Tricyclic Antidepressant Overdose in a Toddler Treated With Intravenous Lipid Emulsion

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http://pediatrics.aappublications.org/content/128/6/e1628.full.html
We report a case that involves the use of intravenous lipid emulsion as an antidote for a drug overdose involving a 20-month-old girl who had ingested a potentially lethal amount of the tricyclic antidepressant (TCA) dothiepin. The patient’s condition continued to deteriorate despite implementation of standard pediatric treatment recommendations for TCA toxicity. Administration of intravenous lipid emulsion in addition to standard therapy (including sodium bicarbonate) and direct-current cardioversion for ventricular arrhythmia led to a successful outcome. The case report is followed by a review of the current evidence underlying this novel therapy and the background on its use. TCA toxicity is addressed specifically. *Pediatrics* 2011;128:e1628–e1632

**ABSTRACT**

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**KEY WORDS**

tricyclic antidepressant overdose, dothiepin, intravenous lipid emulsion, Intralipid

**ABBREVIATIONS**

TCA—tricyclic antidepressant
ILE—intravenous lipid emulsion

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Tricyclic antidepressants (TCAs), despite being largely replaced by more-modern agents for the first-line treatment of depression, remain commonly in use as second-line agents. They also are still used frequently in the management of chronic neuropathic pain and therefore are widely available. They have potent anticholinergic effects and manifest cardiotoxicity and neurotoxicity in overdose. Adequately powered, randomized, controlled trials of potential treatments for TCA overdose are lacking, and current recommendations are based mainly on animal studies, case reports, and expert opinion.

**PATIENT PRESENTATION**

A 10-kg, 20-month-old girl presented to the emergency department of a district general hospital 1 hour after ingesting her grandmother’s medication, including 45 mg/kg dosulepin. At presentation, the patient was noted to be drowsy but responsive to voice and had obvious nystagmus. She subsequently developed a tonic-clonic seizure and, despite rectal and intravenous administration of diazepam, her seizures persisted.

Thiopentone (5 mg/kg) was administered and resulted in seizure termination. Suxamethonium (2 mg/kg) was used to facilitate tracheal intubation. A nasogastric tube was passed, gastric lavage was attempted, and activated charcoal (1 mg/kg) was administered. A radial arterial line was placed, and the patient’s initial hemodynamic parameters were relatively stable. Electrocardiography showed narrow-complex tachycardia with a rate of 130 beats per minute, and the patient’s blood pressure was 80/40 mm Hg.

The patient’s QRS complexes began to broaden progressively despite the administration of a sodium bicarbonate infusion (8.4%; 10 mL diluted in 500 mL of saline solution, initiated at 30 mL/hour), according to guidelines published in Toxbase, an online poison information database provided by the UK National Poisons Information Service. The patient developed ventricular tachycardia with a rate of 180 beats per minute, although her systolic blood pressure (measured through invasive monitoring) was maintained at 80 mm Hg. In the presence of ongoing deterioration despite exhaustion of national guidelines on managing pediatric TCA overdoses, an intravenous lipid emulsion (ILE) was administered, in light of recent case reports on its successful use for treatment of TCA toxicity among adults.

A bolus dose of 10 mL of ILE (1 mL/kg) (Intralipid, 20% [Fresenius Kabi, Warrington, England]) was administered, followed by an infusion of 150 mL/hour (0.25 mL/kg per minute). Within minutes after administration of the ILE, the patient’s QRS complexes began to narrow. Her heart rate continued to increase; when it was >200 beats per minute, her blood pressure decreased to 60/30 mm Hg. A synchronized direct-current shock of 50 J was delivered (Fig 1), and narrow-complex sinus tachycardia (150 beats per minute) was immediately restored (Fig 2), which was associated with return of the baseline blood pressure.

