Low-dose lipid emulsion for pediatric vasoplegic shock due to quetiapine and fluvoxamine overdose: a case report

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Background: Intravenous lipid emulsion (ILE) therapy was originally used for treatment of for local anesthetic systemic toxicity. Over the last decade, it has been successfully used to treat severe toxicity of numerous lipophilic substances. The mechanism by which ILE therapy treats lipophilic drug toxicity was originally purported to be due to the lipid sink mechanism; however, further research suggests that several other factors likely play more substantial roles, including free fatty acid provision to cardiomyocytes, positive inotropic effect, ion channel modulation, and nitric oxide synthase inhibition. No standardized dosing recommendation exists for ILE treatment of pediatric lipophilic drug toxicity. Several case reports have documented successful resuscitation of such overdoses using much lower dosages of ILE than are used for local anesthetic toxicity.

Case Description: We present a case of a 17-year-old male who presented to the emergency department (ED) with quetiapine and fluvoxamine overdose who rapidly progressed to refractory vasoplegic shock requiring ILE support. Following administration of low-dose ILE, the patient's hemodynamic state substantially improved, and he survived to discharge with relatively minor comorbidities.

Conclusions: This case highlights the successful use of low-dose ILE therapy for selective serotonin reuptake inhibitor (SSRI) and antipsychotic drug toxicity. Our experience suggests there may be a lower dosing range for ILE therapy that is safe and efficacious for the treatment of pediatric vasoplegic shock secondary to antipsychotic and SSRI toxicity.

**Keywords:** Pediatrics; lipid emulsion; case report; quetiapine; fluvoxamine

Introduction

Intravenous lipid emulsion (ILE) therapy was originally proposed for treatment of local anesthetic systemic toxicity (1). More recently, ILE has also been used to treat severe toxicity of numerous lipophilic substances (2-5). However, there are currently no dosing recommendations for toxicity of medications excluding local anesthetics; several case reports have documented successful resuscitation of such overdoses using much lower dosages of ILE than are used for local anesthetic toxicity (5). Pediatric ILE dosing is a weight-based proportion of the adult dose; as such, there is a paucity of research guiding recommendations of ILE therapy dosing in pediatric cases of lipophilic drug overdose (6). As suicide attempts via ingestion of selective serotonin reuptake inhibitor (SSRI) and/or antipsychotics, especially among adolescents, are becoming increasingly common in the United States (7), further research into ILE administration for lipophilic

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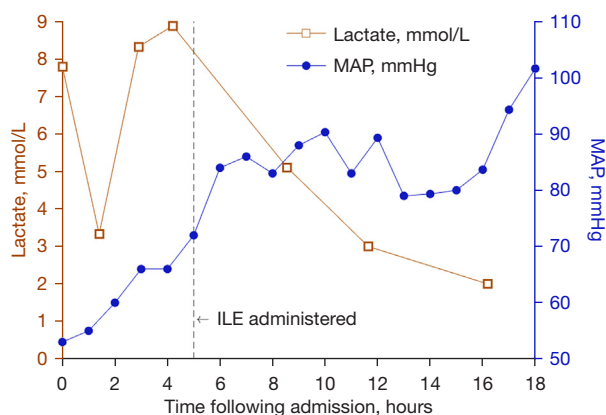
Figure 1 Lactate concentration and MAP as a function of time. The time of ILE administration (5 hours following admission) is indicated. Of note, lactate concentrations were collected arterially with the exception of the value at hour 8, which was a venous sample. Due to serum lipemia following ILE administration, laboratory values subsequent to ILE therapy should be interpreted with caution. MAP, mean arterial pressure; ILE, intravenous lipid emulsion.

medication toxicity in pediatric patients is warranted. We present a case of a 17-year-old male in severe vasoplegic shock and subsequent multiorgan failure from an intentional quetiapine and fluvoxamine overdose who was successfully resuscitated with low-dose ILE therapy. We present the following article in accordance with the CARE reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-53/rc).

Case presentation

A 17-year-old male with a history of depression was found unresponsive 14 hours after a suicide attempt where he ingested 130 mg/kg quetiapine and 32 mg/kg fluvoxamine. He presented to an outlying emergency department (ED) where initial vitals were: Glasgow coma scale (GCS) 3, heart rate (HR) 140 beats/min, blood pressure (BP) 80/40 mmHg. First arterial blood gas (ABG) revealed a respiratory acidosis of pH 7.16/PCO_2 94 mmHg/PaO_2 300 mmHg/HCO_3 33.5 mEq/L/base excess +1.6 mEq/L, with an elevated lactate of 7.8 mmol/L. He was intubated and central venous access obtained. He received 4 L normal saline, activated charcoal, 4 amps of sodium bicarbonate, and started on a norepinephrine infusion prior to pediatric intensive care unit (PICU) transport. On PICU arrival, patient continued to have GCS 3, mean arterial pressure (MAP) 53 mmHg and HR 154 beats/min.

