Prolonged Laboratory Interference After Administration of Intravenous Lipid Emulsion Therapy

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Abstract

Background Pancreatitis and laboratory interference are rarely reported complications of intravenous lipid emulsion (ILE) therapy. We report a case of significant laboratory interference after ILE administration.

Case Report A 43-year-old female was admitted to the hospital after an unwitnessed ingestion of propranolol, tramadol, zolpidem, and alprazolam. She was intubated and treated with intravenous normal saline, insulin/glucose, and norepinephrine infusions due to hypotension. Two bolus doses and one maintenance dose of 20 % ILE were administered. Beginning approximately 2 h after ILE administration, laboratory assays were unable to be performed due to the presence of lipemia. The patient developed refractory hypotension and was transferred to a tertiary care center. Upon admission to the ICU, the patient received one additional bolus of 20 % ILE. Laboratory assays were again attempted but were unable to be adequately performed due to a pinkish-white discoloration of the patient's blood. Percutaneous femoral extracorporeal membrane oxygenation (ECMO) was initiated, but laboratory interference noted with the arterial blood gas analyzer prevented the analysis of oxygenation. The patient's hemodynamic condition did not improve; she expired 31 h after initial admission.

Case Discussion In one previous report, centrifugation was effective in removing more than 90 % of glycerol-banked triglycerides, thus minimizing lipid interference with laboratory assays. We noted persistent laboratory interference for

more than 20 h after ILE administration, despite ultracentrifugation of specimens.

Conclusion Clinicians should be aware that ILE administration may cause significant and prolonged interference with laboratory assays, which may affect the monitoring of critically ill patients.

Keywords Laboratory · Antidotes · Intravenous fat emulsion · Propranolol

Introduction

Intravenous lipid emulsion (ILE) therapy is recommended with increasing frequency as an antidote for toxicity from lipophilic drugs. Several potential mechanisms of action for ILE therapy have been postulated, including the possibilities that ILE causes lipophilic drugs to be sequestered from tissue receptors into an extended plasma lipid phase (the “lipid sink” theory). Additional potential mechanisms of action include ILE-induced increased myocardial uptake and utilization of free fatty acids and increased myocardial intracellular calcium concentrations. The American College of Medical Toxicology currently recommends the use of ILE for patients who experience hemodynamic instability or other refractory complications that are unresponsive to other standard resuscitation therapies and are presumed to be a consequence of lipophilic drug toxicity [1]. ILE therapy is utilized in the treatment for systemic local anesthetic toxicity and has been used as an early treatment after intentional drug overdose as well, although it is generally not recommended as a first-line agent in that circumstance [2]. While there are many reports of successful outcomes after administration of ILE, the potential adverse effects of this therapy are rarely published. We report

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a case of prolonged interference with laboratory assays as a complication of ILE therapy.

Case Report

A 43-year-old, 63-kg female was found alone in a hotel room with agonal respirations and nonpalpable carotid pulses, approximately 12 h after checking in. She had a past medical history significant for depression; she was employed as a physician's assistant. Multiple pill bottles were found nearby; a total of 12 g of propranolol, 1.5 g of tramadol, 200 mg of zolpidem, and 15 mg of alprazolam were unaccounted for. The patient was taken to a local hospital where she was noted to have a blood pressure of 64/47 mmHg and a heart rate of 81/min. She was intubated and treated with intravenous normal saline and norepinephrine infusions. Initial laboratory findings included a creatinine of 1.9 mg/dL, a glucose of 528 mg/dL, an undetectable salicylate level, and an acetaminophen concentration of 12.2 mcg/mL. A urine toxicology screen for drugs of abuse was positive for benzodiazepines and opioids; PCP, cocaine, amphetamines, barbiturates, and marijuana were not detected. After consultation with a medical toxicologist, insulin, glucose, and glucagon infusions were initiated, and the patient was admitted to the intensive care unit (ICU) where a bedside echocardiogram demonstrated an ejection fraction (EF) of 20 %. Due to the presence of persistent hypotension and cardiogenic shock after presumed propranolol intoxication, two 1.5 mL/kg bolus doses and one maintenance dose (0.25 mL/kg/min) of 20 % ILE were administered 8 h after her initial admission. Beginning approximately 2 h after ILE administration, laboratory assays (including chemistry, hematology, coagulation, and blood gases) were unable to be performed due to the presence of lipemia in the collected samples. The patient developed worsening hypotension; repeat echocardiography showed global hypokinesis with an EF of 10–17 %. A vasopressin infusion was ordered, and the patient was transferred to a tertiary care center where she remained hypotensive despite norepinephrine, vasopressin, dobutamine, and epinephrine infusions. Upon admission to the ICU, the patient received one additional 1.5 mL/kg bolus of 20 % ILE without improvement in her hemodynamic condition. Laboratory assays were again attempted but were unable to be adequately performed due to a pink discoloration of the patient's blood; despite ultracentrifugation (Airfuge®; Beckman Coulter, Brea, CA) of the undiluted specimen for 10 min, the plasma appeared opaque and pinkish white (Fig. 1). Percutaneous femoral extracorporeal membrane oxygenation (ECMO) was initiated at the bedside, but oxygenation was not able to be monitored due to laboratory interference noted with arterial blood gas analyzers. The patient's hemodynamic condition did not improve with ECMO; she became increasingly difficult to ventilate,

Fig. 1 Lipemic appearance of blood after ILE administration

experienced an asystolic cardiac arrest, and was unable to be resuscitated. She was pronounced dead 31 h after her initial admission. A plasma propranolol concentration was obtained 23 h after the patient's initial hospital admission, after the patient had received ILE. The propranolol concentration, which was processed (after ultracentrifugation) by high-performance liquid chromatography/tandem mass spectrometry at a reference laboratory, was found to be 3.5 mg/L (reference range <0.5 mg/L). Assays for tramadol, zolpidem, and alprazolam were not performed.