Table 1 lists the arterial blood gas findings. The ILE infusion was continued for 1 hour after the bolus, to ensure extension of the infusion period into the expected peak plasma concentration period (which occurs 3 hours after ingestion of dothiepin). The patient was transferred to the PICU and remained in stable condition with narrow QRS complexes and adequate blood pressure. She was sedated, given ventilation, and monitored overnight. The following day, she was extubated successfully and had no additional neurologic or cardiovascular complications. She was transferred to the ward on day 2 and

<table>
<thead>
<tr>
<th>Table 1: Arterial Blood Gas Findings</th>
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<tr>
<td>At Admission</td>
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<tr>
<td>pH</td>
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<tr>
<td>Pco₂, kPa</td>
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<tr>
<td>Pao₂, kPa</td>
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<tr>
<td>Bicarbonate level, mmol/L</td>
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<tr>
<td>Base excess, mEq/L</td>
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<td>Lactate level, mmol/L</td>
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At admission indicates immediately after the seizure; at 20 minutes, before ILE administration and after bicarbonate administration; at 60 minutes, after ILE administration.

FIGURE 1

Defibrillation rhythm tracing of synchronized 50-J shock.
was discharged from the hospital on day 3. She remains well.

**DISCUSSION**

**TCAs in Overdose**
The mechanism of toxicity of TCAs in overdose stems from their anticholinergic effects in the autonomic nervous system and brain, as well as blockade of cardiac sodium channels. There also is a degree of $\alpha_1$-adrenoceptor blockade and serotonin reuptake inhibition. Morbidity and death are primarily attributable to neurologic and cardiovascular manifestations of these effects (Table 2). Death usually is a result of ventricular arrhythmias, which frequently are refractory to defibrillation.

The mainstay of management is supportive care. Gastric decontamination (for patients who present within 1 hour after ingestion), although routinely performed, is not supported by clinical trials. Recommendations regarding the use of alkalizing agents such as sodium bicarbonate are made on the basis of the fact that, in an alkaline environment, the protein binding of TCAs would be increased and bioavailability reduced.

TCA-induced arrhythmias are complicated by the fact that commonly used antiarrhythmic drugs, such as amiodarone, are contraindicated because of prolongation of the QT interval. Class 1a and 1c antiarrhythmic agents also are contraindicated because of sodium channel blockade. Anticonvulsants such as phenytoin also block sodium channels and therefore are contraindicated in the treatment of TCA-induced seizures. Hemodialysis is of little value because of the large volume of distribution of TCAs.

**ILE as an Antidote for Drugs in Overdose**
The use of ILE as a potential treatment for drugs in overdose arose from an extension of its use in treating bupivacaine-induced cardiotoxicity. The discovery of the potential benefit of ILE as a therapy for local anesthetic toxic-
ity occurred from a chance observation of a patient with a carnitine deficiency who was undergoing anesthesia. The patient seemed to be particularly susceptible to bupivacaine-induced arrhythmias. An effort to link carnitine deficiency to the underlying mechanism of bupivacaine cardiotoxicity resulted in the discovery that pre-loading with lipid seemed to be cardioprotective, attenuating the adverse hemodynamic effects of bupivacaine.3 This finding was confirmed in subsequent animal studies, which demonstrated increased resistance to bupivacaine-induced asystole in rats. The protective effect was observed when lipid was used as a preloaded infusion or during resuscitation.4

A follow-up study compared ILE and saline solution in the resuscitation of dogs with bupivacaine-induced cardiotoxicity. That study demonstrated that a 20% Intralipid bolus followed by an infusion could rescue dogs when administered 10 minutes after circulatory arrest with a potentially lethal dose of bupivacaine. The survival rate in the treatment group was 100%, compared with a mortality rate of 100% in the control group.5

