Local anesthetic toxicity can have catastrophic outcome in an otherwise benign procedure. Introduction of even a small amount of local anesthetic into the bloodstream can cause cardiac arrest in a healthy patient. Most healthcare facilities rely on standard resuscitative techniques to treat such events; however, treatment via infusion of lipid emulsion has been used successfully to stabilize the condition of some patients in a safe, effective, and rapid manner.

The online databases consulted included Academic Search Premier, CINAHL, and MEDLINE. The key words included in the search were “Intralipid,” “local anesthetic toxicity,” “lipid infusion,” and “lipid sink.”

Lipid therapy has shown great promise for the treatment of patients facing cardiovascular collapse due to local anesthetic toxicity. However, the slow adoption of this novel evidence-based practice by healthcare facilities endangers patients who may not receive the best available care when the need is most dire. Current evidence suggests that infusion of lipid emulsion should be considered among the primary treatments for local anesthetic toxicity and be made readily available in every facility’s operating or procedure room, and hospital staff should be trained in its use when local anesthetic toxicity is suspected.

Keywords: Intralipid, lipid emulsion, lipid infusion, lipid sink, local anesthetic toxicity.

Objectives
At the completion of this course the reader should be able to:
1. Recognize the seriousness of local anesthetic toxicity and the potential benefit of lipid infusion as a treatment.
2. Discuss a possible mechanism of action for lipid infusion as a treatment for local anesthetic toxicity.
3. Recognize the evidence gathered from published animal studies regarding the efficacy of lipid infusion as a treatment for local anesthetic toxicity.
4. Discuss published case studies regarding lipid infusion treatment, including common symptoms of local anesthetic toxicity, standard treatment protocol, and potential complications of a lipid infusion treatment.
5. Discuss evidence that contradicts the efficacy of lipid infusion as a treatment for local anesthetic toxicity.

Introduction
Cardiac toxicity due to misapplication of local anesthetic (LA) in an otherwise routine procedure can have disastrous effects. Studies of animals with LA toxicity have shown that administration of lipid emulsions may evoke a favorable response. Moreover, there are now human case reports in the literature suggesting that lipids are an effective adjunct treatment in resuscitating human patients in cardiovascular collapse due to LA toxicity when the currently accepted protocol failed to produce positive results,1-3 that is, treatment with epinephrine, atropine, and cardiopulmonary resuscitation. The potentially lethal nature of LA toxicity precludes performing a randomized trial involving human participants; however, early reports have been promising for the use of lipid emulsions in the treatment of LA toxicity.

History and Review of Literature
• Epidemiology. Thanks to improved regional anesthesia techniques and availability of less toxic LAs, rates of LA toxicity have declined in the past 25 years.4 The most current estimates of LA toxicity in adults range from 7.5 to 20 per 10,000 peripheral nerve blocks and about 4 per 10,000 epidurals.5 However, due to the potentially catastrophes effects, customers of LA toxicity have been shown that administration of lipid emulsions may evoke a favorable response. Moreover, there are now human case reports in the literature suggesting that lipids are an effective adjunct treatment in resuscitating human patients in cardiovascular collapse due to LA toxicity when the currently accepted protocol failed to produce positive results,1-3 that is, treatment with epinephrine, atropine, and cardiopulmonary resuscitation. The potentially lethal nature of LA toxicity precludes performing a randomized trial involving human participants; however, early reports have been promising for the use of lipid emulsions in the treatment of LA toxicity.

* AANA Journal Course No. 29: The American Association of Nurse Anesthetists is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center Commission on Accreditation. The AANA Journal course will consist of 6 successive articles, each with objectives for the reader and sources for additional reading. At the conclusion of the 6-part series, a final examination will be printed in the AANA Journal. Successful completion will yield the participant 6 CE credits (6 contact hours), code number: 31507, expiration date: July 31, 2010.
strophic nature of a toxic response to an LA, any incident of toxicity must be considered a relevant event.

**Discovery of Lipid Rescue**

The discovery that an infusion of lipids may aid in the resuscitation of a patient in cardiac arrest due to LA toxicity was an incidental, serendipitous finding by Weinberg et al. The group sought to confirm the accidental observation by pretreating rats with an infusion of lipids and then measuring the dose of bupivacaine required to induce asystole. Indeed, rats that had been pretreated with a lipid infusion were able to withstand greater doses of bupivacaine before experiencing asystole. Moreover, higher concentrations of lipids allowed the rats to withstand even greater doses of bupivacaine. In addition, the investigators demonstrated that rats receiving a toxic dose of bupivacaine were more readily resuscitated (measured as survivability) in conjunction with lipid infusion. This experiment provided direct evidence that lipids had the ability to counteract the toxic effects of bupivacaine in the bloodstream in a rat model.

