Delayed-Onset Seizure and Cardiac Arrest After Amitriptyline Overdose, Treated With Intravenous Lipid Emulsion Therapy

abstract

In recent years, intravenous lipid emulsion (ILE) therapy has emerged as a new rescue antidote for treatment of certain toxicities, including cyclic antidepressants, and as the primary treatment of toxic manifestations after local anesthetic exposure. We present a case of a 13-year-old girl who developed delayed seizures and cardiac arrest after amitriptyline ingestion. As part of the treatment, she was treated with ILE therapy. The patient’s laboratories were not interpretable for several hours after the lipid emulsion. The patient developed pancreatitis after the ILE therapy. This case is unique; not only is it one of the first reported cases of lipid emulsion being used in a pediatric patient, but in that the patient developed delayed toxicity and iatrogenic harm from the ILE. *Pediatrics* 2012;130:e432–e438

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KEY WORDS

amitriptyline, pancreatitis, TCA, lipid, cardiac arrest

ABBREVIATIONS

ARDS—adult respiratory distress syndrome
CA—cyclic antidepressants
CPR—cardiopulmonary resuscitation
ILE—intravenous lipid emulsion
TCA—tricyclic antidepressant

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Depression is a common problem in Western society, with a lifetime prevalence exceeding 16%. Numerous medications have been used to combat this disease, including cyclic antidepressants (CAs). Despite the decreasing use of CAs, their use remains common, and is associated with significant morbidity and mortality. Traditionally, intravenous sodium bicarbonate has been the mainstay of therapy for treatment of dysrhythmias and intraventricular conduction delay. In recent years, however, intravenous lipid emulsion (ILE) therapy has been suggested as a possible rescue antidote in the management of lipophilic drug toxicity, including CAs.

The use of ILE therapy in humans is not new; it has been used for years as part of parenteral nutrition. When used for parenteral nutrition, potential complications include allergic reaction, fat emboli, immunosuppression, pancreatitis, hypertriglyceridemia, and thrombophlebitis. The experience with ILE as a resuscitative drug in humans, however, is much more limited. Initial case reports of ILE therapy for the treatment of lipophilic drug toxicity have primarily been limited to patients exhibiting severe, life-threatening toxicity. Serious complications of ILE when used as a resuscitative drug have not previously been reported. In this case report, we describe a 13-year-old girl who developed pancreatitis after ILE therapy. Recently, cases are emerging in which ILE is being used for non–critically ill patients. Clinicians should be aware of the indications of ILE therapy, and its potential for complications, especially in light of its more liberal use.

**CASE PRESENTATION**

A 13-year-old previously healthy girl was found lying unresponsive in a prone position after ingesting an unknown quantity of her mother’s amitriptyline tablets, 150 mg each. The patient was last seen in her normal condition 2 hours earlier.

On arrival of the emergency medical services, the patient was noted to be bradypnic with a respiratory rate of 6 breaths per minute and was euglycemic. Intravenous access was established and the patient’s ventilations were assisted via a bag-valve-mask. She was transported to the emergency department where she was intubated with etomidate and vecuronium. Gastric decontamination was not performed. A urine drug screen via immunoassay was positive for tricyclic antidepressants. An initial electrocardiogram revealed a sinus tachycardia with a ventricular rate of 120 beats per minute. The QRS duration was 76 milliseconds, and the QTc was 477 milliseconds. The patient was transferred to a pediatric referral center.

