Asystole Immediately Following Intravenous Fat Emulsion for Overdose

Jon B. Cole · Samuel J. Stellpflug ·
Kristin M. Engebretsen

Published online: 12 February 2014
© American College of Medical Toxicology 2014

Abstract Use of intravenous fat emulsion (IFE) for the treatment of poisoned patients in extremis is increasing. Little literature exists describing failures and complications of IFE. We describe two cardiac arrests temporally associated with IFE. A 50-year-old woman presented after ingesting 80 total tablets of metoprolol 25 mg and bupropion 150 mg. Bradycardia and hypotension were refractory to calcium salts, catecholamines, and high dose insulin (HDI). With a pulse of 40/min and mean arterial pressure (MAP) of 30 mmHg, 100 mL of 20 % IFE was given; within 30 s, brady-asystolic arrest occurred. Pulses returned after 3 min of CPR. The patient died on hospital day 4 of multisystem organ failure (MSOF). A 53-year-old man presented after ingesting of 3,600 mg of diltiazem and 1,200 mg of propranolol. Bradycardia and hypotension were refractory to calcium salts, catecholamines, HDI, bicarbonate, and atropine. With a pulse of 30/min and a MAP of 40 mmHg, 150 mL of 20 % IFE was given; within 1 min, a brady-asystolic arrest occurred. Pulses returned after 6 min of CPR. The patient died on hospital day 7 of MSOF. Reported cases of IFE failures or potential complications are sparse. This report adds only case experience, not clarity. We report two cardiac arrests that were temporally associated with IFE.

Keywords Intravenous fat emulsion · Cardiac arrest · Poisoning · Shock · Resuscitation

J. B. Cole (✉)
Hennepin Regional Poison Center, Department of Emergency
Medicine, Hennepin County Medical Center, 701 Park Ave,
Minneapolis, MN 55415, USA
e-mail: jonbcole@gmail.com

S. J. Stellpflug · K. M. Engebretsen
Clinical Toxicology Service, Department of Emergency Medicine,
Regions Hospital, 640 Jackson Street, Saint Paul, MN 55101, USA

Introduction

Intravenous fat emulsion (IFE) is a promising therapy for the treatment of poison-induced cardiogenic shock (PICS) [1, 2]. Literature is accumulating regarding the success of IFE for poisoned patients in extremis [3–5]. Though IFE was initially described as a therapy for the poisoned patient in cardiac arrest [6], some have advocated for its earlier use in resuscitation [7]. A recent position statement from the American College of Medical Toxicology indicated that IFE is “a reasonable consideration for therapy, even if the patient is not in cardiac arrest [8].” Others have cautioned that the data on IFE is not yet conclusive and that extrapolation to all patients with refractory PICS may not yet be appropriate [9, 10]. A paucity of literature exists describing failures and complications of IFE. We describe two patients with PICS, cared for by bedside medical toxicologists, who both experienced cardiac arrest essentially immediately following administration of an IFE bolus.

Case 1

A 50-year-old woman presented after ingesting metoprolol 25 mg tablets and bupropion 150 mg extended-release tablets. The patient stated she swallowed a total of 80 tablets in a suicide attempt. These medications were reportedly regularly taken by the patient in addition to her only other prescribed medication, fenofibrate. The exact time of ingestion was unknown, but based on collateral information it was likely 30–60 min prior to presentation. On initial evaluation, she was drowsy, but oriented to person, place, and time with no other symptoms; initial blood glucose was 77 mg/dL. Her vital signs included blood pressure 135/86 mmHg, heart rate 76 bpm, respiratory rate 12/min, temp 98.2 °F, and oxygen saturation 99 %. Shortly after arrival, she experienced a seizure and was intubated for airway protection. An orogastric tube was

placed, and 50 g activated charcoal was given 45 min after she arrived. ECG was notable for normal intervals without signs of ischemia. Shortly after intubation, the patient developed gradual but severe bradycardia and hypotension unresponsive to intravenous (IV) fluid, 2 mg glucagon, and 3 g calcium gluconate. Central venous and arterial lines were placed, norepinephrine infusion was started, and high dose insulin (HDI) therapy was initiated and rapidly titrated up to 10 U/kg/h. The patient experienced no hypoglycemia. The patient continued to experience worsening hypotension that briefly responded to boluses of 0.5 mg of epinephrine; norepinephrine was weaned and an epinephrine infusion was started. An additional 3 g calcium chloride and 10 mg glucagon were given for progressive hypotension and bradycardia. With a mean arterial pressure (MAP) of 40 mmHg and a heart rate of 40 bpm, 100 mL of 20 % IFE was administered IV. Within 30 s, the patient had a brady-asystolic arrest. She received 1 mg each of epinephrine and atropine and 3 min of CPR; after which, she had return of spontaneous circulation (ROSC). A transvenous pacemaker, Swan-Ganz catheter, and intra-aortic balloon pump were placed. The subsequent cardiac output was 5.7 L/min. An echocardiogram revealed an ejection fraction of 55 %. Despite an initial improvement from this aggressive therapy, the patient developed multisystem organ failure and expired on hospital day 4. Postmortem serum drug concentrations were as follows: bupropion 130 ng/mL (therapeutic range 50–100) and hydroxybupropion 480 ng/mL (600–2000). Metoprolol was not detected on the same sample.

