

Hyperinsulinemic Euglycemia and Intravenous Lipid Emulsion Treatments for Calcium Channel Blocker and Beta Blocker Poisoning: A Report of Two Cases

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Abstract

Poisoning with calcium channel blockers and beta blockers are associated with high mortality and morbidity rates, especially in children. Treatment of poisoning with these drugs includes administration of atropine, glucagon, calcium and inotropic agents as clinically needed; and newer approaches like hyperinsulinemic euglycemia and intravenous lipid emulsion therapies. We herein present two refractory cases of calcium channel blocker and beta blocker poisoning that underwent hyperinsulinemic euglycemia and intravenous lipid emulsion interventions.

CASE.1

A 17-year-old female patient has been brought to our setting unconscious and recalcitrantly hypotensive and bradycardic after taking 8 tablets of 90 mg diltiazem hydrochloride and 5 tablets of 500 mg paracetamol + 30 mg caffeine. The patient was given saline, atropine, repeating doses of calcium gluconate, dopamine, noradrenaline, hyperinsulinemic euglycemia treatment, hemodiafiltration, and lipid administration. She achieved a full recovery during follow-up, and was discharged with cure.

CASE.2

A 17-year-old girl, who developed an unresponsive hypotension after ingesting 12 tablets of 12.5 mg carvedilol, 6 – 7 tablets of 450 mg diosmin + 50 mg hesperidin, and 6–7 tablets of 10 mg metoclopramide HCl, was treated with saline, glucagon, calcium gluconate, dopamine, noradrenaline, and administration of hyperinsulinemic euglycemia and lipid. The patient responded well to the treatment, and was discharged with cure.

The newer treatment modality of lipid emulsion has been reported to achieve promising results by several reports in the literature; however, there are a limited number of published cases regarding its use in children. Further studies to assess the pediatric utilization of these treatment approaches are needed.

Key Words: Beta blockers, Calcium channel blockers, Child, Lipid, and Poisoning.

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1- INTRODUCTION

Cardiovascular drug poisoning, in particular with calcium channel blockers and beta blockers, causes high mortality and morbidity rates (1). Diltiazem hydrochloride is a nondihydropyridine calcium channel blocker which is widely used for treating arrhythmias, angina pectoris, migraine and hypertension. Notwithstanding that this drug lacks an official approval for its pediatric use, pediatric intoxication cases are common (2). Out of a total of 10,031 intoxication cases in America in 2006, 4,086 were reported to be with calcium channel blockers (3). Carvedilol, which is used for treating congestive heart failure, is a highly lipophilic non-selective beta adrenergic blocker with additional alpha-1 adrenergic blockade effects (4).

Although the pediatric effects of carvedilol have not yet been clearly defined, a nine-year study in the USA reported that among 111 carvedilol intoxication cases, 4 showed drowsiness or hypotension (5). Despite its unique pharmacological properties, carvedilol intoxication is treated the same way as intoxication with any adrenergic receptor blockers. Patients may develop hypotension, bradycardia, arrhythmias, bronchospasm, seizures, hypoglycemia or hyperglycemia; and therapies include atropine, glucagon, calcium, inotropic agents, hyperinsulinemia euglycemia, and intravenous lipid emulsion treatment as a novel option (6). Two refractory cases of calcium channel blocker and beta blocker poisoning that underwent hyperinsulinemia euglycemia and intravenous lipid emulsion interventions were discussed in this report.

2- CASE REPORT

2-1. Case .1

Upon her parents' discern, a 17-year-old girl without any previously documented

medical problem had been taken to an outside institution approximately two hours after her suicidal ingestion of 8 tablets of 90 mg diltiazem hydrochloride and 5 tablets of 500 mg paracetamol + 30 mg caffeine. She had been unconscious at the time of admission, and had been performed a gastric lavage followed by administration of activated charcoal. Her vitals had been as follows: heart rate 75 bpm, blood pressure 63/20 mmHg, SpO₂ 80%. She had been treated with 20 ml/kg saline, 0.6 ml/kg calcium gluconate (10%), and 10 mcg/kg/min infusion of dopamine.