**Lipid Sink Theory**

The most widely accepted theory for the mechanism of action of lipid emulsion therapy is the “lipid sink” theory, which postulates that infusion of lipids creates a lipid compartment within the plasma that remains separate from the aqueous phase of the plasma. Lipophilic LAs are drawn into this separate lipid sink, thereby reducing the concentration of LA in the aqueous phase of plasma. Weinberg et al. performed a study using radiolabeled bupivacaine on isolated rat hearts showing that a lipid emulsion increases the rate at which bupivacaine is eliminated from cardiac tissue and accelerates recovery from bupivacaine-induced asystole. This finding appears to support the lipid sink theory. In addition, the lipid sink theory was recently supported by a case in which a patient with cardiovascular failure following overdose of bupropion and lamotrigine was successfully resuscitated using lipid infusion after conventional resuscitative efforts failed. Blood work for the patient after lipid infusion showed levels of lipophilic bupropion decreasing in parallel with serum triglyceride levels. The same dramatic relationship was not observed with nonlipophilic lamotrigine.

Bania et al. showed that lipid infusion led to an increase in resuscitation and survivability of dogs with verapamil toxicity. Harvey and Cave demonstrated that lipid infusion leads to rapid and complete reversal of clampimaine-induced hypotension and can prevent cardiovascular collapse in a case of severe clampimaine toxicity. Lipid infusion should be considered a viable treatment for any case of toxicity in which the suspected toxin is lipophilic.

**Human Trials**

With the completion of 2 animal studies confirming the therapeutic benefits of lipid infusion for the treatment of bupivacaine toxicity, human trials would seem to be the next logical step to confirm the efficacy and safety of such treatment. Unfortunately, the critical and emergency nature of LA toxicity makes it impossible to conduct such trials without placing human subjects in life-threatening situations. Therefore, we are left to rely on the accumulation of individual case reports documenting the success or failure of lipids in the treatment of patients with LA toxicity. History has shown successful adoption of other treatments via this method, such as dantrolene used in the treatment of malignant hyperthermia and defibrillators used to treat cardiac arrest, both of which posed similar ethical difficulties before use in a clinical environment. An unfortunate disadvantage of this system of adoption is the time it takes to accumulate evidence regarding the efficacy of the treatment. If the treatment is, in fact, effective, then each day that passes without adoption puts additional patients at unnecessary risk.

**Case Studies Reported in Peer-Reviewed Journals**

The list of documented case reports of patients with LA toxicity successfully treated by lipid emulsion therapy continues to grow. The first case was reported by Rosenblatt et al. in Anesthesiology. In this case, a 58-year-old man was admitted for arthroscopic rotator cuff repair of the right shoulder. Vital signs were normal at the beginning of the procedure, although the patient reported a history of angina on exertion and sometimes at rest. An interscalene block was performed with 20 mL of 0.5% bupivacaine and...
20 mL of 1.5% mepivacaine. Approximately 30 seconds after removal of the block needle, a tonic-clonic seizure developed, at which time 50 mg of propofol was given intravenously and oxygen was given through a face mask. The seizure stopped for approximately 90 seconds and then began again. This time, 100 mg of propofol was administered. The ECG showed asystole, and the patient was without pulse or blood pressure. At this point, advanced cardiac life support was initiated, including tracheal intubation and chest compressions. During the first 20 minutes of life support, the clinician administered a total of 3 mg of epinephrine, 2 mg of atropine, 300 mg of amiodarone, and 40 U of arginine vasopressin. Defibrillation was also administered at increasing energy levels in accordance with advanced cardiac life support protocols. An assortment of arrhythmias was noted during this phase, although the end result, and the most frequently occurring, was pulseless ventricular tachycardia and asystole. After 20 minutes, a member of the code team suggested trying administration of a lipid emulsion.

At this time, 100 mL of 20% fat emulsion (Intralipid, Fresenius Kabi AB, Sweden) was given intravenously while cardiac compressions continued. A 360 J defibrillation shock was given as well. Within seconds, a single sinus beat appeared on the ECG, and 1 mg of atropine and 1 mg of epinephrine were administered. Chest compressions continued. Within 15 seconds, the cardiac rhythm returned to sinus at 90 beats per minute (bpm), and a pulse and blood pressure became apparent. Lipid emulsion was infused during the next 2 hours at a rate of 0.5 mL/kg per minute. The patient was extubated 2.5 hours later, monitored overnight, and discharged home the next day. During the next 2 weeks, there was no evidence of complications secondary to the lipid infusion.

A subsequent cardiac catheterization of the patient revealed total occlusion of the right coronary artery and an ejection fraction of 32%, for which he received an implantable cardiac defibrillator. The study authors noted that this event resulted in a 100-mL bag of 20% lipid emulsion being made immediately available in all places where peripheral nerve blocks may be performed throughout the facility.