Upon arrival in the ICU, the patient’s blood pressure was 130/67 with a heart rate of 110. Her respiratory rate was 14; she was not overbreathing the ventilator. Her saturations were 100% while receiving 45% oxygen. The pupils were 2 mm and sluggishly reactive bilaterally. Her saturations were 100% while breathing 45% oxygen. The pupils were 2 mm and sluggishly reactive bilaterally. Superficial lacerations were noted over the distal forearm. There was no rigidity or clonus, and her examination was otherwise normal. The patient was following commands, and was started on a midazolam infusion at 2 mg/h for sedation and a fentanyl infusion at 50 μg/h for analgesia. Serum chemistry studies, obtained ~6 hours after she was initially found were essentially unremarkable. Triglycerides were 82 mg/dL. A comprehensive urine drug screen via gas chromatography/mass spectrometry revealed amitriptyline and nortriptyline only. The repeat electrocardiogram (Fig 1), performed 7 hours post ingestion revealed mild intraventricular conduction delay, with a QRS of 102 milliseconds, and the patient was started on a sodium-bicarbonate infusion consisting of 150 mEq sodium bicarbonate and 40 mEq potassium in a liter of 5% dextrose solution at a rate of 125 mL/h.

Approximately 19 hours after ingestion, the patient experienced a generalized tonic-clonic seizure, which continued intermittently for 1 hour. During this time span, she received a total of 20 mg of intravenous lorazepam. The patient subsequently developed wide-complex dysrhythmias and had no detectable pulses. Cardiopulmonary resuscitation (CPR) was immediately started. Over the ensuing 30 minutes, the patient received a total of 350 mEq (6.4 mEq/kg) of sodium bicarbonate, 2 boluses of epinephrine (0.1 mg/kg each), 2 g of magnesium sulfate, 2 mg/kg of intravenous lidocaine, and 10 mg intravenous midazolam. During this time, the patient’s rhythm degenerated from a wide-complex dysrhythmia to torsades de pointes. The patient received additional lorazepam, along with phe- nobarbital. An arterial blood gas was obtained revealing a pH of 7.52, pCO2 of 49 mm Hg, bicarbonate 41 mmol/L, and a PO2 of 481 mm Hg. Chemistry studies on the blood gas revealed a sodium of 149 mmol/L, potassium 2.6 mmol/L, a lactate acid of 11.6 mmol/L, and an ionized calcium of 3.66 mg/dL.

Approximately 30 minutes after CPR was first initiated, 20% ILE was administered. The patient received 2 intravenous boluses of 1.5 mg/kg ILE over 3 minutes each, with each bolus 5 minutes apart. A continuous infusion of 0.25 mg/kg/minute for 30 minutes was commenced. Before the first bolus of ILE, the patient was in a sinus tachycardia alternating with a wide-complex tachycardia. Because the first ILE bolus did not result in sustained sinus rhythm, a second bolus was administered, which terminated the dysrhythmias. After the ILE infusion was completed, the patient remained sedated and ventilated. She had received a total of 4 mg of supplemental midazolam throughout the night. A serum total tricyclic level was 2718 ng/mL (therapeutic < 299 ng/mL).
remained in a sinus tachycardia. CPR continued during and between the first and second bolus, as no pulse was detected. The patient’s seizure and dysrhythmias activity subsequently was terminated within ∼2 minutes of the second ILE bolus, and palpable pulses were detected. Of note, the phenobarbital and the ILE were administered nearly simultaneously. After the cardiac arrest, the patient was hypotensive, requiring infusions of both norepinephrine and dopamine.

Post cardiac arrest, therapeutic hypothermia was commenced. The patient was started on continual electroencephalographic monitoring, which revealed the presence of α coma, but no ongoing seizure activity post code. Four days after ingestion, the patient began to intermittently follow commands, yet remained quite somnolent for an additional 2 days. An MRI study of the brain performed 7 days after ingestion was normal. A bedside echocardiogram performed 30 minutes after the cardiac arrest revealed normal biventricular size.

FIGURE 1
ECG on arrival to PICU (top) and on completion of resuscitation (bottom).
without any pericardial effusion. A repeat echocardiogram 2 days later was not significantly changed. The estimated left ventricular ejection fraction was 50% to 55%. A follow-up echocardiogram nearly 1 month after ingestion was essentially normal, with left ventricular ejection fraction of ~65%.