She was referred to our pediatric intensive care unit for further care. At the moment of presentation to our pediatric emergency department about 7 hours after her initial admission, she was unconscious and revealed a body temperature of 36°C, a heart rate of 46 bpm, and a blood pressure of 60/40 mmHg. She was loaded with 10 ml/kg saline and given 0.6 ml/kg calcium gluconate. Upon persistence of hypotension despite two consecutive administrations of 1 mg atropine, noradrenaline (0.2mcg/kg/min), and dobutamine (10mcg/kg/min) infusions were initiated. Her heart rate increased from 46 bpm to 69 bpm, and blood pressure raised to normal limits for duration of 10 minutes, after which the patient went hypotensive again.

Complete blood count, serum biochemistry and arterial blood gas analyses results were as follows: hemoglobin 10.3 g/dl; WBC 26,900 /mm³; platelets 341,000 /mm³; glucose 246 mg/dl; BUN 20 mg/dl; creatinine 1.95 mg/dl; Na 136 mEq/L; K 3.7 mEq/L; AST 16 U/L; ALT 9 U/L; CK-MB 2.8 ng/ml; troponin I 0.02 ng/ml; total Ca/ionized Ca 9.6/1.13 mg/dl; blood pH 7.08; PaO₂ 79.1 mmHg; PaCO₂ 36.5mmHg; HCO₃ 9.7 mmol/L; base excess -17.6; lactate 10.7mmol/L. The 8th hour serum paracetamol concentration was 1.3mcg/ml.

The patient was taken into to our pediatric intensive care unit and revealed a PRISM II (complete words) score of 55 (99.9%), PIM score of 93.9% and PELOD of 42 (99.3%). She was placed on mechanical ventilator. Upon detection of activated charcoal particles within the tracheal aspirate material, cefoperazone was commenced for a presumed diagnosis of aspiration pneumonia. Repeating doses of 0.6 ml/kg infusion of calcium were implemented, and a hyperinsulinemia euglycemia intervention was started with 0.5 U/kg insulin and 0.5 g/kg/hour glucose. Her pupils were dilated without any response to light.

An adrenaline infusion of 0.4 mg/kg/min was commenced for hypotension and persistent metabolic acidosis. During the follow-up, doses of infused inotropes were increased and 0.2 mg/kg/min milrinone infusion was commenced. A glucagon loading dose of 0.1 mg/kg/hour, followed by 0.07 mg/kg/hour maintenance infusions were given. The patient's metabolic acidosis persisted despite infusing bicarbonate and hemodiafiltration was started. Two hours after the onset of hemodiafiltration, 100ml ClinOleic (AUST R) 20% lipid emulsion was intravenously pushed. Starting about 5 minutes after the lipid bolus, a 1-hour infusion of 200ml and another 1-hour infusion of 500ml lipid emulsion were administered consecutively.

Bradycardia was completely resolved, and blood pressure and metabolic acidosis showed some amelioration within 1 hour after the initial intravenous bolus of lipid. Five and 9 hours after intravenous lipid push, metabolic acidosis recovered and blood pressure went within normal limits, respectively. Serum lactate concentration, which was 16mmol/L at the time of lipid loading, reduced to 2.7mmol/L after 11 hours. Hemodiafiltration circuits occluded and the procedure was therefore ceased by the 16th hour of lipid treatment. Echocardiographic examination revealed

an ejection fraction (EF) rate of 64% on the first day of hospitalization, while she was under inotropic support. On the second day, plasmapheresis was performed. Her vital signs stabilized and inotropes gradually stopped after 48 hours of hospitalization. She was extubated on the 3rd day. Follow-up did not reveal any additional problems. She was referred to our pediatric emergency follow-up care ward on day 7. She underwent a final consultation with the pediatric psychiatry department, and discharged home on the 9th day with cure, after scheduling her outpatient control visits.