Case 2

A 53-year-old man presented after an ingestion of 3,600 mg of long-acting diltiazem and 1,200 mg of propranolol. These amounts are estimated based on a text he sent to his daughter and number of pills remaining in his prescribed pill bottles. The time from ingestion to presentation was unknown. The patient was on both of those medications regularly, along with warfarin, lorazepam, olmesartan, and fluoxetine. On arrival, he had a heart rate of 30 bpm, a systolic blood pressure of 50 mmHg, an oxygen saturation of 70 % with respiratory failure, and a pre-hospital blood glucose of 109 mg/dL. He was intubated with correction of the hypoxia, and an arterial line, central venous catheter, and Foley catheter were placed. A bedside echocardiogram revealed very poor contractility. The patient received 2 mg each of epinephrine and atropine along with 3 g calcium chloride with a definite but transient improvement in hemodynamic parameters. A dopamine infusion was also started at 20 mcg/kg/min. An ECG revealed bradycardia with a third degree heart block and a QRS of 160 ms. With subsequent QRS narrowing, 250 mEq of sodium bicarbonate was administered. A sodium

bicarbonate infusion was started. HDI was started and rapidly titrated up to 10 U/kg/h. The patient responded well to the combination of insulin and bicarbonate; however, the insulin bag ran out and there was a delay of 15 min in replacing it. Prior to the insulin running out, the blood pressure had climbed to 110/52 mmHg and the heart rate to 68 bpm. In the 15 min following the insulin running out, the heart rate returned to 30 bpm and MAP to 40 mmHg. The patient was given 150 mL of 20 % IFE; within 1 min, he suffered a brady-asystolic arrest. Six minutes of chest compressions were done; during which, an additional 1 mg each of epinephrine and atropine were given resulting in a MAP of 50 mmHg. During chest compressions, he received a 400 U bolus of insulin with 50 g of dextrose. The patient did not experience hypoglycemia. Upon ROSC, the patient's MAP was 60 mmHg with a heart rate of 30 bpm. Transcutaneous pacing was attempted which captured only 2 of every 3 beats. A transvenous pacemaker was placed with capture. Echocardiography revealed a 55 % ejection fraction. The patient experienced worsening hypotension that was treated with infusions of norepinephrine, phenylephrine, and vasopressin. A dobutamine infusion was started as well for bradycardia refractory to transvenous pacemaker. Though the patient's bradycardia improved and his pacemaker was no longer needed, his hypotension worsened further and was treated with an intra-aortic balloon pump. Coronary angiogram performed simultaneously revealed stenosis of the circumflex artery but with adequate flow, and it was determined that stenting would supply more risk than benefit. His troponin rose to >80 ng/mL after an initial concentration was found to be not elevated, and the cause of the cardiac ischemia was thought to be multifactorial and likely due to the overdose and subsequent lack of perfusion as opposed to primary coronary artery disease. Endoscopy, performed to evaluate for bezoar, was negative. The patient suffered two additional cardiac arrests, and on hospital day 7 he expired. The propranolol concentration on hospital day 2 was 53 ng/mL (therapeutic range 30–100); the diltiazem concentration on hospital day 5 was 100 ng/mL (100–200).

Discussion

Cases of IFE treatment failures or potential complications are sparse in the literature. Additionally, the relationship between IFE and other resuscitation medications has not been fully elucidated. Our cases represent treatment failures not only of usual measures but also IFE. It is particularly noteworthy that IFE has been used successfully to treat overdoses of all four medications ingested by these patients. Successful resuscitation with IFE has been documented with overdoses of metoprolol [2], diltiazem [11], propranolol [12], and bupropion [6]. The presence of three of four of these medications is documented in our two cases. Case 1 is clearly a massive bupropion

overdose; the lack of detectable metoprolol on the postmortem blood in this case is hard to interpret. Either the metoprolol component of her overdose was trivial or the drug had been metabolized by the time she expired 4 days after her overdose. With a published half-life of 3–9 h [13], it is conceivable that metoprolol was not detectable and yet still contributory to her demise. This report adds only case experience rather than clarity; however, the temporal relationship of the IFE and the cardiac arrests is difficult to ignore.