Another successful case was reported by Litz et al a month later in the journal Anaesthesia. However, this was a case of ropivacaine-induced asystole. An 84-year-old woman was admitted for surgery to correct a Dupuytren contracture under a brachial plexus block. Inadvertently, 40 mL of 1% ropivacaine was administered, rather than the intended 0.5% ropivacaine. After 15 minutes, the patient lost consciousness and experienced a tonic-clonic seizure. She was ventilated with 100% oxygen and 150 mg of thiopental was administered to stop the seizure. A few minutes later, severe bradycardia and asystole developed. Cardiopulmonary resuscitation was started, along with 3 mg of epinephrine given in 1-mg increments. After 10 minutes, these measures failed to restore cardiac activity. A 100-mL bolus of 20% fat emulsion was administered, followed by a continuous infusion of 10 mL/min while chest compressions were continued. After infusion of 200 mL of the fat emulsion (Intralipid), wide-complex tachyarrhythmia was observed and chest compressions were discontinued. Pulse and blood pressure became palpable and stronger. After 3 hours of monitoring in the intensive care unit, the patient was extubated. She recovered completely and was discharged home 4 days later.

Yet another case of LA toxicity successfully treated by lipid infusion was reported by Foxall et al in 2007. The case involved a 75-year-old woman who was admitted for surgical repair of a fractured femur while anesthetized with a lumbar plexus block. Her medical history was positive for severe chronic obstructive pulmonary disease with shortness of breath on exertion and stable angina. A 22-gauge needle was used to inject 20 mL of 0.5% levobupivacaine into the region of the fourth lumbar vertebra. Within seconds of the injection, the patient became unresponsive and had a tonic-clonic seizure. A presumptive diagnosis of LA toxicity was immediately made, and 100% oxygen was administered via face mask. Two minutes later, a second short seizure occurred. Although a radial pulse could not be palpated, a carotid pulse was maintained throughout the incident. An ECG displayed an altered QRS pattern with reducing voltage and broadening of the QRS complex. The heart rate was unchanged at 110 bpm, but the arterial pressure measured 60/40 mm Hg. Metaraminol was administered, and the patient was intubated. Four minutes after the levobupivacaine injection, a 100-mL bolus of 20% fat emulsion (Intralipid) was administered over 5 minutes via the peripheral intravenous line.

Following administration of the lipid emulsion, arterial pressure measured 90/60 mm Hg, and the ECG showed rapid normalization of the QRS pattern. Unfortunately, it is not possible to determine if the recovery of the arterial pressure was due to the effects of the fat emulsion infusion or the metaraminol. However, heart rate, arterial pressure, and the ECG pattern remained stable for 10 minutes following the lipid infusion, and the patient was able to undergo surgical repair of the femur. She recovered uneventfully. In this case, the attending clinicians felt obliged to introduce lipid infusion at the first onset of symptoms of LA toxicity rather than waiting to see if the condition would gradually deteriorate to cardiac arrest.

A similar case of using lipid infusion as a precaution against impending cardiovascular collapse was reported by McCutchen and Gerancher. The patient was an 82-year-old woman admitted for right total knee arthroplasty. Her history was positive for well-controlled hypertension, hypothyroidism, and hyperlipidemia. An initial injection of 30 mL of 0.5% ropivacaine with 5 µg/mL of epinephrine was administered through a femoral peripheral catheter. A second injection of 30 mL of 0.5%
bupivacaine with epinephrine was made using the Labat approach for sciatic nerve block. Twenty seconds after completion of the second injection, a tonic-clonic seizure occurred; 3 mg of midazolam was administered, and the patient was turned to a supine position. Thirty seconds later, the seizure relented. A minute later, a second seizure occurred that resolved spontaneously. ECG monitoring demonstrated ventricular tachycardia at a rate of 200 bpm. Although the patient remained unresponsive, she continued to breathe unassisted, femoral and carotid pulses remained palpable, and the blood pressure cuff delivered a reading of 114/64 mm Hg. Concerned that the patient may be manifesting early signs of LA toxicity, the clinicians decided to administer 100 mL of 20% fat emulsion (Intralipid) approximately 3 minutes after termination of the second seizure; 150 mg of intravenous amiodarone was also given. Ventricular tachycardia persisted, and the femoral pulse diminished as the noninvasive blood pressure cuff began to cycle for the second time. A 120 J countershock was administered with immediate return to normal sinus rhythm. An additional 400 mL of fat emulsion was infused during the next 15 minutes. Although a cardiovascular surgeon and bypass team were standing ready, bypass proved to be unnecessary as the patient’s blood pressure, heart rate, and rhythm remained stable and she gradually grew more alert and responsive with a complete return to normal in 2 hours. Although it is not possible to determine if the patient’s condition would have rebounded without lipid administration, there is ample evidence that lipid infusion counteracts the effects of LA toxicity.\textsuperscript{5,6,10}

No less than 4 successful cases of lipid infusion treatment of LA toxicity were reported in the May 2008 issue of Anesthesia & Analgesia. The first involved a 13-year-old girl who was admitted for meniscectomy of her left knee with a lumbar plexus block given under general anesthesia.\textsuperscript{13} No significant medical history was reported. The patient had a heart rate of 84 bpm, an arterial blood pressure of 88/45 mm Hg, and an oxygen saturation of 99%. Following general anesthesia induction, a lumbar plexus block was administered using a total of 22 mL of a mixture of equal volumes of 1% lidocaine with added epinephrine and 0.75% ropivacaine. Fifteen minutes after administration of the LA, ventricular tachycardia of 150 bpm developed along with a widening QRS pattern, the arterial blood pressure increased to 120/92 mm Hg, and the oxygen saturation decreased to 92%. End-tidal carbon dioxide remained unchanged at 41 mm Hg. Sevoflurane was decreased to 1%, nitrous oxide was discontinued, and the lungs were manually ventilated with 100% oxygen.