2-2. Case .2

A 17-year-old female patient with no previously known medical problem was taken to our pediatric emergency department by her parents about 2 hours after taking 12 tablets of 12.5mg carvedilol, 6- 7 tablets of 450mg of diosmin + 50mg hesperidin, and 6- 7 tablets of 10mg metoclopramide hydrochloride for suicidal purposes. The patient underwent a gastric lavage, was monitored and given oxygen with reservoir oxygen mask. She was in confusion with a Glasgow Coma Scale score of 13. Her vitals were as follows: body temperature 36.5°C, heart rate 55 bpm, respiratory rate 20/min, blood pressure 75/50 mmHg, SpO₂ 100%. She was given a 20 ml/kg saline for hypotension. Her heart rate increased to 71 bpm; however, hypotension persisted. Intravenous 5 mg glucagon was loaded and a 5 mg/hour glucagon infusion was commenced. She received 3 courses of 0.6 ml/kg calcium gluconate (11 mg/kg). Upon persistence of hypotension, an insulin-glucose regimen of 0.1 U/kg/hour insulin and 0.5 g/kg glucose, along with 10 mcg/kg/min dopamine and 0.1 mcg/kg/min noradrenaline was added to the treatment. Glucagon had to be stopped by the 2nd hour of infusion since it ran out of the hospital stocks. Her blood pressure

recovered by the 3rd hour of admission; however, hypotension developed again after 3 hours. Another course of 10 ml/kg saline was given as required according to the fluid balance charts, and ClinOleic (AUST R) lipid emulsion (20%) with a volume of 1.5 ml/kg was intravenously pushed. Her blood pressure increased to normal levels within 30 minutes, and no additional infusion was needed. About 4 hours after stopping glucagon and 3 hours after the lipid treatment, another course of hypotension occurred. She revealed a blood pressure of 87/53 mmHg, and a blood glucose concentration of 33 mg/dl. She got an intravenous push of 2 ml/kg 10% dextrose, and was given a fluid resuscitation to maintain her blood levels between 100 – 200 mg/dl.

After a normotensive period, she went hypotensive again and was given another course of glucagon (8 hours after the initial glucagon treatment). Her laboratory results upon admission were as follows: WBC 7.530 /mm³; hemoglobin 10.9 g/dl; platelets 343.000 /mm³; glucose 112 mg/dl; BUN 8 mg/dl; creatinine 0.69 mg/dl; Na 136 mEq/L; K 3.8 mEq/L; AST 20 U/L; ALT 11 U/L; CK-MB 0.6 ng/ml; troponin I 0,003 ng/ml; total Ca/ionized Ca 9.5/1.21 mg/dl; blood pH 7.39; PaO₂ 79.8 mmHg; PaCO₂ 36.4 mmHg; HCO₃ 227mmol/L; base excess -2.2. The patient was referred to our pediatric intensive care unit for close monetarization and further care. Upon her vitals' being stable, supportive treatments gradually stopped 24 hours after the ingestion of intoxicating agents. Upon recovering completely without any complications, she was discharged home with cure.

4- DISCUSSION

Intravenous lipid emulsion therapy was initially used in treating local anesthetic poisoning, and has been recently being recruited for the treatment of intoxications with various lipophilic drugs

such as calcium channel blockers, beta blockers, tricyclic antidepressants, several other antidepressants and antipsychotics (7, 8). Regarding the pharmacokinetic characteristics of the intoxicating agents in our cases, carvedilol is highly lipophilic with a plasma protein binding rate of 98-99%, whereas diltiazem hydrochloride is bound 70-80%. There are several published case series in the literature (Table.1) (9-15). Although its exact mechanism of action is not clear, lipid emulsion is thought to exert its effects through (1) driving the drug towards the plasma, thus diminishing the tissue drug levels and toxicity, (2) supplying an energy resource for the damaged myocardial tissue when used in higher doses, (3) acting on the sodium channels, and (4) performing inotropic effects through calcium channel activation (16, 17). There are limited data regarding the use of lipid treatment for calcium channel blocker and beta blocker poisoning in children. Sebe et al. reported two cases of carvedilol intoxication: the first being a 23-year-old patient with hypotension and bradycardia after taking 750mg carvedilol, who was successfully treated with glucagon and three courses of 3 mg/kg lipid; the second being a 26 year-old patient, who ingested 625mg carvedilol, developed hypotension and responded well to glucagon and 1.5 ml/kg lipid administration (18).

