Management of Calcium Channel Blocker Poisoning

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Introduction

Calcium channel blocker poisonings are the leading cause of death from cardiovascular medication-related overdoses [1, 2]. Clinical effects in the poisoned patient may include hypotension, bradycardia, atrioventricular conduction disturbances, pulmonary edema, stroke, bowel ischemia, altered mental status, and cardiac arrest. Many immediate and sustained-release preparations exist, hence pharmacokinetics are highly variable. Calcium channel blockers are generally lipophilic and highly-protein bound, rendering traditional extracorporeal elimination methods such as hemodialysis largely ineffective.

Dihydropyridines
- Nicardipine
- Nifedipine
- Isradipine
- Amlodipine
- Felodipine
- Nimodopine
- Nisoldipine
- Nitrendipine

Non-Dihydropyridines
- Verapamil
- Diltiazem
- Bepridil

Calcium channel blockers act at L-type calcium channels and are generally divided into two unique pharmacologic classes based on their preferred sites of action.

Dihydropyridine (i.e. nifedipine, amlodipine) overdoses primarily cause hypotension with reflex tachycardia through their peripheral vasodilatory effects on vascular smooth muscle. The toxicity from non-dihydropyridines (i.e. verapamil, diltiazem), tends to be more severe owing to their primary effects on the myocardium [3]. This may lead to bradydysrhythmias, depressed myocardial contractility, and circulatory collapse [4]. It should be noted that in severe poisonings from either class, this selectivity may be lost [2].

The management of hemodynamically unstable patients with calcium channel blocker toxicity

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can be quite challenging, and responses to therapeutic interventions can be variable. Traditional therapies include intravenous fluid resuscitation, and the administration of calcium salts, glucagon, and vasopressor agents. Refractory bradycardia and atrioventricular nodal blocks may necessitate the use of atropine and temporary pacemakers. More contemporary treatment strategies including the use of intravenous lipid emulsions and high-dose insulin euglycemic therapy have shown great promise.

Case Presentation

A 47 year old female with a history of depression and chronic migraine headaches was brought to the emergency department by her spouse immediately following a witnessed intentional ingestion of approximately sixty 120 mg sustained-release verapamil tablets. On arrival, she was alert and oriented. Vital signs were as followed: pulse 62, blood pressure 95/62, respiratory rate 16, temperature 37.2, and pulse oximetry 99 % on room air. Her EKG showed normal sinus rhythm with normal intervals. IV access was established and a liter of normal saline was administered. Laboratory studies that include routine toxicologic screening tests were unremarkable. She was treated with 50 g of oral activated charcoal and admitted to the intensive care unit for close monitoring. Upon arrival to the ICU, her repeat vital signs revealed a pulse of 42 and blood pressure of 74/42. Her repeat EKG is shown below (Fig. 7.1). An arterial blood gas was obtained: pH 7.12, pCO_2 26, HCO_3 12, lactate 7.2 and glucose 350. An additional 2 L of normal saline were rapidly infused. She was treated with 2 g of IV calcium gluconate, 5 mg of IV glucagon followed by a continuous infusion, and a norepinephrine drip that was titrated for a goal mean arterial pressure of 65. Despite these measures, she remained hypotensive and bradycardic.

Question What do you think is causing her hyperglycemia and what therapeutic intervention(s) could be considered at this point to improve her hemodynamic stability?

Answer Impaired insulin secretion due to calcium channel blocker inhibition of pancreatic Beta cells, coupled with increased stress-mediated glucose mobilization account for her hyperglycemia. High-dose insulin euglycemic therapy should be considered at this point. Her metabolic acidosis is secondary to both a lactic acidosis from impaired tissue perfusion, and ketoacidosis similar to that seen with DKA due to relative hypoinsulinemia.

Based on her weight of 50 kg, an insulin bolus of 50 units IV was given followed by an infusion of 50 units/h. Approximately 45 min after initiation of the insulin infusion, her pulse normalized to 65 and her blood pressure improved enough to gradually wean the norepinephrine drip. Her glucose was monitored every 30 min, and ultimately she did require a continuous dextrose infusion to maintain serum glucose concentrations above 150 mg/dL. Her metabolic acidosis improved over the course of several hours, as did her serum lactate. Serum electrolytes were monitored closely. She developed mild hypokalemia but repletion was not necessary. Approximately 24 h following admission, the insulin infusion was discontinued and her vitals remained stable. She was discharged the next morning to an inpatient psychiatric facility.