Because LA toxicity was suspected, a 150-mL bolus of 20% lipid emulsion (Medialipid, Braun, Melsungen, Germany) was injected over 3 minutes. Medialipid is a lipid emulsion used for parenteral nutrition of pediatric patients. Within 2 minutes of the lipid infusion, heart rate, blood pressure, oxygen saturation, and the QRS pattern returned to near normal levels (except for an ST depression on the ECG that persisted for 30 minutes before normalizing), and the patient was able to have surgery completed with no further complications. This case was remarkable not only for the young age of the patient but also for the different brand of lipid emulsion used, implying that the exact formulation of the lipid emulsion may not be important (Table 1).

Litz et al\textsuperscript{14} described the case of a 91-year-old man who was admitted for olecranon bursitis surgery. The medical history was positive for chronic obstructive pulmonary disease, hypertension, coronary ischemic heart disease, myocardial insufficiency, and reflux esophagitis complicated by repeated gastrointestinal bleeding. An infracavicular brachial plexus block was achieved using 30 mL of 1% mepivacaine. Due to an incomplete block of the ulnar nerve after 15 minutes, an additional 10 mL of 1% procainamide was administered. Within 5 minutes, the patient began to complain of dizziness, nausea, and agitation and became unresponsive to verbal commands. Oxygen was administered by mask, and 12.5 mg of intravenous dolasetron was given to treat the nausea. The heart rate increased from 76 to 92 bpm, and the blood pressure increased from 160/70 to 190/90 mm Hg. In addition, an ECG exhibited supraventricular extrasystole with intermittent bigeminy. Because LA toxicity was suspected, an initial 50-mL bolus of 20% fat emulsion was injected and another 50 mL injected 3 minutes later. This

### Table 1. Comparison of Different Brands of Lipid Emulsions

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Intralipid</th>
<th>Liposyn III</th>
<th>Medialipid</th>
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<tbody>
<tr>
<td>Oils</td>
<td>100% soybean oil</td>
<td>100% soybean oil</td>
<td>50% soybean oil and 50% medium chain triglycerides</td>
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<tr>
<td>Triglycerides (g/L)</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Phospholipids (g/L)</td>
<td>12</td>
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<td>12</td>
</tr>
<tr>
<td>Glycerol (g/L)</td>
<td>22</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Intralipid, Fresenius Kabi AB, Uppsala, Sweden; Liposyn III, Hospira, Lake Forest, Illinois; Medialipid, Braun, Melsungen, Germany; Clinoleic, Baxter, Maurepas, France.
was followed by a continuous infusion of the fat emulsion at a rate of 0.25 mL/kg per minute. The patient regained consciousness 5 minutes after the first injection of fat emulsion (Intralipid). Because extrasystole persisted on the ECG, the fat emulsion infusion was continued to a total dose of 200 mL, at which time the extrasystole disappeared and surgery was performed without complication. Litz et al14 suspected LA toxicity due to an additive effect of prilocaine on top of mepivacaine. Measurements taken by Litz et al14 of plasma concentrations of mepivacaine and prilocaine before and after lipid infusion seem to support the lipid sink mechanism of action.

Warren et al3 reported the case of a 60-year-old man admitted for revision of left upper extremity basilica vein fistula to be performed under supraclavicular brachial plexus block. His medical history was positive for hypertension, type 2 diabetes mellitus, end-stage renal disease, and coronary artery disease. His blood pressure was 147/77 mm Hg, and heart rate was 63 bpm. The block was performed by injecting 30 mL of 1.5% mepivacaine followed by 10 mL of 0.5% bupivacaine. After 5 minutes, the patient began to exhibit labored breathing followed by apnea, unresponsiveness, and no palpable pulse. Cardiopulmonary resuscitation was initiated, but the cardiac rhythm progressively degenerated. During the next 10 minutes, a number of interventions were attempted, including 1 mg of atropine, a total of 3 mg of epinephrine in 1-mg increments, 40 U of vasopressin, 100 mL of 8.4% sodium bicarbonate, and 6 g of magnesium sulfate. In addition, 11 successive defibrillations were given up to 360 J that elicited some transient perfusing heart rhythms but failed to restore sustained cardiovascular activity.