Discussion

The adverse effects of ILE, when administered in parenteral nutrition therapy regimens, include allergic or anaphylactoid reactions, abdominal pain, fever, and jaundice. Acute lung injury has also been reported to occur in patients who receive parenteral nutrition containing ILE and in patients who receive ILE as antidotal therapy, although it is unclear whether the etiology in the latter group is the ILE infusion or the underlying critical illness [3, 4]. Pancreatitis has also been reported to occur in patients who received ILE for antidotal therapy [4].

ILE administration has been reported to cause interference with various laboratory assays. Blood specimens obtained from patients receiving ILE may appear lipemic; the lipemia has been reported to cause interference with colorimetric, turbidimetric, and indirect ion-selective electrode assays [5, 6]. Colorimetric assays use spectrophotometry to measure the absorption of light in a particular specimen. These assays may become unreliable in the presence of lipemia, as lipemia causes increased

light scatter and altered light absorption due to the lipid particles suspended in solution [5]. Lipemia causes falsely low results from indirect ion-selective electrode assays through a reduction in the apparent aqueous volume of the specimen [6]. Standard laboratory assays for hemoglobin, hematocrit, platelet counts, blood gasses, electrolytes, liver transaminases, acetaminophen, salicylates, and coagulation studies have been reported to be unreliable when lipemia is present and when colorimetric or indirect ion-selective electrode analyzers are utilized [7–9]. Point-of-care assays which utilize direct ion-selective electrode techniques (e.g., Siemens RAPIDLab; Siemens Healthcare Diagnostics, Tarrytown, NY) may not be susceptible to this unreliability [6]. Centrifugation can be useful for separating lipemic fractions from the remainder of a blood sample by removing the source of the interference, allowing for more accurate laboratory analysis of the specimen. In one laboratory model, centrifugation was reported to remove more than 90 % of glycerol-banked triglycerides in blood, thus dramatically reducing the potential for lipid interference [5]. Although ultracentrifugation was used in the case reported here, it was not successful in minimizing lipemic interference during the hospital's laboratory analyses. The reference laboratory, however, did not report any lipemic interference during their analysis of the patient's blood. As ultracentrifugation requires very high forces (200,000–600,000×*g*) to clear lipids, it is possible that the hospital's ultracentrifuge was not powerful enough to adequately remove the lipids from this patient's blood [10].

The presence and duration of laboratory interference after ILE administration are variables. The lipemic appearance of blood has been reported to occur for several days after infusion of ILE [11, 12]. Previous reports of ILE administration have described no laboratory interference as well as interference lasting up to 25 h after infusion of ILE [4]. It is unclear what factors contribute to the degree of laboratory interference, but it is possible that infusion of multiple or large doses of ILE could result in decreased ILE clearance and increased serum persistence, leading to prolonged laboratory interferences. Lipid emulsions are often classified by their mean droplet size (MDS); in general, intravenous lipid emulsion (ILE) formulations have a MDS less than 1.0 µm [13]. These formulations are typically metabolized by lipoprotein lipase found along the vascular endothelium, while larger lipid formulations (MDS greater than 1.0 µm) are metabolized by reticuloendothelial system (RES) macrophages found in the microvasculature of the lungs, liver, spleen, and bone marrow [13]. Administration of a high-dose ILE can increase the likelihood for lipid particles to coalesce and form larger-

sized droplets, which theoretically could overwhelm the RES and lead to decreased clearance of ILE [14]. This, in turn, could lead to persistence of ILE in a patient's blood, causing prolonged interference with laboratory assays.

In the case presented here, laboratory interference began 2 h after ILE was administered and persisted until the patient expired 21 h later. Due to the inability to adequately analyze arterial blood gasses, the adequacy of ECMO and mechanical ventilation for this patient could not be assessed. In a critically ill patient, the inability to obtain accurate laboratory information can be detrimental to patient care and challenging to medical caregivers who are accustomed to relying on laboratory testing for intensive care management. Collection of blood samples prior to initiation of ILE therapy has been recommended by some authors; however, in clinical practice, this may not be practical as laboratory parameters often need to be measured after this therapy has been administered [5].

Conclusions

Lipemia is a potential complication of antidotal ILE therapy. The presence of lipemia after administration of ILE therapy may result in significant and prolonged interference in analysis of laboratory specimens, which can lead to difficulties in the management of critically ill patients. Clinicians who administer ILE in antidotal form should be cognizant of this potential complication and should judiciously consider the risks and benefits of ILE therapy before recommending its use in overdose patients.

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