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TOXICOLOGY INVESTIGATION

Complications Following Antidotal Use of Intravenous Lipid Emulsion Therapy

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Abstract The primary objective is to identify and describe the complications associated with the use of intravenous lipid emulsion (ILE) therapy as an antidote for lipophilic drug toxicity. This study is a retrospective chart review of patients treated with ILE at two academic medical centers between 2005 and 2012. Based on previously reported complications, we hypothesized that pancreatitis, ARDS, and lipemia-induced laboratory interference might occur. Clinical definitions of these complications were defined a priori. Subjects treated with ILE who did not develop at least one complication were excluded. A total of nine patients were treated with ILE during the study period, six of whom experienced potential complications as a result of the ILE. Two patients developed pancreatitis, and four patients had lipemia-induced interference of interpretation of laboratory studies, despite ultracentrifugation. Laboratory interference precluded one patient from being an organ donor. Three patients developed ARDS; although temporally associated, a causal relationship between ILE and the development of ARDS cannot be clearly established. As ILE is increasingly used for less severe cases of drug toxicity, clinicians should be aware of potential complications associated with its use. A risk–benefit assessment for the use of ILE should be implemented on a case-by-case basis.

Keywords Pancreatitis · Intravenous lipid emulsion · Lipid · Antidote

Introduction

During the past decade, fatalities from intentional and unintentional drug overdoses have increased substantially [1, 2]. Lipophilic drugs, including the antiarrhythmic agents verapamil and propranolol, as well as the tricyclic antidepressants, continue to be a significant source of morbidity and mortality [3]. The use of intravenous lipid emulsion (ILE) therapy has recently emerged as a rescue antidote for the treatment of lipophilic drug toxicities [3–6]. While its exact mechanism is not known, ILE likely involves movement of the lipophilic drug down its concentration gradient; the drug moves from tissue into the vascular compartment [7, 8]. Intravenous lipid emulsion has been recommended for the treatment of lipophilic drug toxicities that do not respond to standard, conventional treatment [8, 9]. As knowledge of its use becomes more common, reports are beginning to emerge of ILE being utilized for the treatment of drug toxicities outside of cardiovascular collapse or cardiac arrest [10, 11]. Only recently have complications, including pancreatitis and lipemia-induced interference with laboratory studies, been described following antidotal use of ILE [4, 12, 13]. As its use becomes more widespread, it is important that clinicians be aware of possible complications. The purpose of this manuscript is to describe

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complications associated with the antidotal use of ILE. The study was prompted by a case reported from one of our centers, which is included and briefly summarized as part of this chart review [13].

Methods

This manuscript is a retrospective chart review of patients treated with ILE at two tertiary care medical centers in the USA, who experienced complications associated with use of ILE. Inclusion criteria were age at least 13 years, treatment with ILE following a known or suspected overdose, and development of a complication possibly attributed to ILE. Potential complications were defined a priori.

At both hospitals, patients with known or suspected poisoning requiring admission were admitted to an inpatient toxicology service. The medical toxicology service at each of these medical centers maintains a registry of all patient encounters. The registries are a comprehensive, consecutive list of all patient encounters maintained by the respective departments. Each registry was reviewed, and all patients who received ILE through the years 2005–2012 (inclusive) were identified and included. The study received approval from the institutional review board at each of the participating medical centers.

Data Abstraction

The data were abstracted on a pre-designed data abstraction sheet and subsequently entered into a spreadsheet by one investigator at each site (ML, AFP). Following data abstraction, a second investigator (AS) reviewed half of the charts for accuracy. The abstracted data included age, sex, agent ingested, amount of lipid administered, and laboratory values including lipase and triglyceride values. One of the cases (case 3) has been previously published as an individual case report [13], but was included in this case series as it met inclusion criteria.

Study Definitions

Clinical definitions for complications and response to ILE were created a priori. Pancreatitis was defined as a lipase amount of >1,000 IU/L with associated symptoms of abdominal pain, nausea, or vomiting. Laboratory interference was defined as an inability to analyze serum chemistry studies for more than 2 h after ILE administration in lipemic serum. A response to ILE was defined as at least a 20 % reduction in vasopressor infusion rates 1 h after administration of ILE. Adult respiratory distress syndrome (ARDS) was defined based on the presence of bilateral interstitial infiltrates and a PaO_2/FiO_2 ratio <200.