Subsequently, an intravenous infusion of 250 mL of 20% fat emulsion (Liposyn III, Hospira, Lake Forest, Illinois) was started centrally (without bolus) to be completed over 30 minutes. Defibrillation attempts continued during the lipid infusion, and the bouts of sustained cardiac rhythm grew progressively longer until wide-complex tachycardia developed. Eventually, after 15 additional defibrillations, hemodynamic stability was attained and the patient was transferred to the surgical intensive care unit. He was discharged 3 days later. Warren et al3 attributed the relatively delayed recovery after infusion of lipid emulsion to the lack of an initial bolus, as suggested by Weinberg et al.5,6,10

Finally, Smith et al15 described a case of an 83-year-old man admitted for total knee arthroplasty under general anesthesia with sciatic nerve block. His medical history was positive for hypertension, type 2 diabetes mellitus, end-stage renal disease, and coronary artery disease. His blood pressure was 147/77 mm Hg, and heart rate was 63 bpm. The block was performed by injecting 30 mL of 1.5% mepivacaine followed by 10 mL of 0.5% bupivacaine. After 5 minutes, the patient began to exhibit labored breathing followed by apnea, unresponsiveness, and no palpable pulse. Cardiopulmonary resuscitation was initiated, but the cardiac rhythm progressively degenerated. During the next 10 minutes, a number of interventions were attempted, including 1 mg of atropine, a total of 3 mg of epinephrine in 1-mg increments, 40 U of vasopressin, 100 mL of 8.4% sodium bicarbonate, and 6 g of magnesium sulfate. In addition, 11 successive defibrillations were given up to 360 J that elicited some transient perfusing heart rhythms but failed to restore sustained cardiovascular activity.

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Finally, Smith et al15 described a case of an 83-year-old man admitted for total knee arthroplasty under general anesthesia with sciatic nerve block. After initial sedation with 50 μg of fentanyl and 2 mg of midazolam, a sciatic nerve block was administered using 0.5% bupivacaine with 1:400,000 epinephrine and 100 μg of clonidine. After a total of 26 mL of LA had been injected in 5-mL increments, the patient suddenly lost consciousness and had a tonic-clonic seizure. The injection was stopped, and 100% oxygen was given through a face mask. The seizure stopped after administration of 2 mg of midazolam. However, the patient was now asystolic and without a palpable pulse. He was intubated, and chest compressions were started.

Local anesthetic toxicity was suspected, and 250 mL of 20% lipid emulsion was administered over 2 minutes. Since asystole persisted, 1 mg of epinephrine and 1 mg of atropine were immediately administered while chest compressions continued. After 2 minutes, wide-complex tachycardia was observed, and there was a palpable femoral pulse. An infusion of lipid emulsion at 0.2 mL/kg per minute was initiated after the initial bolus. Within another 2 minutes, the irregular tachycardia normalized and eventually converted to normal sinus rhythm. Within 90 minutes, the patient was awake and responsive. Smith et al15 noted that 2 providers directly involved in the resuscitation efforts in this case recently completed simulation training that was provided to residents at the facility regarding recognition and management of LA-induced cardiac toxicity. This case demonstrates that simulation training may be a helpful tool in preparing clinicians to recognize and manage rare but life-threatening situations with novel treatments.

Case Studies Reported Online
In addition to cases published in peer-reviewed journals, an online website provides members of the healthcare community an opportunity to post their own personal experiences with lipid infusion in a “Post your cases” section.16 Even though these cases have not been published in a peer-reviewed journal, the number of positive outcomes reported is remarkable, and the lack of negative outcomes is noteworthy. There are at least a dozen cases posted regarding successful use of lipid infusion to treat LA toxicity. In some cases, patients were treated using conventional resuscitative techniques for hours before lipid infusion was attempted, after which stabilization was achieved in a matter of minutes. In such cases, the patient may have been placed at considerable risk for ischemic tissue damage to the heart and brain, a risk that could have been avoided had lipid infusion been instituted earlier in the treatment plan.

Complications of Lipid Therapy
Intralipid is an emulsion composed of soybean oil, egg yolk phospholipids, glycerol, and water (Table 2 and Table 3). Therefore, patients allergic to soybean protein, egg yolks, or egg whites may demonstrate hypersensitivity. Also, in patients with a compromised fat metabolism function, such as dysfunction of the liver, pancreas, or kidney, lipid infusion may exacerbate the underlying condition. These contraindications are primarily a concern when lipid infusion is used as a long-term supplement for patients with parenteral nutrition requirements. The
Intralipid is manufactured by Fresenius Kabi AB, Uppsala, Sweden.

Table 2. Major Components of 20% Intralipid

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Soybean oil</td>
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</tr>
<tr>
<td>Glycerol</td>
<td>2.25</td>
</tr>
<tr>
<td>Egg yolk phospholipids</td>
<td>1.2</td>
</tr>
<tr>
<td>Water</td>
<td>76</td>
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Table 3. Major Component Fatty Acids of Soybean Oil

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Chemical formula</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Linoleic</td>
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</tr>
<tr>
<td>Oleic</td>
<td>C_{18}H_{34}O_{2}</td>
<td>19-30</td>
</tr>
<tr>
<td>Palmitic</td>
<td>C_{16}H_{32}O_{2}</td>
<td>7-14</td>
</tr>
<tr>
<td>Linolenic</td>
<td>C_{18}H_{30}O_{2}</td>
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<tr>
<td>Stearic</td>
<td>C_{18}H_{36}O_{2}</td>
<td>1.4-5.5</td>
</tr>
</tbody>
</table>

Discussion

Whereas the earliest case reports documenting lipid infusion for patients with LA toxicity focused on treating a patient already in asystole, more recent case reports document clinicians using lipid infusion to defuse LA toxicity before it reached that climax. This might indicate a trend of growing awareness or acceptance of lipid treatment among the clinical community. Patients with LA toxicity seem to follow a similar course of symptoms including tachycardia, widening QRS pattern on the ECG, tonic-clonic seizure, and, finally, asystole. A clinician familiar with these symptoms will be more able to recognize LA toxicity at a stage before it becomes fatal. There appears to be a greater percentage of elderly patients in the collection of case reports, which may indicate a greater susceptibility of this age group to LA toxicity. Documentation of additional case studies should be encouraged so that additional patterns may be recognized and investigated.