Principles of Management

Gastrointestinal Decontamination

Activated charcoal effectively binds calcium channel blockers and should be administered in patients with stable airways and preserved mental status who present within the first 2 h following ingestion. Although clinical evidence supporting the use of multi-dose activated charcoal is lacking, it is reasonable to consider repeat charcoal dosing when sustained-release preparations are involved [2, 5]. Gastric lavage is generally not recommended since the procedure may increase vagal tone, exacerbate hemodynamic instability, and can provoke cardiac arrest [6, 7]. Whole bowel irrigation may be considered in

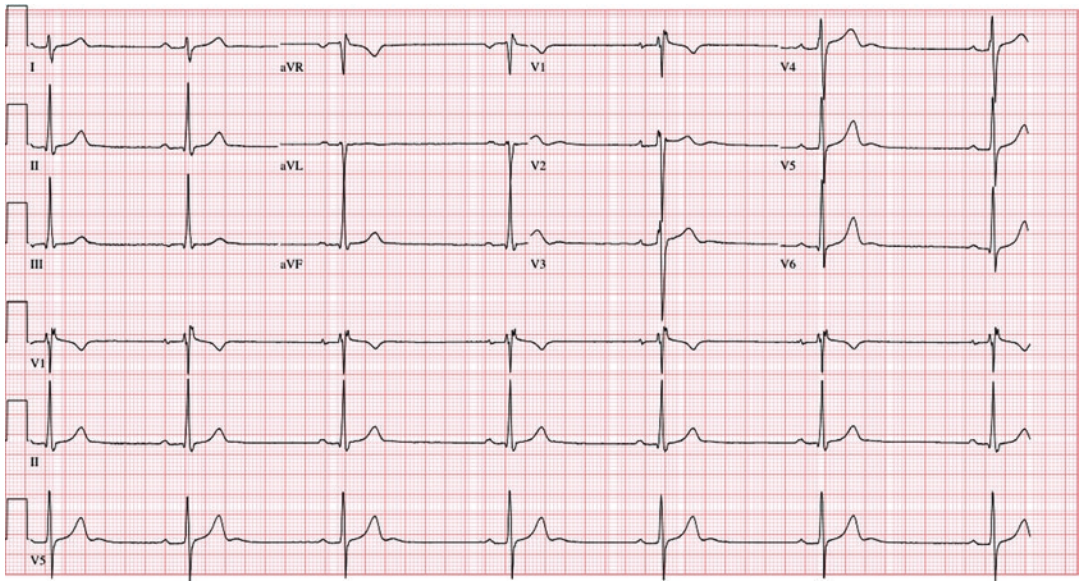

Fig. 7.1 12-lead EKG revealing sinus bradycardia

cases of sustained-release preparations, or when decontamination is delayed beyond a time-frame where activated charcoal would be of benefit [6]. Whole bowel irrigation should be avoided, however, in patients with depressed mental status, ileus, airway compromise, or hemodynamic instability [8].

Hemodynamic Support

The initial management of hypotension due to calcium channel blocker toxicity should include aggressive intravenous fluid resuscitation. In more severely poisoned patients, several therapeutic options may also be considered.

Calcium Salts

The use of calcium gluconate and calcium chloride in the management of calcium channel blocker toxicity seems intuitive. Increased serum calcium concentrations would be expected to overcome calcium channel blockade via a gradient effect, thereby improving myocardial contractility [6]. Animal studies suggest the use of calcium confers both hemodynamic benefits and improves mortality. Human studies are limited to case series, and the reported benefits are inconsistent [7, 9]. The response seen with calcium is often transient, and repeat dosing may be needed [2]. Despite conflicting evidence regarding benefit, use is generally recommended and adverse effects are rare.