Case Reports

A total of nine patients received ILE. Laboratory interference due to lipemia was observed in four patients. Pancreatitis developed in two patients, both of whom also had laboratory interference. A third patient was suspected to have pancreatitis, although the lipase was not measured during peak symptomatology. When it was measured, it was mildly elevated. Three patients developed ARDS, two of whom had evidence of laboratory interference, and one who developed pancreatitis (Table 1). Three patients did not experience any potential complication of ILE and were excluded. Of the three excluded patients, one died. The other two patients survived without developing any of the pre-specified complications.

Case 1

A 13-year-old girl ingested an unknown quantity of amitriptyline. She was found comatose and had an initial QRS of 76 ms, although she subsequently developed severe intraventricular conduction delay. Approximately 19 h post-ingestion, the patient experienced multiple generalized tonic–clonic seizures followed by a wide-complex tachycardia without detectable pulses. She received multiple advanced cardiac life support (ACLS) medications including multiple doses of sodium bicarbonate. Two boluses of ILE were administered. Lipemia precluded laboratory interference for 3 h. Hypertriglyceridemia and pancreatitis developed. The patient developed ARDS, but ultimately made a full recovery.

Case 2

A 36-year-old woman presented following an ingestion of an unknown amount of verapamil and propranolol. The patient presented hypotensive with a systolic blood pressure of 70 by palpation and a heart rate of 52 beats per minute (bpm). She subsequently developed a bradycardic, wide-complex rhythm that deteriorated into an asystolic cardiac arrest. She was intubated and placed on infusions of epinephrine, sodium bicarbonate, and 20 % ILE (0.42 mL/kg IV bolus, followed by an infusion at 0.23 mL/kg/min for 1 h). One and three-quarter hours after administration of ILE, the patient's epinephrine infusion was decreased from 0.896 to 0.768 mg/hr. Laboratory studies were obtained 2 h after the ILE infusion was complete. There was no reported interference of the labs due to lipemia. The initial laboratory studies revealed an elevated AST and ALT at 294 and 303 IU/L, respectively, prompting the administration of N-acetylcysteine. Her AST and ALT improved over the subsequent 3 days, and N-acetylcysteine was discontinued. The triglycerides were noted to be 408 IU/L (normal <200 mg/dL) on hospital day 21, the first time they were measured during her hospitalization. A lipase was not measured. The patient had a prolonged hospital

Table 1 Summary of complications in patients receiving intravenous lipid emulsion therapy

Case	Pancreatitis	Laboratory interference	Adult respiratory distress syndrome
1	Yes	Yes	Yes
2	No	No	Yes
3	No	Yes	Yes
4	Yes	Yes	No
5	Possible	No	No
6	No	Yes	No

stay due to the development of ARDS and encephalopathy post cardiac arrest. Ultimately, she made a full recovery and was able to be discharged from the hospital.

Case 3

A 40-year-old man with history of Down syndrome presented 30 min following an ingestion of extended-release verapamil. On arrival in the emergency department, his blood pressure was 72/51 mmHg, with a heart rate of 88 bpm, and the patient subsequently developed an accelerated junctional rhythm. The patient received activated charcoal, calcium, and insulin, and was started on continuous infusions of epinephrine, norepinephrine, dobutamine, vasopressin, and phenylephrine. In addition, the patient received sodium bicarbonate for metabolic acidosis. The patient was administered 20 % ILE (1.5 mL/kg bolus, followed by 0.25 mL/kg/min for 30 min) for refractory hypotension. There was no significant improvement in hemodynamics after ILE was administered. He developed refractory acidosis and anuria, requiring continuous veno-venous hemodialysis (CVVHD). Vasopressor requirements increased 3 h after ILE administration and did not begin to decline for more than 12 h after ILE administration. Arterial blood gases could not be analyzed for 12 h due to lipemia. Point-of-care electrolytes were measurable approximately 12 h after administration of ILE, but despite ultracentrifugation, lipemia prevented analysis of serum chemistry studies for 25 h following the administration of ILE. The filters on the CVVHD circuit clotted multiple times over the first 12 h, presumably due to lipemia. The patient developed ARDS with moderate bilateral pleural effusions. The lipase remained normal. The patient was ultimately discharged home, fully recovered.

