Use of Lipid Emulsion in the Resuscitation of a Patient With Prolonged Cardiovascular Collapse After Overdose of Bupropion and Lamotrigine

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Animal studies show efficacy of intravenous lipid emulsion in the treatment of severe cardiotoxicity associated with local anesthetics, clomipramine, and verapamil, possibly by trapping such lipophilic drugs in an expanded plasma lipid compartment ("lipid sink"). Recent case reports describe lipid infusion for the successful treatment of refractory cardiac arrest caused by parenteral administration of local anesthetics, but clinical evidence has been lacking for lipid's antidotal efficacy on toxicity caused by ingested medications. A 17-year-old girl developed seizure activity and cardiovascular collapse after intentional ingestion of up to 7.95 g of bupropion and 4 g of lamotrigine. Standard cardiopulmonary resuscitation for 70 minutes was unsuccessful in restoring sustained circulation. A 100-mL intravenous bolus of 20% lipid emulsion was then administered, and after 1 minute an effective sustained pulse was observed. The patient subsequently manifested significant acute lung injury but had rapid improvement in cardiovascular status and recovered, with near-normal neurologic function. Serum bupropion levels before and after lipid infusion paralleled triglyceride levels. This patient developed cardiovascular collapse because of intentional, oral overdose of bupropion and lamotrigine that was initially refractory to standard resuscitation measures. An infusion of lipid emulsion was followed rapidly by restoration of effective circulation. Toxicologic studies are consistent with the lipid sink theory of antidotal efficacy. [Ann Emerg Med. 2008;51:412-415.]

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INTRODUCTION

Poisoning caused by intentional drug overdose is an important cause of cardiac arrest that may be resistant to standard resuscitation measures.[1] Local anesthetic overdose, a rare complication of regional or tumescent anesthesia, may also cause refractory cardiotoxicity and has prompted research potentially applicable to other poisonings.[2,3] In particular, intravenous lipid emulsion resuscitates rats[4] and dogs[5] from bupivacaine-induced cardiovascular collapse and cardiac arrest. Lipid infusion is also efficacious in animal models of severe cardiotoxicity caused by a number of additional medications, notably, clomipramine and verapamil.[6,7] Lipid infusion was recently reported to resuscitate patients with refractory bupivacaine/mepivacaine-related cardiac arrest[8] and ropivacaine-induced asystole.[9] However, similar clinical experience using lipid infusion for the treatment of toxicity caused by ingested medications is lacking.

CASE REPORT

A 17-year-old, 55-kg girl was found unresponsive at home, 5 hours after sending a telephone text message to a friend, saying that she was dying. The patient's medical history was significant for bipolar and attention deficit disorders. Her medications included mixed salts of amphetamine, bupropion, and lamotrigine. Labeled prescription bottles of bupropion (Wellbutrin XL, GlaxoSmithKline, Research Triangle Park, NC; 150 mg) and lamotrigine (Lamictal, GlaxoSmithKline, Research Triangle Park, NC; 100 mg) were found at the scene,

and the missing pill counts suggested ingestion of up to 7.95 g of bupropion and 4 g of lamotrigine. The paramedic's evaluation revealed a Glasgow Coma Scale score of 3, blood pressure 108/72 mm Hg, pulse rate 112 beats/min, respiratory rate 8 breaths/min, room air SpO_2 92%, and blood glucose 91 mg/dL by rapid bedside test. Therapy in the field included oxygen at 15 L/minute through a nonrebreather mask, insertion of a nasopharyngeal airway, and intravenous naloxone 2 mg.