A chest radiograph obtained 4 hours post arrest/post ILE revealed bilateral interstitial infiltrates, which progressed to be most consistent with adult respiratory distress syndrome (ARDS). A large right pleural effusion developed on the right, and a small left pleural effusion developed. On the fourth day post ingestion, a pig-tail catheter was placed in the right hemithorax to drain the right pleural effusion and improve ventilation. The patient was extubated 6 days after ingestion. Laboratory studies immediately after ILE administration were not able to be adequately interpreted for nearly 3 hours because of the profound lipemia. A repeat total tricyclic level 22 hours after ingestion (3 hours post ILE) was 4946 mg/mL. Serum lipase and triglyceride concentrations were added onto the initial blood from when she arrived in the PICU. These values were 182 IU/L and 82 mg/dL respectively. Three hours post ILE, the patient’s triglycerides were 1091 mg/dL, and these peaked ~18 hours post ILE (37 hours post ingestion) at 8611 mg/dL. The patient’s lipase was initially normal, but began to increase 3 days after ILE was administered. Approximately 40 hours post ILE, the lipase was normal at 79 U/L. The following day (~65 hours post ILE), however, the lipase began to increase, and reached a maximum of 1849 U/L 5 days post ILE. A trend of the relevant chemistry values is demonstrated in Fig 2. Although the patient remained intubated during the peak elevation in the lipase, we believe this did represent a true pancreatitis, rather than an isolated elevation in a laboratory value, as ultimately, once extubated, the patient was complaining of epigastric pain, which increased after eating. Nonetheless, no advanced imaging of the pancreas was performed.

The patient had a relatively prolonged hospital course, which was notable for weight loss, deconditioning, aspiration pneumonia (*Staphylococcus aureus*), and superficial thrombophlebitis involving the bilateral upper extremities. Of note, the ILE was administered via a femoral central line placed during the code, and not in an upper extremity vein. The patient was seen by psychiatry multiple times during the hospitalization, and ultimately, 28 days after the ingestion, she was able to be discharged from the hospital on sertraline with close outpatient follow-up.

One year later, the patient is doing well in school, maintaining good grades. She has no neurologic abnormalities, and had a normal physical examination. She has not had any subsequent seizures.

**DISCUSSION**

Amitriptyline is a CA, which is commonly used for the treatment of depression, migraines, and various chronic pain syndromes. Structurally, it is a tertiary-amine, which gets demethylated to

![FIGURE 2](image-url)
form nortriptyline.16 Toxicity from tricyclic antidepressants (TCAs) generally occurs within the first 2 hours after ingestion, and certainly within 6 hours after ingestion.17,18 The effects observed in overdoses are predictable based on the receptor binding. Hypotension occurs as a result of myocardial depression owing to sodium channel blocking properties, as well as α antagonism. Seizures occur as a result of sodium channel blockade and γ-aminobutyric acid antagonism. Intraventricular conduction delay occurs as a result of sodium channel blockade, whereas QT prolongation occurs as a result of potassium efflux blockade. Central nervous system depression can occur as a result of antagonism of the 1H receptors, whereas antimuscarinic effects are the result of M1 receptor antagonism.18,19 Intravenous fluid resuscitation, hypotonic sodium bicarbonate, and the use of direct-acting vasopressors have traditionally been the mainstay of therapy.18,20,21 In addition to sodium bicarbonate, benzo diazepines should be used for seizure activity. In general, anticonvulsants, such as phenytoin, should be avoided in toxin-induced seizures. In the case of CA specifically, data are conflicting, but their use should be avoided.22