Case 4

A 20-year-old man was found unresponsive with empty bottles of doxepin and citalopram. During the evaluation by EMS, the patient was noted to be hypotensive and tachycardic. He had a generalized tonic–clonic seizure and was subsequently intubated. Upon arrival in the ED, the patient's blood pressure was 68/32 mmHg with a heart rate of 150 bpm. His initial treatment in the ED included administration of lorazepam, fosphenytoin, and 150 mEq intravenous sodium bicarbonate for a QRS of 126 ms. The patient experienced a brady–asystolic arrest and was resuscitated with epinephrine. A second brady–asystolic arrest occurred, prompting the administration of additional intravenous epinephrine and sodium bicarbonate. The patient continued to have hemodynamic instability, prompting the administration of 20 % ILE (1.5 mL/kg bolus, followed by 0.25 mL/kg/min for 30 min). Two hours after the first ILE bolus, the patient again became bradycardic, prompting an additional bolus and infusion of ILE. In total, the patient received 1,550 mEq sodium bicarbonate in addition to the ILE. Initial laboratory studies were notable for a pH of 6.66, arterial lactate of 14.9 mmol/L, and lipase of 32 IU/L. Despite ultracentrifugation, chemistry studies could not be obtained for 16 h after the second dose of ILE due to lipemia. No evidence of shock liver developed. The trigylcerides peaked at 3,648 mg/dL 1 day post ILE, but fell to 85 mg/dL the following day.

The patient's lipase began to rise on hospital day five and reached a peak of 2,951 IU/L on hospital day six. He was complaining of epigastric pain at that time. The pain improved, and he was transferred to inpatient psychiatry on hospital day 8. He returned the following day complaining of increasing abdominal pain and was not tolerating oral food or liquid. His lipase was 2,941 IU/L. Hepatobiliary ultrasound was unrevealing, and a computerized tomography scan of the abdomen and pelvis revealed pancreatitis without hemorrhage or pseudocyst formation. The patient returned to the inpatient psychiatry following resolution of his abdominal pain.

Case 5

A 20-year-old woman developed a generalized seizure following administration of bupivacaine by an anesthesiologist for a T8 paravertebral block. The patient was immediately intubated, and a bolus of 20 % ILE (2 mL/kg) was administered, followed by an infusion of 0.25 mL/kg/min. Upon arrival in the ICU, the patient was noted to be tachycardic with a heart rate of 178 bpm, but normotensive (107/70 mmHg). The ILE infusion of 0.25 mL/kg/min was discontinued after 3 h, and the patient was extubated shortly thereafter. Laboratory studies were obtained 1 h after the completion of the ILE infusion, and no laboratory interference was noted. The lipase on hospital day 2 was 23 IU/L. The patient developed persistent epigastric pain and nausea after extubation. No lipase was obtained until day 14, at which time the patient's symptoms were improving. The lipase was 185 IU/L (normal ≤51 IU/L), suggesting pancreatitis to be the cause of the patient's persistent pain, as no other etiology

was found. The patient continued to improve and ultimately made a full recovery.

Case 6

A 39-year-old man was found at home unresponsive by his mother, surrounded by empty pill bottles of metoprolol and diltiazem. Upon arrival of EMS, the patient was in an asystolic cardiac arrest. Cardiopulmonary resuscitation was begun, and he received a total of 2 mg of intravenous epinephrine and was transported to an outlying ED. Upon arrival in the ED, he was intubated, where he had multiple brief, recurrent cardiac arrests requiring CPR. During the resuscitative efforts, the patient received an unknown quantity of 20 % ILE, with ultimate return of spontaneous circulation. He was transferred to a tertiary care medical center, where neuroimaging revealed cerebral edema with loss of gray–white matter differentiation and effacement of the sulci. Profound lipemia resulted in laboratory interference, which ultimately precluded organ donation. The patient subsequently died.

Discussion

Intravenous lipid emulsion therapy is emerging as a new antidote for treating lipophilic drug toxicity. In this study of patients receiving ILE at two toxicology centers, ILE was administered to nine patients. Six patients developed laboratory interference, pancreatitis, or ARDS. Although causality cannot be proven, there was a temporal association between the administration of ILE and the development of both pancreatitis and laboratory interference.

Several complications have been described with intravenous administration of lipid emulsion. These complications can occur when lipid is given as part of intravenous nutrition or used as an antidote, and can be divided into immediate and delayed complications [14]. Immediate complications include pyrogenic reactions and fat overload. Delayed adverse reactions from lipid infusions are more likely to be seen in higher doses, such as would be expected with antidotal use [14]. These complications include acute lung injury and fat accumulation, which can manifest as fat embolism, hemolytic anemia, and hyperlipidemia [4, 14, 15]. While acute lung injury has been observed following large doses of lipid, it is difficult to clinically discern if the lung injury is the result of the lipid or the result of critical illness [4]. In our series, three patients developed ARDS. However, because critically ill patients can develop lung injury, it is certainly possible that the lung injury was simply the result of their illness, rather than ILE administration.