These studies supported the use of ILE as a potential therapy enabling clinicians to treat the refractory arrhythmias associated with local anesthetic toxicity. The first human case that tested this theory occurred in 2006 in New York, New York, when Rosenblatt et al6 administered 20% ILE to resuscitate successfully a 58-year-old man after prolonged cardiac arrest secondary to local anesthetic toxicity after an interscalene block. After that case, ILE took its place beside dantrolene in anesthesia departments throughout the world, as a potential anesthesia rescue drug.7,8 Three possible mechanisms have been proposed for its mode of action. (1) In the “lipid sink” hypothesis, the infused lipid acts as a pharmacokinetic drug compartment into which lipid-soluble bupivacaine molecules “sink” and are rendered inactive. (2) Augmentation of cardiac energy supplies through provision of excess substrate may overcome the blockade of fatty acid transport into cardiac mitochondria. (3) Direct activation of voltage-gated cardiac calcium channels may increase cytosolic calcium levels and improve cardiac performance.

The use of ILE as a rescue therapy for other drugs in overdose (beyond local anesthetic toxicity) has evolved because ILE may inactivate other lipid-soluble drugs through the same mechanism. As a result, there has been an explosion of published and unpublished reports on the successful use of ILE in reversing the toxicity of a variety of drugs. A systematic review assessing the efficacy and safety of ILE in the management of acute poisoning was published recently.9

The first use of ILE to treat TCA overdose occurred in Canada in 2010, when ILE was administered to a 27-year-old male patient who had intentionally ingested 4.25 g of amitriptyline and developed vasopressor-refractory shock after cardiac arrest. Return of spontaneous circulation was achieved after pulseless, ventricular tachycardic cardiac arrest (with a total arrest time of 22 minutes). Despite the return of spontaneous circulation, extremely high-dose vasopressor infusions (1 μg/kg per minute norepinephrine and 0.25 μg/kg per minute epinephrine) were required to maintain a mean arterial pressure of >65 mm Hg. Administration of 100 mL of 20% Intralipid followed by a 400-mL infusion over 30 minutes enabled rapid weaning of vasopressors and normalization of serum lactate levels (from 9.7 mmol/L).2

Lipid Registry
Definitive assessment of the efficacy and safety of ILE therapy is difficult. Patients who might benefit often have ingested >1 cardiotoxic drug and frequently present in extremis. As a result, high-quality trials are almost impossible to undertake.

An Internet-based registry (the Lipid Registry [www.lipidregistry.org]) was established by an international collaboration of clinical investigators (the Lipid Injection for the Purpose of Antidotal Effect in Lipophilic Medicine Intoxication Study Group) to enable clinicians to report their uses of ILE. Their aim is to compile a prospective database on the clinical use of ILE as an antidote, in an effort to accrue evidence for this therapy.

**Pediatric Use of ILE**

Intralipid (20%) has been licensed for pediatric use as parenteral nutrition for >20 years and has an excellent safety profile, albeit at infused doses much lower than those recommended for lipid rescue.10 Concerns have been raised regarding the effects of pediatric lipid infusions, but they are related to long-term, high-dose, propofol infusions for critically ill children and the risk of propofol infusion syndrome.11 There are published reports of pediatric use of ILE as an antidote to local anesthetic toxicity, including reports of a 40-day-old infant who developed local anesthetic toxicity after a caudal block for hernia repair and a 13-year-old child who developed broad-complex arrhythmia after a lumbar plexus block.12,13 There have been no published reports (or registered cases in the Lipid Registry) of pediatric use of ILE as a potential therapy for drugs in overdose except for treatment of local anesthetic toxicity.

**CONCLUSIONS**

In a pediatric setting, this is the first reported use of ILE as an antidote to drugs in overdose other than treatment of local anesthetic toxicity. The patient recovered fully and with no obvious sequelae to date. This case adds
weight to the growing body of evidence regarding the effectiveness of ILE as an antidote for cardiotoxic lipophilic drugs in overdose and its favorable pediatric safety profile. Recently updated guidelines on Toxbase now advocate the use of 20% ILE for treatment of severe pediatric cardiotoxicity after TCA poisoning.

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