Vital signs on arrival to the emergency department (ED) approximately 6 hours after the estimated time of ingestion were blood pressure of 123/77 mm Hg, pulse rate 116 beats/min, respiratory rate of 14 breaths/min, and SpO_2 of 100% (in 100% oxygen by nonrebreather mask). Physical examination revealed no eye opening or verbal response, but withdrawal from painful stimuli (Glasgow Coma Scale score 6). The initial chest radiograph result was normal. An ECG revealed sinus tachycardia, with a pulse rate of 114 beats/min, prolonged QRS-interval duration of 0.122 seconds, prolonged QTc of 0.485 seconds, and a prominent terminal R-wave in lead aVR (see Figure E1, available online at http://www.annemergmed.com). Hemoglobin level was 13.9 g/dL. Sodium level was 134 mmol/L, and albumin level was 2.9 g/dL. All other electrolytes, glucose, blood urea nitrogen, creatinine, calcium, bilirubin, total protein, alkaline phosphatase, hepatic transaminases, magnesium, troponin, creatine phosphokinase, and coagulation study results were normal. Treatment in the ED during 3 hours was supportive, including 100% oxygen by nonrebreather mask and nasopharyngeal airway and intravenous fluid administration. Before transfer to the ICU, increased responsiveness and some eye opening were observed.

Soon after arrival to the ICU, approximately 10 hours postingestion, the patient had a tonic-clonic seizure, followed quickly by cardiovascular collapse, characterized by a pulseless, wide complex rhythm. Advanced cardiac life support (ACLS) was initiated with chest compressions, but pulseless ventricular tachycardia and ventricular fibrillation then developed. The initial 18 minutes of resuscitation included tracheal intubation, 11 electrical defibrillations, 6 1-mg doses of epinephrine, amiodarone 300 mg, and magnesium 1 g, without return of effective circulation. Within 2 minutes of an intravenous bolus of sodium bicarbonate 50 mEq, a pulse was palpated, with a blood pressure of 84/55 mm Hg and pulse rate of 97 beats/min. An ECG at this time revealed a wide complex rhythm (QRS 0.152 seconds) (see Figure E2, available online at http://www.annemergmed.com). This spontaneous circulation was sustained for 17 minutes, when pulseless electrical activity with a wide complex rhythm recurred, and ACLS was resumed. Interventions included an unsuccessful attempt to transcutaneously pace the heart, 12 1-mg boluses of epinephrine, 2 more 50-mEq boluses of sodium bicarbonate, and 1 g of calcium chloride. The patient also received continuous infusions of high-dose norepinephrine and epinephrine. An arterial blood gas drawn 10 minutes into ACLS revealed pH 7.252, pCO_2 46.6 mm Hg, pO_2 48.1 mm Hg, and serum bicarbonate 20.1 mEq/L. A transient pulse was detected by Doppler ultrasonography after some epinephrine boluses but was never sustained. One to two hundred milliliters of bright-red secretions were suctioned from the endotracheal tube during resuscitation.

Fifty-two minutes into the second period of ACLS, a single 100-mL bolus of 20% lipid emulsion (Intralipid) was given intravenously, and approximately 1 minute later, a sustained palpable pulse was observed (see Figure E3, available online at http://www.annemergmed.com). During the next 15 minutes, the widened QRS narrowed, a sinus rhythm returned, and pressor therapy was reduced. Arterial blood gas 14 minutes postresuscitation revealed pH 7.196 and serum bicarbonate 12.2 mEq/L. An additional 100 mEq of sodium bicarbonate was infused. Pulseless ventricular tachycardia developed 90 minutes later, and the patient was given 1 mg epinephrine, with chest compressions for 1 minute, when the ventricular tachycardia resolved. A chest radiograph immediately after the resuscitation showed pulmonary edema. Thirty minutes after the resuscitation, an echocardiogram showed a low-normal ejection fraction.

The following day, the ECG revealed sinus rhythm, with QRS 0.090 seconds. Chest radiography showed bilateral pneumonia, left pleural effusion, and consolidation of the bilateral upper lobes. An electroencephalogram indicated diffuse cerebral dysfunction, consistent with medication and sedation effect or anoxic brain injury; however, the presence of vertex waves and sleep spindles indicated that thalamocortical connections were intact. No epileptiform abnormalities were observed. Forty hours after the resuscitation, the patient was observed to squeeze her hand on command and was soon transferred to a regional pediatric ICU (PICU).