His initial electrocardiogram (EKG) revealed prolonged QTc of 537 milliseconds (HR 145 beats/min) with narrow QRS. Despite additional fluid resuscitation, a sodium bicarbonate infusion, and escalation of vasoactive infusions to 29 μg/min of norepinephrine, 11 μg/min of epinephrine and 16 mU/min of vasopressin, he remained in vasoplegic shock, with an ABG of pH 7.28/PCO_2 41 mmHg/PaO_2 77 mmHg/HCO_3 19.3 mEq/L/base deficit –7.1 mEq/L, with rising lactate of 8.9 mmol/L, and MAP 66 mmHg.

Dialysis and extracorporeal membrane oxygenation (ECMO) were precluded as therapeutic options given the lipophilic nature of the ingested medications and the severity of vasoplegia, respectively. ILE therapy was discussed with toxicology experts and implemented by hour 5 of PICU admission. A shortage of lipid emulsion supply at the hospital necessitated the use of lower doses than current poison control recommendations. Standard recommendations include a 20% lipid emulsion solution administered as a 1.5 mL/kg bolus over 1 minute, followed by a 0.25 mL/kg/min continuous infusion. The patient received a 1 mL/kg bolus over 1 minute followed by 0.05 mL/kg/min continuous infusion for 2 hours (i.e., 67% and 20% of the current dosing recommendations, respectively).

Hemodynamic improvement was noted within 30 minutes of starting the ILE therapy. MAP increased by 10 mmHg after the initial ILE bolus. The patient's hemodynamics continued to steadily improve, and within 2 hours of ILE initiation, patient had a MAP of 84 mmHg. ABG 7 hours following ILE initiation showed improving shock with pH 7.37/PCO_2 36 mmHg/PaO_2 106 mmHg/HCO_3 20.8 mEq/L/base deficit –3.9 mEq/L, lactate 3.0 mmol/L (*Figure 1*). Within 24 hours of initiating ILE therapy, the sodium bicarbonate infusion was stopped, and epinephrine and vasopressin were weaned off. By hospital day 3, norepinephrine was discontinued. For 19 hours after ILE therapy was administered, serum electrolytes could not be obtained secondary to the lipemic nature of the blood. Once the blood's lipemic nature improved, the initial chemistries obtained revealed a severe rhabdomyolysis (peak creatinine kinase 448,929 U/L on hospital day 2). The drug-induced rhabdomyolysis resulted in acute tubular necrosis (ATN) and subsequent oliguric-anuric acute kidney injury (AKI) warranting hemodialysis (HD) initiation on hospital day 2. He received daily HD treatment from hospital day 2–6 and then was weaned to three times weekly HD sessions from hospital day 7–21 [peak serum creatinine (sCr) 10.9 mg/dL, blood urea nitrogen (BUN) 113 mg/dL on hospital day 11].

The patient was extubated on hospital day 5 and returned to full neurological baseline. His urine output spontaneously returned on hospital day 19, and he was weaned off HD support by hospital day 21. He was discharged to inpatient psychiatry on hospital day 41 with stage 3 chronic kidney disease (CKD) (sCr 1.13 mg/dL, BUN 16 mg/dL). At the patient's most recent outpatient nephrology follow up, he demonstrated continued renal recovery to stage 2 CKD (sCr 1.01 mg/dL, BUN 11 mg/dL).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's legal guardian for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Given the high prevalence of depression the United States, suicide attempts with intentional overdoses of SSRIs and atypical antipsychotics are becoming increasingly common. SSRI overdose frequency has increased 20-fold in the last decade, with a 30% increase in adolescent overdoses in the past 3 years (over 10,000 cases per year) (7). Although SSRI toxicity most frequently presents with symptoms of serotonin syndrome including high fever, seizures, mydriasis, and unconsciousness, overdose may also cause cardiotoxicity via inhibition of multiple myocardial ion channels, resulting in sinus bradycardia, QT, or QRS prolongation (8). While atypical antipsychotic overdoses are less frequently reported (over 3,000 cases per year), they are associated with much higher mortality rates and are also cardiotoxic (7). Antipsychotic cardiotoxicity is mediated by alpha-1-adrenergic antagonism, resulting in vasoplegia and reflex tachycardia, as well as tachycardia due to antimuscarinic activity (9).