In our small study, pancreatitis was diagnosed in two patients and may have been present in a third based on symptoms and a mildly elevated lipase. While it has been recognized for several years that antidotal use of ILE has the potential to cause hypertriglyceridemia [14], pancreatitis has only recently been described [13]. The only prior published case of pancreatitis, a 13-year old who developed cardiac arrest following an amitriptyline overdose, was included in this manuscript (case 1). It is possible that cases of delayed pancreatitis following the antidotal use of ILE are under-reported as they may occur after poison centers have terminated telephone follow-up. It is well known that hypertriglyceridemia can induce pancreatitis [16–18]. Although the exact mechanism for triglyceride-induced pancreatitis is not known, it is believed that free fatty acid formation occurs as the result of hydrolysis of triglycerides by the pancreas. This free fatty acid formation results in free radical formation and significant inflammatory changes in the pancreas, with resultant pancreatitis [13, 15]. Serum triglyceride concentrations above 1,000 mg/dL are generally required to ascribe causality for acute pancreatitis to hypertriglyceridemia [18]. In this study, two patients (cases 3 and 4) developed pancreatitis, with questionable pancreatitis in a third (case 5). The two patients with clear evidence of pancreatitis had both clinical manifestations (e.g., abdominal pain and nausea) and elevation of serum lipase. These two patients had serum triglyceride concentrations of 8,611 and 3,648 mg/dL following ILE that normalized in the ensuing days. Pancreatitis following hypoperfusion is rare, typically is associated with pancreatic hemorrhage and necrosis, and carries a high mortality rate [19]. Furthermore, it is considered a diagnosis of exclusion [19]. It is impossible to completely exclude hypoperfusion as a cause of pancreatitis in this case series. However, there was a strong temporal association of profound hypertriglyceridemia, a known cause of pancreatitis, with the onset of symptoms. Resolution of the symptoms occurred coincident with normalization of the triglycerides. Therefore, ILE-induced hypertriglyceridemia is the most likely cause of the pancreatitis observed in these patients.

In the current study, laboratory interference due to lipemia prevented the laboratory from reporting results in four subjects. In two of these subjects, laboratory studies could not be performed for more than 12 h, despite ultracentrifugation of the blood. Ability to analyze blood gases was also delayed. In critically ill patients with acid–base and electrolyte disturbances, inability to obtain laboratory studies inhibits provision of optimal care. Interference of laboratory analysis by lipemia has been described previously in a single case series, although the duration of laboratory interference was not reported [4, 20]. In one patient, laboratory interference prevented the patient from being a transplant candidate. Despite a bench model suggesting that centrifugation ameliorates laboratory interference, serial ultracentrifugations did not allow laboratory analysis in the clinical setting, as discussed above [12].

It should be noted that not all complications are equal. For example, a mild elevation in the lipase occurring in an asymptomatic individual is significantly different than that in a patient with abdominal pain and vomiting, who requires

hospitalization strictly due to pancreatitis. Similarly, if a patient was asymptomatic and ability to obtain laboratory studies was delayed, this would be of little clinical consequence. However, in a critically ill patient, inability to rapidly assess electrolytes and renal function can negatively affect their care. In case 4, the patient developed QT prolongation and ventricular ectopy following 1,550 mEq of sodium bicarbonate, and it was not possible to measure the potassium.

The two patients with confirmed pancreatitis each received two boluses of ILE followed by an infusion, while the patient with questionable pancreatitis had a prolonged infusion and received a significant total volume of lipid. It is not known if large volumes administered in a short time span or an overall longer infusion may predispose the development of pancreatitis.

In this study, complications associated with ILE were relatively common. While it is impossible to definitively determine causality with this study design, given the temporal association and biologic plausibility, ILE is strongly implicated as the etiology of pancreatitis and laboratory interference. Based on currently available evidence, and the possibility of complications, the authors believe that ILE should be reserved for hemodynamically unstable patients in whom supportive efforts have failed.

Conclusion

In this multi-center retrospective study of patients treated with ILE for life-threatening lipophilic drug toxicity, several complications were observed. Laboratory studies were uninterpretable for a prolonged period of time in four subjects, and clinically relevant pancreatitis developed in at least two subjects. A risk–benefit analysis should be performed for each patient prior to the administration of ILE. Given the still limited experience with antidotal use of ILE, patients who have been treated with ILE should be observed for the development of complications.

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