The patient was hospitalized in the PICU for 24 days, after which she was transferred to an affiliated inpatient rehabilitation unit. Her PICU course was marked predominantly by significant acute lung injury, requiring chest tube placement for pleural fluid evacuation, airway pressure release ventilation, inhaled nitric oxide, endotracheal surfactant, and antibiotic therapy. Oxygenation improved gradually, with nitric oxide discontinuation by PICU day 5, chest tube removal on day 12, tracheal extubation on day 17, and resumption of spontaneous ventilation on room air by day 20.

Pressor therapy (epinephrine, vasopressin, and norepinephrine infusions) and amiodarone were weaned rapidly and discontinued by PICU day 2. An echocardiogram on PICU day 6 demonstrated normal myocardial function. Brain magnetic resonance imaging showed lesions consistent with mild hypoxic injury in the cerebellum and hippocampi, as well as a complex nonenhancing pineal cyst. The patient was gradually weaned from intravenous sedatives and switched to oral levetiracetam for seizure prophylaxis. By PICU discharge, she was conversant and talkative, with slight tremor, mild memory deficits, and fine motor incoordination, which are being addressed with rehabilitation therapy.

Table. Serum triglyceride, bupropion, and lamotrigine levels in relation to time after ingestion, clinical events, and lipid infusion.

Time, h*	Triglyceride, mg/dL	Bupropion, ng/mL (TR=50–100)	Lamotrigine, μg/mL (TR=3–14)
6.5	103	180	26
10 (Seizures followed shortly by cardiovascular collapse)	N/A	N/A	N/A
11.5 (Lipid infusion)	N/A	N/A	N/A
12.75	681	880	24
18.25	81	390	21
28.75	33	62	18

TR, Therapeutic range; *N/A,* data not available.
*Approximate interval after estimated time of ingestion.

An ED urine drug immunoassay was positive for amphetamines, cannabis, and benzodiazepines and negative for barbiturates, cocaine, opiates, phencyclidine, and cyclic antidepressants. Blood alcohol level was 1 mg/dL, acetaminophen was undetectable, and salicylate level was 2.7 mg/dL. The patient had serial triglyceride, bupropion, and lamotrigine levels measured in serum saved from routine laboratory specimens drawn at the ED evaluation and 3 subsequent samples drawn during the course of her first hospital day (Table). The bupropion level was highest 77 minutes after lipid infusion and then decreased over time in parallel with the serum triglyceride level. This relationship was not observed with lamotrigine.

DISCUSSION

Bupropion is a unicyclic aminoketone antidepressant with dopamine-, norepinephrine-, and serotonin-reuptake-inhibiting properties. In large overdose, it may also manifest sodium channel blockade.[10] Bupropion toxicity is typically associated with sinus tachycardia, hypertension, tremor, agitation, and seizures and occasionally with significant cardiac effects, especially with cardiotoxic coingestants. Fatal bupropion overdoses are reported, with bupropion concentrations of 430 ng/mL and 446 ng/mL measured in 2 such cases.[11,12] Lamotrigine is a phenyltriazine derivative that blocks voltage-dependent sodium channels. It is used primarily for anticonvulsant effects but is also prescribed for bipolar disorder. Lamotrigine overdose typically manifests as ataxia, nystagmus, and occasionally coma and seizures.[13] Serious cardiotoxicity has not been reported.