Glucagon

Glucagon increases intracellular cyclic-AMP and has been shown in animal models to have positive inotropic and chronotropic effects. Furthermore, glucagon has been shown, in some cases, to reverse 2nd and 3rd degree heart blocks [10]. Evidence for its efficacy in humans is limited to case reports, and treatment failures have been described [2, 7]. Glucagon dosing is not well-established, but an initial dose of 3–5 mg IV followed by a continuous infusion has been suggested, with an additional dose of 4–10 mg IV 5 min after the initial dose if no response is achieved [6].

Atropine

Atropine may be considered for symptomatic bradycardia, but is often ineffective in the setting of severe poisonings. Standard advanced cardiac life support (ACLS) dosing guidelines should be used. Because of its anticholinergic effects on GI motility, it's use may potentiate absorption of

sustained-release calcium channel blocker formulations [6].

Vasopressor Support

When hemodynamic stability cannot be achieved through the use of fluid resuscitation and other initial pharmacologic strategies, vasopressor support may be necessary. Norepinephrine, dopamine, epinephrine, isoproterenol, dobutamine, and phenylephrine have all been used to achieve improvements in blood pressure, and no studies have demonstrated the superiority of one agent over another [2]. Multiple agents may be required simultaneously to achieve hemodynamic stability, and some have reported use of vasopressor doses far in excess of what would typically be considered the referenced maximum [4]. Although improvements in blood pressure are typically achieved, one must be mindful that the increase in systemic vascular resistance will also increase afterload. This may paradoxically lead to an undesirable decrease in cardiac output, as well as an increase in the cardiac oxygen requirement in an already energy-depleted myocardium [3, 6].

High-Dose Insulin Therapy

In recent years, high-dose insulin therapy for the treatment of calcium channel blocker poisonings has gained increasing attention. Calcium channel blockers directly inhibit the calcium channel-mediated release of insulin by the pancreas, leading to systemic hypoinsulinemia (Fig. 7.2). Because carbohydrates are the preferred metabolic substrate of myocardial cells when under duress, the impairment of intracellular glucose transport secondary to insulin depletion further worsens cardiac contractility already impaired by the calcium channel blockers themselves [11]. High-dose insulin restores myocardial glucose utilization and corrects systemic ketoacidosis when present. Insulin has also been shown to have direct positive inotropic effects on myocytes [11]. Furthermore, insulin has been shown to induce vasodilation which improves microvascular perfusion in tissues including the myocardium [12]. Insulin also promotes increased catecholamine sensitivity [11]. The combination of these effects may ameliorate the cardiogenic shock seen with calcium channel blocker toxicity.

Animal models suggest the mortality benefit from high-dose insulin therapy is superior to that seen with calcium salts, glucagon, and vasopressors. One human observational study showed that high-dose insulin therapy resulted in a >10 mmHg sustained increase in systolic blood pressure in all patients receiving high dose insulin boluses and infusions, and numerous case series and case reports detail beneficial hemodynamic responses [2, 13, 14].

Although definitive dosing guidelines have not been established, most recommend an initial insulin bolus be given at a dose of 1 U/kg IV followed by an infusion 1 U/kg/h which may be titrated upward [6]. Higher bolus doses of 10 U/kg and infusions up to 22 U/kg/h have been reported [3]. The clinical response to high-dose insulin may take 15–60 min. Many sources advocate initiation of high-dose insulin therapy very early on in the management of these patients (before they become unstable) [6, 14, 15]. Serum glucose should be monitored every 30 min during the initial course of treatment and supplemental dextrose should be administered, although supplementation may not be necessary if the initial glucose exceeds 300 mg/dL [6]. Mild hypokalemia should be anticipated due to intracellular shifts and may actually augment myocardial cellular function by improving intracellular calcium transport. Potassium repletion should be considered if serum levels fall below 2.8–3.0 mEq/L [12].