As a group, TCAs, including amitriptyline, are quite lipophilic, with a large volume of distribution.16 These properties make the TCAs especially well suited to the use of ILE. Although most data for ILE is derived from local anesthetic toxicity,23–25 its use has been demonstrated to be beneficial in animal models of other lipophilic drugs, including verapamil,26,27 propranolol,28 and tricyclic antidepressants.7,8 Various mechanisms of action have been proposed for ILE in the treatment of lipophilic drug toxicity. Perhaps the most widely accepted theory, however, is the so-called “lipid sink” theory. This theory suggests that the rapid intravenous administration of lipid results in the movement of lipophilic drugs down the concentration gradient. Thus, the lipophilic drug gets pulled from the site of toxicity (eg, peripheral tissues) into the vascular compartment.9,29 Therefore, in essence, ILE reduces the volume of distribution of a lipophilic drug.9 A second theory involves providing large concentrations of a myocardial substrate to overcome myocardial inhibition.29 During normal conditions, free fatty acids are the preferred substrate for myocardial adenosine triphosphate production, whereas carbohydrates are the preferred substrate in shock states.29 Some local anesthetics inhibit carnitine acetyltransferase, which moves fatty acids across the inner mitochondrial membrane. The use of ILE may provide enough fatty acids to overcome the blockade.29

Last, it has been demonstrated that the administration of long-chain fatty acids may increase voltage-dependent calcium currents in cardiac myocytes.30 There are no randomized trials indicating the exact timing as to when ILE should be administered. Because antiepileptic experience with this drug is relatively limited, and side effects with its use are just being reported, its use should be reserved for those patients who are experiencing life-threatening toxicity that is refractory to standard therapies.

This case is unique for several reasons. First, although the patient did develop early toxicity, as is characteristic of most TCA ingestions, the patient’s toxicity became substantially worse many hours into her course. It is unclear, however, why the patient had such a delayed onset before the onset of seizures. It is possible that this resulted from on-going absorption. The delayed seizure likely created a metabolic acidosis. It has been hypothesized that seizure-induced acidosis results in worsening cardiotoxicity by increasing the amount of free drug, as the result of liberating the antidepressant from circulating proteins.31,32 This patient did have an increase in the total tricyclic concentration after the seizure and lipid emulsion (2718 mg/mL to 4946 mg/mL). Although there were several hours between these 2 levels, the levels did increase substantially. It is unlikely that this increase in concentrations is the result of ongoing absorption. More likely, the delayed rise in the total tricyclic concentrations was the result of redistribution into the vascular compartment from the ILE. Because the total tricyclic levels measure both bound and unbound drug, dissociation from albumin as a result of acidosis should not result in a change in the total tricyclic level. As such, the most likely explanation for the substantial increase in drug concentration is redistribution to the vascular compartment after the ILE, which is consistent with its proposed mechanism.

Second, this patient developed substantial hypertriglyceridemia and pancreatitis after the ILE. The patient had no history of elevated triglycerides before this case, and triglycerides were normal on admission. Thus, the most likely explanation for the marked hypertriglyceridemia and pancreatitis is the ILE. An elevation in a serum amylase without clinical evidence of pancreatitis has been described only once in the literature,33 and clinical pancreatitis has yet to be described as a complication of resuscitative ILE. Other etiologies of pancreatitis were excluded based on history and abdominal ultrasound. The patient did develop ARDS. It is not possible to state if the ARDS was the result of the ILE or simply a result of her critical illness. Of note, however, an ARDS-like picture is possible after lipid as a result of a fat-emboli, as part of the so-called fat-emboli syndrome, which is characterized by
the respiratory distress, altered mental status, and petechial rash. Fat-emboli syndrome is typically encountered after long-bone trauma.34

The patient's laboratories were not interpretable immediately after the use of ILE because of profound lipemia. The inability to obtain laboratory studies can be quite problematic in a critically ill patient. In this case in particular, the patient received sodium bicarbonate, which can lower the serum potassium. The inability to obtain a serum potassium immediately after cardiac arrest can have significant implications in the treatment of such patients.

CONCLUSIONS

A case of a 13-year-old girl with severe amitriptyline toxicity characterized by recurrent seizures and ventricular arrhythmias is presented. This patient not only had delayed seizures, but had iatrogenic complications including pancreatitis. Pancreatitis has not been previously described as a complication of ILE. This case highlights the need for caution when using novel antidotal therapies. At this point, the use of ILE should remain reserved for those cases of severe, life-threatening toxicity, unresponsive to standard therapies.

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