Toxicologic causes of cardiovascular collapse in the case of agents with profound sodium channel– or calcium channel–blocking properties may require unique therapeutic interventions, such as infusions of sodium bicarbonate or calcium salts, respectively.[1] Animal studies during the past decade have established that intravenous infusion of lipid emulsion is highly effective in treating cardiac arrest caused by overdose of bupivacaine, a potent sodium channel–blocking local anesthetic.[3-5] Further work has extended the use of intravenous lipid therapy to animal models of clomipramine and verapamil toxicity.[6,7] Recent case reports have indicated similar clinical efficacy of lipid infusion in treating refractory cardiac arrest during regional anesthesia with bupivacaine/mepivacaine and ropivacaine.[8,9]

It has been suggested that the efficacy of lipid therapy results in part from the rapid formation of an expanded lipid compartment within the intravascular space that draws tissue-bound drug off cellular receptor sites and into the plasma, where it becomes trapped in the transiently expanded lipid phase. This "lipid sink" theory is consistent with the lipophilicity of cardiotoxic local anesthetics and that of the other study drugs for which lipid therapy has been effective.[3,4] Bupropion is also highly lipophilic, having a lipid/aqueous partition coefficient (log P 3.47) that is comparable to that of bupivacaine (log P 3.64).[14] Our patient's bupropion level peaked after lipid administration, suggesting such a "lipid sink" effect. An alternative explanation for the late rise in bupropion level may be delayed absorption, observed especially with the sustained-release formulation. Unfortunately, blood specimens had not been drawn immediately before and after lipid infusion, and thus we were unable to distinguish these phenomena. However, the bupropion concentration subsequently decreased in parallel with the serum triglyceride concentrations, and no such increase and decrease in parallel with triglyceride levels was observed for lamotrigine, a drug of low lipophilicity (log P −0.19).[14] Bupivacaine is also a potent inhibitor of mitochondrial fatty acid transport, and another putative mechanism of lipid therapy for bupivacaine overdose is enhanced fatty acid intracellular transport and use,[3,7] although it is unknown whether this might apply as well to bupropion toxicity.

Intravenous lipid emulsion (Intralipid, a predominantly soybean oil product with pH 6-8.9[15]) has a long history of safe use in critically ill patients, although avoiding overly rapid infusion rates (greater than 100 mL/hour) is recommended to mitigate fat overload, with potential adverse effects including pulmonary injury.[3,7,15] Our patient did manifest severe acute lung injury but had significant risk factors for this syndrome after protracted resuscitation, high-dose pressor therapy, and the appearance of hemorrhagic pulmonary secretions before lipid administration. Two previous case reports of rapid lipid infusion for regional anesthetic overdose did not describe acute lung injury,[8,9] but this issue warrants further study and vigilant monitoring in any future use of bolus lipid therapy.

The patient reported here experienced catastrophic, refractory cardiovascular toxicity after ingesting large amounts of bupropion and lamotrigine. After combined periods of unsuccessful cardiopulmonary resuscitation lasting 70 minutes, including 3 50-mEq bolus doses of sodium bicarbonate, administration of lipid emulsion was considered in the context of the known sodium channel–blocking effects of bupropion and the reported efficacy of lipid therapy in the treatment of sodium channel blockade caused by local anesthetic toxicity. A 100-mL bolus dose of 20% lipid

emulsion was followed almost immediately by sustained return of effective circulation (this bolus dose was based on the published case reports, although in those cases an additional slow infusion was administered[8,9]). Our patient subsequently recovered, with normal cardiovascular and near-normal neurologic function. Although a causal relation between lipid therapy and recovery cannot be proved by one clinical observation, the temporal relationship of lipid administration with the rapid and sustained cardiovascular improvement in our patient, within the context of previous laboratory studies and the case reports of successful resuscitation in local anesthetic overdoses, suggests a potential therapeutic benefit for this novel antidotal therapy, which warrants further evaluation.