Invasive Circulatory Support

The use of temporary transcutaneous and transvenous pacemakers, and intra-aortic balloon pump counter pulsation therapy have been described in the setting of severe bradycardia and high-degree atrioventricular blocks in calcium channel blocker poisonings when medical management fails to adequately reverse cardiogenic shock [2, 6, 7]. At times, obtaining successful pacemaker capture may be difficult in these patients. Furthermore, improvement in hemodynamics may be variable owing to the persistent impaired cardiac inotropy, and it is unclear based

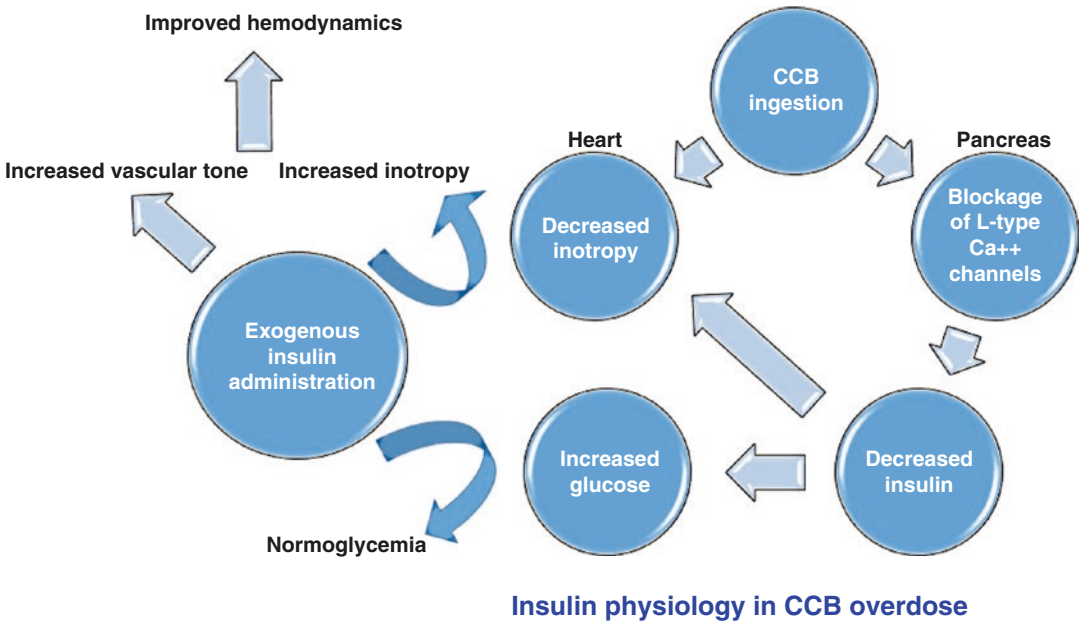

Fig. 7.2 *CCB* calcium channel blocker. L-type Ca++ channels: voltage-gated calcium channels

on case reports whether pacemakers improve clinical outcomes [7, 16]. There are reports describing the successful use of intra-aortic balloon pumps and extracorporeal life support in the setting of refractory shock due to severe calcium channel blocker poisonings, and these techniques may be considered on a case by case basis when other treatment strategies fail [17–19].

Evidence Contour

Intravenous Lipid Emulsions

The use of intravenous lipid emulsion therapy in the management of systemic toxicity from local anesthetics is well-described [6]. More recently, investigators have advocated for the use of intravenous lipid emulsions to treat poisonings due to other lipophilic drug classes including tricyclic antidepressants, beta blockers, and calcium channel blockers [20].

Intravenous lipid emulsion therapy in the context of calcium channel blocker toxicity may be beneficial for several reasons. One proposed mechanism is that lipid emulsions act as a "lipid sink", sequestering lipophilic toxins away from the aqueous plasma phase. In a case report of a verapamil overdose, plasma concentrations of this drug were nearly undetectable following administration of an intravenous lipid emulsion [21]. A second proposed benefit of intravenous lipid emulsions is that they directly stimulate insulin secretion [22]. Thirdly, lipids may promote an increased intracellular calcium concentration in myocytes counteracting the negative inotropic effects seen in these overdoses [23]. Lastly, lipids may serve as a supplementary fuel source for the myocardium, which prefers to derive energy from fatty acids under normal conditions [6].

