for patients with MICs greater than or equal to 2 micrograms/mL.

References available upon request

FORMULARY UPDATE FOR AUGUST 2009

The Pharmacy and Therapeutics Committee recently approved the actions listed below. The formulary effective date is specified for each decision is indicated next to the topic.

ADDITION WITH RESTRICTION

Lacosamide (Vimpat®)

September 15, 2009

Lacosamide, a second generation anti-epileptic drug (AED) that is available in an oral and intravenous (IV) formulation, was added to the formulary in IV formulation only. This decision adds a second IV antiepileptic medication to the formulary. IV lacosamide will be restricted to inpatient use only in those patients who have failed other therapeutic agents.

200-mg/20-mL vials

Clevidipine (Cleviprex®)

October 15, 2009

Clevidipine is a new dihydropyridine IV calcium channel blocker that is short-acting and vasoselective. It was added to the formulary with restrictions to the critical care areas (ie, ICUs, ORs, ED) and the Interventional Radiology area (must be monitored by anesthesia). Safety concerns with clevidipine include its contraindications in patients with soy or egg-allergies. Since the product contains lipids, the bottle must be changed every 4 hours to avoid microbial growth.

0.5-mg/mL in single-use vials

Doripenem (Doribax®)

October 1, 2009

The primary carbapenem of choice will be changed to doripenem. Meropenem will still be available with prescribing restricted to the following services: pediatrics, infectious diseases, hematology/oncology, and in those patients with suspected or documented meningitis.

500-mg vials

Esomeprazole (Nexium®)

October 15, 2009

Esomeprazole was determined to be an effective alternative to other available proton pump inhibitors (PPI) and added to the formulary as the primary PPI for all patient populations (ie, adult, pediatric, neonate). Therefore, all other PPIs (pantoprazole, omeprazole, and lansoprazole) will be removed from the formulary.

20- and 40-mg capsules; 10-, 20-, and 40-mg oral suspension packets; 20- and 40-mg vials

AUTOMATIC THERAPEUTIC SUBSTITUTION (ATS) PROTOCOL

Doripenem (Doribax®)

October 1, 2009

The Anti-infective Subcommittee approved the ATS for carbapenem antibiotics. Orders written for meropenem will now be converted to the appropriate dose of doripenem. A 4-hour infusion time will be automatically used in intensive care units for critically ill patients and in patients with cystic fibrosis until a pathogen is identified. The infusion time can be deescalated to 1 hr if *Pseudomonas* or *Acinetobacter* is not identified or if the physician indicates that he/she wants to reduce infusion time. Dosing must also be adjusted in patients with renal failure per the protocol. The protocol is available on the *Formulary and Drug Information Resources* Web page.

LINE EXTENSIONS

September 15, 2009

- Diltiazem 12-mg/mL extemporaneous suspension
- Esmolol (Brevibloc®) 10-mg/mL vials
  - *Will only be available in the Operating Rooms and Institute of Psychiatry*
- Morphine suspension 0.4-mg/mL extemporaneous suspension [pediatric use only]
- Japanese encephalitis vaccine (Ixiaro®) [restricted to the outpatient clinics] (*for use in patients 17 years of age or older.)*

October 15, 2009

- Esmolol (Brevibloc®) 2-g/100-mL IV solution

DELETIONS

September 15, 2009

- Oil of wintergreen
- Benzethonium/benzocaine 0.1%/20% (Americaine®) spray/ointment
- Rubella virus vaccine (Meruvax II®) single-dose vial
- Measles live virus vaccine (Attenuvax®) single-dose vial
- Cromolyn sodium (Intal®) 800-microgram/puff inhaler

October 15, 2009

- Esmolol (Brevibloc®) 1-g/100-mL IV solution
- Pantoprazole (Protonix®) 20- and 40-mg tablets; 40-mg injection; 2-mg/mL extemporaneous suspension
- Lansoprazole (Prevacid®) 15- and 30-mg capsules; 3-mg/mL extemporaneous suspension
- Omeprazole (Prilosec®) 2-mg/mL extemporaneous suspension