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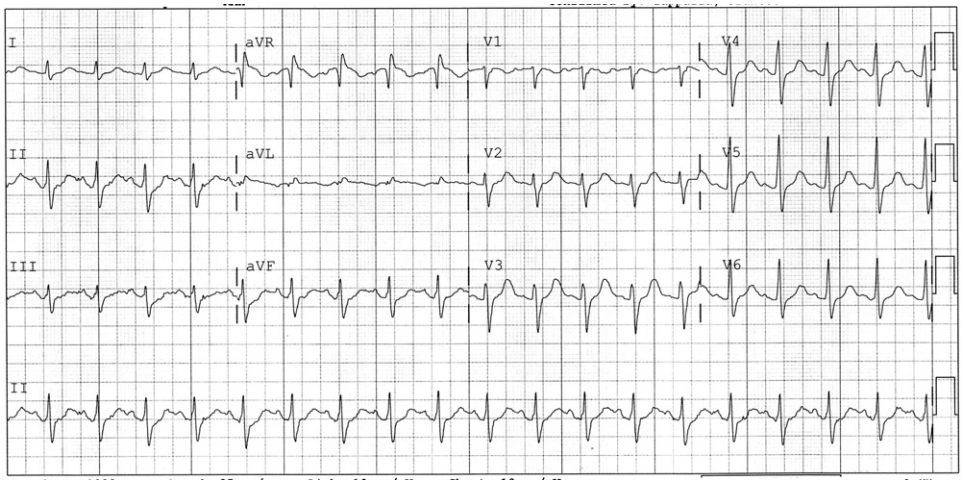

Figure E1. The electrocardiogram taken in the emergency department shows sinus tachycardia, nonspecific intraventricular conduction delay, mildly prolonged QTc and a prominent terminal R wave in lead aVR, consistent with sodium channel blockade.

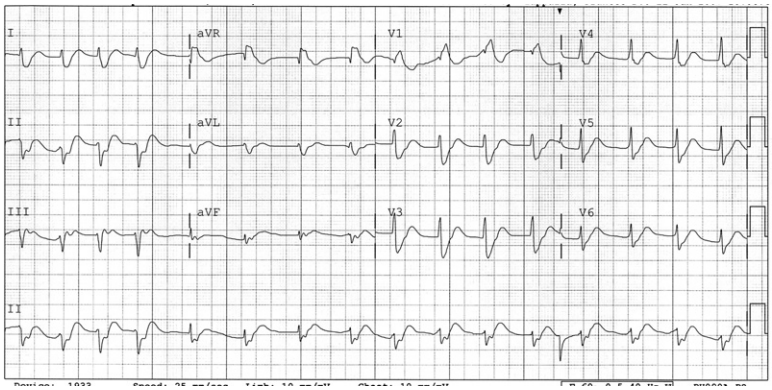

Figure E2. The electrocardiogram from the intensive care unit just prior to onset of recurrent pulseless electrical activity shows wide QRS complex rhythm.

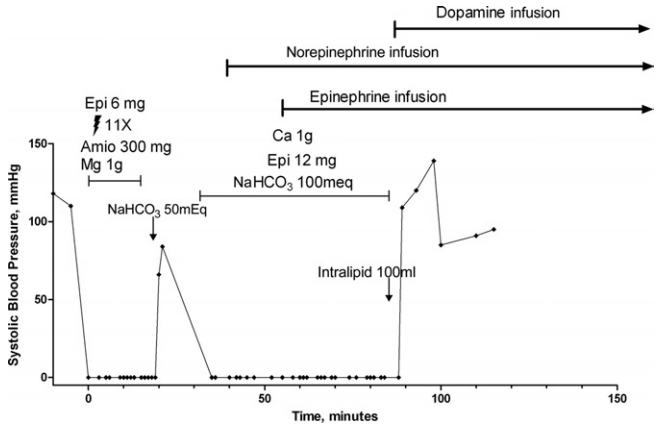

Figure E3. Summary of resuscitation measures over time. Key: Epi= epinephrine (administered as 1 mg doses); Amio=amiodarone, Mg=magnesium sulfate, NaHCO3= sodium bicarbonate; Ca=calcium chloride; Systolic blood pressure = spontaneous systolic blood pressure in absence of chest compressions.