Though a tremendous amount of success has been reported with the use of IFE in hemodynamically unstable poisoned patients, the literature is not uniformly supportive. Failure of IFE to significantly alter amitriptyline and nortriptyline concentrations in human volunteers was reported in the 1980s [14]. More recently, Cave et al. failed to demonstrate a difference in hemodynamic parameters or QRS duration between IFE and hypertonic sodium bicarbonate in a rabbit model of IV flecainide poisoning. In this model, no “lipid sink” was observed either, contrary to what is commonly thought to be the primary mechanism of action of IFE [15].

Some of the disconnect may be related to the route of poisoning. The vast majority of studies supporting the use of IFE for overdose involve animals poisoned via the IV route. This is in stark contrast to most human case reports demonstrating success with IFE; outside of local anesthetic toxicity, most poisonings in these cases occurred via the orogastric route. Reporting bias in these human cases may lead one to believe the extrapolation between IV and oral poisoning is more scientifically sound than it may in fact be.

In a murine model of parathion poisoning conducted by Dunn et al. [16], rats were orogastrically poisoned with parathion and then randomized to control, IFE at 5 min after poisoning (to coincide with the initial effects of parathion) and IFE at 20 min after poisoning (to coincide with the peak effects of parathion). Their primary outcome was the percentage of rats that experienced apnea. No difference was found between the control group and the group receiving IFE at 5 min. Rats receiving IFE at 20 min had a delay in onset of apnea, but no difference was observed in the number of animals experiencing respiratory arrest. Thus, IFE appeared ineffective during the absorption phase of parathion and at best delayed, but did not prevent toxicity when given later.

Perichon et al. conducted a study involving a rodent model of amitriptyline toxicity in which rats were orogastrically poisoned. Subsequent administration of IFE was associated with increased mortality, no improvement in hemodynamic parameters and increased blood concentration of amitriptyline [17]. The authors postulated this could have occurred from two different mechanisms. First, they inferred there was increased gastric absorption of drug allowing more swift delivery of drug to high blood flow organs such as the heart. Second, they hypothesized the presence of lipid in the blood may have retarded redistribution of drug from

those same high blood flow organs, maintaining a temporary increased concentration of drug around key tissues such as the myocardium. This same group found similar results when the same model was applied to verapamil; rats poisoned with verapamil were more bradycardic and hypotensive and experienced decreased survival when compared to controls or calcium as a therapy [18].

IFE has also been demonstrated to affect other resuscitation medications including lidocaine [19], amiodarone [20], and epinephrine [1, 21]. The effect on epinephrine is particularly noteworthy. Carreiro et al. conducted a study where rats were infused with either saline or IFE, then given epinephrine infusions. IFE-treated rats experienced a significant difference in MAP response to epinephrine; a delay in peak effect of epinephrine was observed as well as a prolongation of epinephrine's effect. The authors were unsure of the specific reason for their findings, but offered epinephrine dissolution in the lipid sink and alteration of calcium homeostasis as explanations. Both of our patients were dependent upon catecholamines at the time of their arrests; if IFE has an effect on epinephrine, it may have reduced its effectiveness in our patients putting them at higher risk for arrest. The interaction between resuscitative drugs, particularly epinephrine, may also be related to the other drugs involved. There is case experience of significant hypertension and tachycardia occurring following IFE administration soon after an epinephrine bolus, which had been given to combat ongoing bradycardia and hypotension, related to a nebivolol overdose. The explanation provided is that the IFE likely bound much more of the nebivolol than the epinephrine [1].

The cause of arrest in our two cases is uncertain. It may have been a result of IFE interaction with other resuscitation medications or a result of a sudden increase in absorption of drug in the GI tract, though this seems less likely given the timing of the arrests in relation to IFE. Though we have no direct evidence for this, an alternative explanation could be a brief lack of oxygen in the lipid-laden blood circulating in the coronary vessels contributing to the arrests. It is also clearly possible these cases were fatal ingestions regardless of therapy making the temporal association between IFE and the arrests unfortunate coincidence. We are well aware of previous case literature dramatically affecting clinical practice; this is not the intent of our report. For instance, an often-cited series [22] of two patients who suffered asystole shortly after receiving physostigmine for the treatment of cyclic antidepressant poisoning dramatically affected the practice of medical toxicology. Through no fault of the authors who merely presented a temporal association, clinical practice was affected in a dramatic manner inappropriate to the level of evidence presented in that series. Our goal is not to replicate this outcome; rather, it is simply to report a strong temporal association of this relatively new therapy with an adverse outcome to generate further inquiry into its potential effectiveness and/or toxicity.

Conclusion

We report two cardiac arrests that occurred immediately after IFE administration. An association with IFE or interaction with other resuscitation medications should be contemplated. IFE should be considered with caution when used in pre-arrest circumstances.