The mechanism by which ILE therapy treats lipophilic drug toxicity is likely multifactorial (10,11). The most historically prominent theory is that of the lipid sink, in which fat-soluble compounds are redistributed away from target organs into the intravascular compartment (1). However, a growing body of evidence supports the contribution of other mechanisms, which include the provision of cardiomyocytes with sufficient free fatty acids to use as an alternate energy source, a direct positive inotropic effect, modulation of calcium and sodium channels, and reduction of vasoplegia through inhibition of endothelial nitric oxide synthase (12-17).

While ILE therapy was originally proposed for local anesthetic systemic toxicity, over the last decade, it has been successfully used to treat severe toxicity of numerous lipophilic substances (1-5). It is currently recommended as an adjunct treatment for overdoses of tricyclic antidepressants, bupropion, calcium channel blockers, beta blockers, cocaine, diphenhydramine, and lamotrigine, as well as for life-threatening toxicity of other lipophilic drugs when other interventions fail (3). There are numerous reports documenting the use of ILE in acute second-generation antipsychotic toxicity in both adult and pediatric patients (2,4,5). While severe SSRI overdoses less frequently result in life threatening toxicity in isolation, ILE therapy has been used to treat toxicity of SSRIs in combination with antipsychotics or other psychotropic medications (2,5).

In addition to vasoplegic shock, our patient's PICU course was complicated by oliguric-anuric AKI secondary to severe rhabdomyolysis and resulting ATN that required 19 days of HD support. Antipsychotics are indeed among the leading causes of drug-induced rhabdomyolysis (18). One case series found a 17% prevalence of myotoxicity in cases of olanzapine overdose, with creatine kinase values peaking 12 hours after ingestion (19). Earlier detection of our patient's rhabdomyolysis and AKI was challenged by an inability to obtain lab results. For 19 hours after ILE administration, serum blood sent to the laboratory could not yield electrolyte results due to processing error caused by lipemia. Once chemistries resulted, it corroborated severe rhabdomyolysis and AKI. There was discussion among the intensive care unit (ICU) team whether the patient's renal morbidity could have been prevented and/or mitigated with earlier detection by serum chemistry studies. However, the sequelae of rhabdomyolysis with AKI requiring HD support was likely inevitable given the degree of the initial toxic ingestion. Addressing the patient's unstable hemodynamics with ILE administration was the critical clinical priority over ability to monitor labs. In fact, by the patient receiving a lower dose of the ILE therapy, it is plausible that the lipemia lasted a shorter overall duration, minimizing the time that serum chemistries could not be obtained.

Common adverse effects of ILE therapy include hypertriglyceridemia, pancreatitis, and phlebitis, were not experienced in this case (10). The patient did experience lipemia, which is an inherent consequence of ILE administration. The ICU team was unable to obtain accurate serum chemistry labs for 19 hours following the

ILE infusion. The mechanisms by which lipemia causes an inability to obtain serum laboratories are several. Lipemic blood causes physical, chemical, and spectrophotometric method interferences, non-homogeneity in the serum sample, and a volume displacement effect between the aqueous and lipid phases (20). All of these factors result in lab processing error and explain why after ILE administration, serum electrolyte laboratories are commonly unobtainable until resolution of lipemia.

The current recommended ILE dosing regimen in the treatment of lipophilic drug overdose by toxicology experts consists of a 1.5 mL/kg lean body mass of 20% lipid emulsion bolus, followed by a continuous infusion of 0.25 mL/kg/min, with options to repeat the bolus or double the infusion rate for persistent cardiovascular instability (6). Because of a limited hospital supply of lipid emulsion, the patient only received 67% of the recommended bolus and only 20% of the recommended continuous infusion rate. There is a paucity of studies describing the effect of ILE therapy in lower doses, particularly in pediatrics. One case report documented successful treatment of quetiapine and citalopram overdose in an adolescent using the recommended bolus dosing followed by a lower infusion dose of 0.025 mL/kg/min over 1 hour (5).

This case highlights the successful use of low-dose ILE therapy for SSRI and antipsychotic drug toxicity and also underscores the importance of early initiation. Our experience suggests there may be a lower dosing range for ILE therapy, both in regard to the current recommended bolus and infusion dosing, that is equally efficacious as current recommendations for the treatment of pediatric vasoplegic shock secondary to antipsychotic and SSRI toxicity. Moreover, using lower doses of ILE therapy may confer additional benefits of less pronounced and/or shorter duration of ILE side effects of lipemia and reduce overall healthcare costs. More research regarding the safe and appropriate dosing ranges of ILE therapy in children is needed.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jeccm.amegroups. com/article/view/10.21037/jeccm-22-53/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jeccm. amegroups.com/article/view/10.21037/jeccm-22-53/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's legal guardian for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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