Lipid Therapy Compared With Vasopressin and Epinephrine

A recent study by Mayr et al attem pted to create a study that best simulates an actual scenario of bupivacaine-induced cardiac arrest followed by administration of bupivacaine. The testing was performed on pigs. Care was used by the study authors to create a study environment that most reflected what would occur in an actual clinical situation. To that end, the pigs were fasted overnight but allowed to drink water. One hour before the procedure, the pigs were prem edicated with azaperone, 4 mg/kg (a veterinary tranquilizer), and atropine, 0.1 mg/kg. Anesthesia was induced with 20 mg/kg of ketamine and 30 mg of pancuronium (a narcotic analgesic similar to meperidine). The pigs were then intubated under spontaneous respiration. Anesthesia was maintained with isoflurane and pancuronium as needed, while muscle relaxation was provided by continuous infusion of pancuronium at 0.2 mg/kg per hour. The animals were allowed to stabilize for 30 minutes at 1% end-tidal isoflurane. Body temperature was maintained with a heating blanket. Paralysis was initially obtained with 0.2 mg/kg of pancuronium, 15 mg of piritramid was given, and 5 IU of heparin was administered intravenously for prevention of intracardiac clot formation. At this point, baseline measurements were recorded, and a single bolus of 5 mg/kg 0.5% bupivacaine was administered via a central venous catheter followed with an immediate flush of 20 mL of saline solution.

To simulate a clinical situation in which a patient is having a tonic-clonic seizure with interrupted spontaneous respiration, mechanical ventilation was ceased immediately after bupivacaine administration, and the pigs were asphyxiated until the occurrence of asystole. After 1 minute of cardiac arrest, mechanical ventilation was resumed with 100% oxygen, and manual chest compressions at a rate of 100/min were initiated. After 2 minutes of basic life support, the animals were randomly given a 4 mL/kg bolus of 20% fat emulsion (Intralipid) followed by a 0.5 mL/kg per minute continuous infusion for 10 minutes or a series of injections of vasopressin with epinephrine, beginning with an injection of 0.4 U/kg of vasopressin with 45 µg/kg of epinephrine, followed 5 minutes later with another identical injection, followed 5 minutes later with an injection of 0.8 U/kg of vasopressin with 200 µg/kg of epinephrine. Three minutes after the initial drug administration, which was lipid infusion or vasopressin with epinephrine, up to 3 monophasic countershocks (at 3, 4, and 6 J/kg) were given if ventricular fibrillation was present. After the second and third drug administrations, the animals were defibrillated with 6 J/kg if ventricular fibrillation was present. If the pig remained asystolic after 9 defibrillation attempts, the experiment was terminated. All 5 pigs that received the vasopressin-epinephrine treatment survived, while all 5 pigs that received the fat emulsion treatment died without restoration of spontaneous circulation, which was defined as an unassisted pulse with a systolic arterial blood pressure of at least 80 mm Hg for at least 5 minutes.

Mayr et al attempted to create a study that best simulated an actual scenario of bupivacaine-induced cardiac arrest followed by administration of bupivacaine.
arrest. Because human trials of such a scenario are impossible, the authors sought to reproduce the actual experience by using animal test subjects with the hope of gaining insight into which is the better treatment plan, a combination of vasopressin with epinephrine or lipid infusion. Indeed, the authors thought the model they used represented “a clinically realistic setting.”[1560] Because the results of this study are in opposition to conclusions reached by earlier animal studies,[3,6,10] as well as case studies reported from clinicians in clinical settings,[1,3,11-15] this study by Mayr et al[17] should be examined closely and critically.

The immediate difference between this study and others that included lipid therapy is the decision to use asphyxiation on the animals until asystole occurred. In previous animal studies, bupivacaine was introduced at a toxic level and spontaneous asystole was allowed to occur. By inducing asystole with asphyxiation, the study authors introduced a factor that is unlikely to occur in a normal clinical setting. Not only is it not possible to determine if the cardiac arrest experienced by the pigs was a result of bupivacaine toxicity or asphyxiation, it also is not possible to know if the cardiac function of the pigs would have degenerated to asystole with the bupivacaine alone. If the asystole was due solely to asphyxiation, it would be expected that vasopressin with epinephrine along with standard resuscitative procedures would have a much more therapeutic effect on the animals compared with treatment with lipid infusion.