The evidence supporting the use of intravenous lipid emulsions in calcium channel blocker poisonings is limited to animal studies and human case reports. Multiple animal studies demonstrate that intravenous lipid emulsions confer a survival benefit compared to placebo in verapamil overdoses [20]. Multiple human case reports suggest a temporal hemodynamic response when intravenous lipid emulsions were used as an adjunct to standard treatments [9, 20, 22, 24, 25]. Others report that required vasopressor support greatly diminished following initiation of intravenous

lipid emulsion therapy [23]. Because multiple confounding therapeutic strategies were used in all of these reported cases, the degree in which intravenous lipid emulsion therapy is beneficial remains unclear.

The optimal dosing for intravenous lipid emulsion has not been established, and recommendations are extrapolated from guidelines that exist for the management of local anesthetic toxicity. Typically, a 20 % lipid emulsion solution is administered at a bolus dose of 1.5 ml/kg based on ideal body weight. This is followed by a continuous infusion of 0.25 ml/kg/min until hemodynamic stability persists for at least 10 min. Some suggest that this bolus may be repeated twice and the infusion may be doubled when clinically necessary [6]. The lipemia resulting from this treatment may interfere with certain laboratory assays.

Sodium Bicarbonate

Acidosis is a common occurrence in calcium channel blocker toxicity secondary to diminished tissue perfusion and ketoacidosis. Correction of the acidosis could theoretically improve hemodynamic stability, but the role of bicarbonate therapy in these instances is unclear. In severe overdoses, a widened QRS complex from fast sodium channel blockade, similar to that seen in tricyclic antidepressant toxicity, may occur. The benefits of sodium bicarbonate in calcium channel blocker toxicity is largely anecdotal, but some advocate for its use when QRS complex prolongation occurs [2].

Methylene Blue

Methylene blue inhibits guanylate cyclase which subsequently decreases cGMP resulting in inhibition of vascular smooth muscle relaxation. Therefore, it might be expected to reverse some of the effects of the dihydropyridine class of calcium channel blockers. Experience with methylene blue in calcium channel blocker toxicity, however, is limited. One case report described an improvement in hemodynamic stability following methylene blue administration to a patient with an amlodipine overdose that had failed to respond to other measures [26]. Another case report demonstrated a similar effect in a mixed calcium channel/beta blocker overdose [27]. While adequate evidence supporting routine use does not exist, methylene blue might be considered as a rescue therapy in severe dihydropyridine poisonings that fail to respond to other treatment strategies [28].

Extracorporeal Albumin Dialysis

Because calcium channel blockers have high volumes of distribution and are largely protein-bound, traditional extracorporeal elimination strategies including hemodialysis and hemoperfusion are generally ineffective. Albumin dialysis with molecular absorbents recirculating system (MARS) therapy offers the ability to remove protein-bound toxins that would otherwise not be cleared by traditional hemodialysis. This technique was successfully in the management of three severely poisoned patients with refractory shock due to calcium channel blocker toxicity, and all three patients survived [29].

References

1. Mowry JB, Spyker DA, Cantilena Jr LR, McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. Clin Toxicol (Phila). 2014;52(10):1032–283.
2. Shenoy S, Lankala S, Adigopula S. Management of calcium channel blocker overdoses. J Hosp Med. 2014;9(10):663–8.
3. Siddiqi TA, Hill J, Huckleberry Y, Parthasarathy S. Non-cardiogenic pulmonary edema and life-threatening shock due to calcium channel blocker overdose: a case report and clinical review. Respir Care. 2014;59(2):e15–21.
4. Levine M, Curry SC, Padilla-Jones A, Ruha AM. Critical care management of verapamil and diltiazem overdose with a focus on vasopressors: a 25-year experience at a single center. Ann Emerg Med. 2013;62(3):252–8.
5. Thanacoody R, Caravati EM, Troutman B, Hojer J, Benson B, Hoppu K. Position paper update: whole

bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol. 2015;53(1):5–12.
6. Jang DH, Spyres MB, Fox L, Manini AF. Toxin-inducedcardiovascular failure. Emerg Med Clin North Am. 2014;32(1):79–102.
7. St-Onge M, Dubé PA, Gosselin S, Guimont C, Godwin J, Archambault PM, Chauny JM, Frenette AJ, Darveau M, Le Sage N, Poitras J, Provencher J, Juurlink DN, Blais R. Treatment for calcium channel blocker poisoning: a systematic review. Clin Toxicol (Phila). 2014;52(9):926–44.
8. Cumpston KL, Aks SE, Sigg R, Pallasch P. Whole bowel irrigation and the hemodynamically unstable calcium channel blocker overdose: Primum non nocere. J Emerg Med. 2010;38(2):171–4.
9. Liang CW, Diamond SJ, Hagg DS. Lipid rescue of massive verapamil overdose: a case report. J Med Case Rep. 2011;5(1):399.
10. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdose: a systematic review. J Toxicol Clin Toxicol. 2003;41(5):595–602.
11. Woodward C, Pourmand A, Mazer-Amirshahi M. High dose insulin therapy, an evidence based approach to betablocker/calcium channel blocker toxicity. Daru. 2014;22(1):36.
12. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol (Phila). 2011;49(4):277–83.
13. Holger JS, Stellpflug SJ, Cole JB, Harris CR, Engebretsen KM. High-dose insulin: a consecutive case series in toxin-induced cardiogenic shock. Clin Toxicol (Phila). 2011;49(7):653–8.
14. Greene SL, Gawarammana I, Wood DM, Jones AL, Dargan PI. Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. Intensive Care Med. 2007;33(11):2019–24.
15. Espinoza TR, Bryant SM, Aks SE. Hyperinsulin therapy for calcium channel antagonist poisoning: a seven-year retrospective study. Am J Ther. 2013;20(1):29–31.
16. McGlinchey PG, Mcneill AJ. Drug overdoses requiring temporary cardiac pacing; a study of six cases treated at Altnagelvin Hospital, Londonderry. Ulster Med J. 1998;67(1):13–8.
17. Janion M, Stepień A, Sielski J, Gutkowski W. Is the intra-aortic balloon pump a method of brain protection during cardiogenic shock after drug intoxication? J Emerg Med. 2010;38(2):162–7.
18. Masson R, Colas V, Parienti JJ, Lehoux P, Massetti M, Charbonneau P, Saulnier F, Daubin C. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation. 2012;83(11):1413–7.
19. Daubin C, Lehoux P, Ivascau C, Tasle M, et al. Extracorporeal life support in severe drug intoxication: a retrospective cohort study of seventeen cases. Crit Care. 2009;13(4):R138.
20. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny J. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol. 2010;48(1):1–27.
21. French D, Armenian P, Ruan W, Wong A, et al. Serum verapamil concentrations before and after Intralipid therapy during treatment of an overdose. Clin Toxicol. 2011;49(4):340–4.
22. Young AC, Velez LI, Kleinschmidt KC. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. Resuscitation. 2009;80(5):591–3.
23. Ozcan MS, Weinberg G. Intravenous lipid emulsion for the treatment of drug toxicity. J Intensive Care Med. 2014;29(2):59–70.
24. Cevik S, Tasyurek T, Guneysel O. Intralipid emulsion treatment as an antidote in lipophilic drug intoxications. Am J Emerg Med. 2014;32(9):1103–8.
25. Doepker B, Healy W, Cortez E, Adkins EJ. High-dose insulin and intravenous lipid emulsion therapy for cardiogenic shock induced by intentional calcium- channel blocker and beta-blocker overdose: a case series. J Emerg Med. 2014;46(4):486–90.
26. Jang DH, Nelson LS, Hoffman RS. Methylene blue in the treatment of refractory shock from an amlodipine overdose. Ann Emerg Med. 2011;58(6):565–7.
27. Aggarwal N, Kupfer Y, Seneviratne C, Tessler S. Methylene blue reverses recalcitrant shock in β-blocker and calcium channel blocker overdose. BMJ Case Rep. 2013;18:2013.
28. Lo JC, Darracq MA, Clark RF. A review of methylene blue treatment for cardiovascular collapse. J Emerg Med. 2014;46(5):670–9.
29. Pichon N, Dugard A, Clavel M, Amiel J, François B, Vignon P. Extracorporeal albumin dialysis in three cases of acute calcium channel blocker poisoning with life-threatening refractory cardiogenic shock. Ann Emerg Med. 2012;59(6):540–4.