Similarly, Barton et al. reported a case that developed cardiorespiratory arrest due to beta-blocker intoxication, and successfully resuscitated and treated with hyperinsulinemia euglycemia and lipid administration without any debilitating complications (19). Although a definitive consensus for dosing of lipid treatment is yet to be established, it is suggested to perform an initial 1.5 ml/kg bolus, which is to be repeated once and to be maintained through 0.25 ml/kg infusions in case of unresponsiveness (20). Montiel et al. used

a 20% lipid emulsion with an initial loading dose of 1.5 ml/kg and a maintenance dose of 0.25 ml/kg for treating an 18-year-old patient who showed hypotension, tachycardia, respiratory failure and hyperglycemia due to diltiazem poisoning. They reported that her vital signs recovered to normal within an hour, and the needs for norepinephrine and hyperinsulinemia euglycemia applications lessened (10). Durak et al. similarly reported a rapid clinical recovery within 30 minutes after administration of hyperinsulinemia euglycemia and 1.5ml/kg lipid in a 13-year-old case showing hypotension and bradycardia due to carvedilol and verapamil poisoning (9).

Despite the implementations of glucagon, hyperinsulinemia euglycemia and inotropic agents, our cases both showed unresponsive courses of hypotension, for which 1.5 mg/kg lipid treatment were commenced. Our first patient needed a post-loading infusion for 2 hours for severe hypotension and bradycardia; whereas a single loading dose initially sufficed for our second case. Nevertheless, hypotension reemerged in our second patient during follow-up, which may be due to the indispensable cessation of glucagon infusion for it could not be provided, or not maintaining the patient with a further lipid infusion, which may further lead to an insufficient tissue clearance and rebound drug effects.

Reports of successfully treated cases with a single dose lipid treatment are available in the literature. However, a post-loading infusion is warranted for the unresponsive cases. In addition, the literature lacks any clear suggestions regarding lipid administration in the clinically deteriorated patients during follow-up. Upon complete recovery of their vital signs, supportive interventions were gradually stopped and both our cases were discharged with cure.

Lipid administration possesses several adverse effects such as infections, pancreatitis, anaphylaxis, thrombophlebitis and interference with laboratory parameters. However, these adverse effects are not marked when lipid is used for treating intoxications (1). Lipid treatment led to changes in laboratory parameters and obstruction in hemodiafiltration in case 1; whereas, no adverse effects occurred in case 2. The newer treatment modality of lipid emulsion has been reported to achieve promising results in several papers in the literature; however, further studies to assess the pediatric utilization of this treatment method are warranted.

5- CONCLUSIONS

The newer treatment modality of lipid emulsion has been reported to achieve promising results in several papers in the literature; however, further studies to assess the pediatric utilization of this treatment method are warranted

6- CONFLICT OF INTEREST: None.

7- ABBREVIATION

SpO₂: Peripheral oxygen saturation,
Bpm: Beats per minutes,
WBC: White blood cell,
BUN: Blood Urea Nitrogen,
AST: Aspartate aminotransferase,
ALT: Alanine aminotransferase,
CK-MB: Creatine kinase-myocardial band,
Ca: Calcium,
PaO₂: Partial pressure of oxygen,
PaCO₂: Partial pressure of carbon dioxide,
HCO₃: Bicarbonate,
PRISM II: Pediatric Risk of Mortality score II,
PIM score: Pediatric Index of Mortality,
PELOD: Pediatric logistic organ dysfunction,
AUST R: Australia,
Na: Sodium.