A subsequent study by Hicks et al[18] examined pigs that were induced to cardiac arrest following administration of a toxic dose of bupivacaine. Ten pigs were included in the lipid-treated group, and 9 pigs were in the saline group. The animals were sedated with 10 mg/kg of ketamine and 4 mg/kg of xylazine. Anesthesia was induced using 40 mg/kg of ß-chloralose, which was chosen for its minimal cardiovascular effects in swine. Following tracheal intubation, the animals were ventilated with room air, and neuromuscular paralysis was achieved with pancuronium. At this point, 10 mg/kg of bupivacaine was administered over 10 seconds, which resulted in cardiac arrest. After 1 minute, standard resuscitation protocols were initiated in all pigs, including external chest compressions (100/min) and positive pressure ventilations with 100% oxygen. At 3 minutes after cardiac arrest, epinephrine (100 µg/kg) and vasopressin (1.5 µg/kg) were administered via intravenous injection. Defibrillations were initiated 8 minutes after cardiac arrest (biphasic 150 J). Additional doses of 15 µg/kg of epinephrine were administered every 3 minutes after the first dose until return of spontaneous circulation (ROSC). Return of spontaneous circulation was defined as an organized ECG rhythm with cardiac output supporting a mean arterial pressure of at least 60 mm Hg for at least 60 seconds.

After 5 minutes of the standard resuscitation protocol, the animals randomly received a bolus of 4 mL/kg of 20% fat emulsion (Intralipid) followed by a 0.5-mL/kg per minute continuous infusion for 10 minutes or an equal amount of saline. Animals achieving ROSC received norepinephrine to maintain a mean arterial pressure between 60 and 85 mm Hg until termination of the study. If ROSC was not achieved after 20 minutes, some of the animals received a bolus of 4 mL/kg of lipid emulsion, and resuscitation was continued for another 10 minutes. In the lipid-treated group, 3 of 10 pigs achieved ROSC. In the saline-treated group, 4 of 9 pigs achieved ROSC. The median time to ROSC was 9 minutes in the lipid-treated group and 8.5 minutes in the saline-treated group. All animals that achieved ROSC received 130 to 145 µg/kg of epinephrine during resuscitation and survived to the 1-hour end point. Although all surviving animals required norepinephrine to maintain mean arterial pressure above 60 mm Hg, animals from the lipid-treated group required higher amounts compared with the saline-treated group (mean ± SEM, 738.6 ± 94.4 vs 487.3 ± 171.0 µg). In animals from both groups that did not achieve ROSC after 20 minutes, the administration of lipid emulsion followed by 10 minutes of resuscitation failed to improve mean arterial pressure.

The study authors concluded that lipid emulsion is not effective in returning spontaneous circulation and agreed with the findings of Mayr et al.[17] Hicks et al.[18] did not rely on asphyxiation to induce cardiac arrest, instead allowing cardiac arrest to occur spontaneously following administration of a toxic dose of bupivacaine. The study authors attribute the conflicting findings of Weinberg et al.[3,6,10] to interspecies differences in rats, dogs, and pigs; the type of cardiopulmonary resuscitation used (open vs closed chest compressions); and the dose of vasopressors used along with lipid infusion.

Further study of the combined effects of epinephrine and lipids was performed by Hiller et al.[19] to determine if epinephrine administered at higher doses has an effect on the action of lipid infusion. The study involved testing of 30 Sprague-Dawley rats. The rats were intubated and mechanically ventilated with 1.5% isoflurane in 100% oxygen. After they had been allowed to stabilize for 10 minutes under anesthesia, bupivacaine was administered as a 20-mg/kg bolus over 20 seconds. This caused asystole in all the rats. Manual chest compressions were started immediately. Mechanical ventilation with 100% oxygen was continued. The rats were then randomly subdivided into 1 of 6 treatment groups: a saline group and 5 lipid groups (designated to receive 0, 1, 2.5, 10, or 25 µg/kg of epinephrine). At 3 minutes after asystole, the saline group received a 5-mL/kg bolus of saline followed by a continuous infusion of saline at 1 mL/kg per minute for 2 minutes followed by an additional 5-mL/kg bolus (at 5 minutes after asystole). At the same time, the lipid groups received 30% fat emulsion (Intralipid) at the same rates and volumes as the saline that was administered to...
Guidelines for the Management of Severe Local Anaesthetic Toxicity

**Signs of severe toxicity:**
- Sudden loss of consciousness, with or without tonic-clonic convulsions
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur
- Local anaesthetic (LA) toxicity may occur some time after the initial injection

**Immediate management:**
- Stop injecting the LA
- **Call for help**
  - Maintain the airway and, if necessary, secure it with a tracheal tube
  - Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing pH in the presence of metabolic acidosis)
  - Confirm or establish intravenous access
  - Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
  - Assess cardiovascular status throughout

**Management of cardiac arrest associated with LA injection:**
- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that they may be very refractory to treatment
- Prolonged resuscitation may be necessary; it may be appropriate to consider other options:
  - Consider the use of cardiopulmonary bypass if available
  - Consider treatment with lipid emulsion