Acknowledgment This manuscript is written in US English and is 2,183 words in length. We have no commercial associations or conflicts of interest to report, and all authors made substantial contributions to the manuscript. No funding was used in production of the paper.

This project was presented at the 2011 North American Congress of Clinical Toxicology as a poster presentation. The reference is listed below:

Cole JB, Ellsworth H, Engebretsen KM, Stellpflug SJ. Failure of High Dose Insulin and Intravenous Fat Emulsion in 2 Patients With Poison-Induced Cardiogenic Shock. *Clin Toxicol*. 2011; 49(6): 537–8 (abstract #55)

References

1. Stellpflug SJ, Harris CR, Engebretsen KM, Cole JB, Holger JS (2010) Intentional overdose with cardiac arrest treated with intravenous fat emulsion and high dose insulin. *Clin Toxicol* 48:227–229
2. Stellpflug SJ, Fritzlar SJ, Cole JB, Engebretsen KM, Holger JS (2011) Cardiotoxic overdose treated with intravenous fat emulsion and high-dose insulin in the setting of hypertrophic cardiomyopathy. *J Med Toxicol* 7(2):151–153
3. Geib AJ, Liebelt E, Manini AF (2012) Toxicology Investigators' Consortium (ToxIC). Clinical experience with intravenous lipid emulsion for drug-induced cardiovascular collapse. *J Med Toxicol* 8(1):10–14
4. Cave G, Harvey M (2009) Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: a systematic review. *Acad Emerg Med* 16:815–824
5. Jamaty C, Bailey B et al (2010) Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. *Clin Toxicol* 48:1–27
6. Sirianni AL, Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, Weinberg GL, Henretig FM (2008) Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. *Ann Emerg Med* 51(4):412–415
7. Weinberg GL (2011) Intravenous lipid emulsion: why wait to save a life? *Emerg Med Austral* 23(2):113–115
8. ACMT Position Statement (2011) Interim guidance for the use of lipid resuscitation therapy. *J Med Toxicol* 7(1):81–82
9. Murray DB, Bateman DN (2011) Use of intravenous lipids. Not yet in all overdoses with failed resuscitation. *BMJ* : 342:d2265
10. Buckley NA, Dawson AH (2013) The intralipid genie is out of the bottle-spin and wishful thinking. *Anaesth & Int Care* 41(2): 154–156
11. Bologa C, Lionte C, Coman A, Sorodoc L (2013) Lipid emulsion therapy in cardiodepressive syndrome after diltiazem overdose—case report. *Am J Emerg Med*. Jul 31(7): 1154.e3–4
12. Meehan TJ, Gummin DD, Kostic MA, Cattapan SE, Waghray R, Bryant SM (2009) Beta blocker toxicity successfully treated with intravenous fat emulsion: a case series. *Clin Toxicol* 47(7):735, abstract #163
13. Package Insert, Lopressor, Novartis Pharmaceuticals, March 2013
14. Minton NA, Goode AG, Henry JA (1987) The effect of a lipid suspension on amitriptyline disposition. *Arch Toxicol* 60:467–479
15. Cave G, Harvey M, Quinn P, Heys D (2013) Hypertonic sodium bicarbonate versus intravenous lipid emulsion in a rabbit model of intravenous flecainide toxicity: no difference, no sink. *Clin Toxicol* 51:394–397
16. Dunn C, Bird SB, Gaspari R (2012) Intralipid fat emulsion decreases respiratory failure in a rat model of parathion exposure. *Acad Emerg Med* 19(5):504–509
17. Perichon D, Turfus S, Gerostamoulos D, Graudins A (2013) An assessment of the in vivo effects of intravenous lipid emulsion on blood drug concentration and haemodynamics following oro-gastric amitriptyline overdose. *Clin Toxicol* 51:208–215
18. Perichon D, Turfus S, Graudins A (2013) Intravenous lipid emulsion does not improve hemodynamics or survival in a rodent model of oral verapamil poisoning. *Clin Toxicol* 51:277, abstract #53
19. Lange DB, Schwartz D, DaRoza G, Gair R (2012) Use of intravenous lipid emulsion to reverse central nervous system toxicity of an iatrogenic local anesthetic overdose in a patient on peritoneal dialysis. *Ann Pharmacother* Dec 46:e37
20. Niiya T, Litonius E, Petaja L, Neuvonen PJ, Rosenberg PH (2010) Intravenous lipid emulsion sequesters amiodarone in plasma and eliminates its hypotensive action in pigs. *Ann Emerg Med* 56(4): 402–408
21. Carreiro S, Blum J, Jay G, Hack JB (2013) Intravenous lipid emulsion alters the hemodynamic response to epinephrine in a rat model. *J Med Toxicol* 9(3):220–225
22. Pentel P, Peterson CD (1980) Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. *Ann Emerg Med* 9(Nov):588–590