8- REFERENCES

1. Watson WA1, Litovitz TL, Rodgers GC Jr, Klein-Schwartz W, Reid N, Youniss J, et al. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med.* 2005; 23:589-666.
2. Deters M, Bergmann I, Enden G, Kutz S, Liebetrau G, Plenert B, et al. Henschel. Calcium channel antagonist exposures reported to the Poisons Information Center Erfurt *Eur J Intern Med.* 2011;22(6):616-20.
3. Blaine E. Benson, Daniel A. Spyker, William G. Troutman, William A. Amlodipine Toxicity In Children Less Than 6 Years Of Age: A Dose-response Analysis Using National Poison Data System Data. *The Journal of Emergency Medicine,* 2010; 39(2):186-93.
4. Bouchard NC, Forde J, Hoffman RS. Carvedilol overdose with quantitative confirmation. *Basic Clin Pharmacol Toxicol* 2008;103:102–3.
5. Forrester MB. Pediatric carvedilol ingestions reported to Texas poison centers, 2000 to 2008. *Pediatr Emerg Care.*2010; 26(10):730-2.
6. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol* 2011;49:277–83.
7. Rothschild L, Bern S, Oswald S, Weinberg G. Intravenous lipid emulsion in clinical toxicology. *Scand J Trauma Resusc Emerg Med* 2010; 18: 51.
8. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny JM. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. *Clin Toxicol (Phila)* 2010; 48: 1-27.
9. Durak F, Can FK, Zengin N, Durak İ, Yıldız K, Anıl AB. Successful Intravenous Lipid Infusion Therapy in a Case with Life-Threatening Poisoning due to Calcium Channel and Beta Blockers. *J Pediatr Emerg Intensive Care Med* 2016;3:151-4.
10. Montiel V, Gougnard T, Hantson P. Diltiazem poisoning treated with hyperinsulinemic euglycemia therapy and intravenous lipid emulsion. *Eur J Emerg Med* 2011;18:121-3.
11. Aaronson PM, Wassil SK, Kunisaki TA. Hyperinsulinemic euglycemia, continuous veno venous hemofiltration, and extracorporeal life support for severe verapamil poisoning: case report (abstract 198). *Clin Toxicol* 2009;47:742.
12. Schult R, Gorodetsky RM, Wiegand TJ. Intravenous lipid emulsion for amlodipine/benazepril toxicity: a case report. *Clin Toxicol.* 2015; 53:251–52.
13. Su J. Early venoarterial extracorporeal membrane oxygenation for refractory shock secondary to amlodipine overdose. *J Am Coll Cardiol.* 2015;65:A627
14. Montague AJ, Topeff JM, Katzung KG, Cole JB. High dose insulin to treat propranolol toxicity in a 7-month-old infant. *Clin Toxicol.* 2015;53:740
15. Cave G, Harvey M. Intravenous lipid emulsion as antidote: how should we chew the fat in 2011? *Crit Care Med.* 2011;39(4): 919-20.
16. Jovic-Stosic J, Gligic B, Putic V, Brajkovic G, Spasic R. Severe propranolol and ethanol overdose with wide complex tachycardia treated with intravenous lipid emulsion: a case report. *Clin Toxicol* 2011;49:426–30.
17. Blaber MS, Khan JN, Brebner JA, McColm R. Lipid rescue for tricyclic antidepressant cardiotoxicity. *J Emerg Med* 2011;43:465–7.
18. Sebe A, Dişel NR, Açıkalin Akpınar A, Karakoç E. Role of intravenous lipid emulsions in the management of calcium channel blocker and β -blocker overdose: 3 years' experience of a university hospital. *Postgrad Med.*2015,127(2):119-24.
19. Barton CA, Johnson NB, Mah ND, Beauchamp G, Hendrickson R. Successful treatment of a massive metoprolol overdose using intravenous lipid emulsion and hyperinsulinemia/euglycemia therapy. *Pharmacotherapy.* 2015;35(5):56-60.
20. Weinberg GL. Treatment of local anesthetic systemic toxicity (LAST). *Reg Anesth Pain Med* 2010; 35: 188-93.

Table-1: Pediatric Cases of Intravenous Lipid Emulsion Treatments for Calcium Channel Blocker and Beta Blocker Poisoning

Cited Literature	Age	Intoxicating agent	Symptoms	Dose and duration of 20% lipid	Additional treatments	Response to Lipid
Durak et al. (9)	13 years	Carvedilol and verapamil	HypotensionBradycardia	1.5 ml/kg/min infusion	Calcium, Glucagon, Inotrops, HIE	Present (within 30 minutes)
Montiel et al. (10)	18 years	Diltiazem	HypotensionTachycardiaRespiratory failure	1.5 ml/kg initial loading; 0.25 ml/kg infusion within 1 hour	Calcium, Inotrops, HIE	Present (within 1 hour)
Aaronson et al. (11)	15 years	Verapamil	Arrhythmia	Not specified	ECMO, HIE	None
Schult et al. (12)	12 years	Amlodipine / benazepril	HypotensionComa	100 ml loading	Not specified	Not specified
Su (13)	17 years	Amlodipine	Bradycardia Hypotension	Not specified	Calcium, Inotrops, HIE, Glucagon, ECMO	None
Montague et al. (14)	7 months	Propranolol	Bradycardia HypotensionComa	1.5 ml/kg infusion within 2 hours	HIE	None

HIE: Hyperinsulinemic Euglycemia; ECMO: Extracorporeal membrane oxygenation.