**Treatment of cardiac arrest with lipid emulsion** (approximate doses are given in red for a 70-kg patient)
- Give an intravenous bolus injection of Intralipid® 20% 1.5 ml.kg⁻¹ over 1 min
  - Give a bolus of 100 ml
  - Continue CPR
- Start an intravenous infusion of Intralipid® 20% at 0.25 ml.kg⁻¹.min⁻¹
  - Give at a rate of 400 ml over 20 min
  - Repeat the bolus injection twice at 5 min intervals if an adequate circulation has not been restored
  - Give two further boluses of 100 ml at 5 min intervals
  - After another 5 min, increase the rate to 0.5 ml.kg⁻¹.min⁻¹ if an adequate circulation has not been restored
  - Give at a rate of 400 ml over 10 min
  - Continue infusion until a stable and adequate circulation has been restored

**Remember:**
- Continue CPR throughout treatment with lipid emulsion
- Recovery from LA-induced cardiac arrest may take >1 h
- Propofol is not a suitable substitute for Intralipid®
- Replace your supply of Intralipid® 20% after use

**Follow-up action:**
- Report cases from the United Kingdom to the National Patient Safety Agency (via www.npsa.nhs.uk). Cases from the Republic of Ireland should be reported to the Irish Medicines Board. Whether or not lipid emulsion is administered, please also report cases to the LipidRescue™ site: www.lipidrescue.org.
- If possible, take blood samples into a plain tube and a heparinised tube before and after lipid emulsion administration and at 1 h intervals afterwards. Ask your laboratory to measure LA and triglyceride levels (these have not yet been reported in a human case of LA intoxication treated with lipid).
- Please read the notes overleaf

"Your nearest bag of Intralipid® is kept .............................................................."

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Figure. Guidelines for the Management of Severe Local Anaesthetic Toxicity (Reproduced with permission from the Association of Anaesthetists of Great Britain and Ireland.)
the saline group. At 5 minutes after asystole, the lipid groups received an injection of epinephrine at 1 of 5 concentrations, including a 0 µg/kg group that was used as a lipid control group.

Return of spontaneous circulation was defined as achieving a rate-pressure product (systolic pressure times heart rate) of at least 30% of baseline value. At 10 minutes after asystole, all chest compressions were ceased, and the animals were observed for sustained or nonsustained recovery. At 15 minutes, the animals were killed. Only 1 of the 5 rats in the saline group had achieved ROSC at 15 minutes, whereas 19 of the 25 rats in the lipid groups were able to achieve and sustain ROSC at 15 minutes. Analysis of the results over time indicates that rats receiving epinephrine attained ROSC at a faster rate than rats receiving lipid infusion alone; however, rats receiving higher doses of epinephrine had difficulty sustaining ROSC beyond 10 minutes. This effect is more pronounced with higher doses of epinephrine, with only 1 of 5 rats in the 25-µg/kg group sustaining ROSC at 15 minutes. All rats that received less than 10 µg/kg of epinephrine were able to sustain ROSC at the end of the experiment. This finding may provide an explanation for the results from Hicks et al., since that study used an initial injection of 100 µg/kg of epinephrine, which is far in excess of what Hiller et al. determined to be deleterious to recovery by lipid infusion.

**Summary**

In a 2006 survey conducted by Corcoran et al., 74% of respondents indicated their hospital would not even consider using lipid emulsions to treat bupivacaine toxicity and that there was “no consensus strategy for how best to treat severe LA toxicity.” It is hoped that these numbers have changed at this point thanks to continuing efforts in the healthcare community to increase awareness of the restorative power of lipid therapy in the treatment of LA toxicity. The use of lipid infusion as a treatment for LA toxicity has recently been adopted as the official protocol by the Association of Anaesthetists of Great Britain & Ireland, suggesting the beginning of wider acceptance of this new and readily available treatment (Figure). A review of the available literature indicates there is not quite a consensus regarding the efficacy of lipid emulsion in the treatment of LA toxicity. Enthusiasm for this new treatment is tempered by recent studies indicating that lipid emulsion is ineffective at returning spontaneous circulation in pigs that have been induced to cardiac arrest via bupivacaine toxicity. It is interesting that both studies contradicting the effectiveness of lipid infusion treatment involved swine models, and further studies may be able to provide explanations for the contradictory findings.

The number of documented case studies on actual human patients cannot be ignored. The great weight of the available evidence supports the inclusion of lipid emulsions as a readily accessible drug in every operating or procedure room where LAs are used. Lipid infusion should be considered a primary treatment for management of a patient with suspected LA toxicity. There is significant documented evidence of its efficacy when used with other standard lifesaving measures in the resuscitation of someone in the throes of LA toxicity. As more clinicians become aware of its effectiveness, fewer patients will be exposed to possibly lethal consequences due to LA toxicity during a planned routine procedure.

**REFERENCES**

15. Smith HM, Jacob AK, Segura LG, Dolger JA, Torsher LC. Simulation education in anesthesia training: a case report of successful resuscita-


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