Respiratory Care

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Non-cardiogenic pulmonary edema and life-threatening shock due to calcium channel blocker overdose and its management: a case report and a clinical review.

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All authors declare no conflict of interest.

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Abstract

Calcium channel blockers (CCB) overdose can be life-threatening when manifest as catastrophic shock and non-cardiogenic pulmonary edema.We describe a case of massive overdose of multiple medications, including sustained-release verapamil that was resistant to conventional support. Initial treatment for CCB overdose is primarily supportive and includes fluid resuscitation. The mechanism of non-cardiogenic pulmonary edema is not well known and reported cases in the literature were successfully treated with mechanical ventilation. Circulatory shock may fail to respond to atropine, glucagon and calcium in severely poisoned patients, and vasopressors are usually required. Attempts to overcome calcium-channel antagonism with the use of supra-therapeutic doses of calcium salts are clinically indicated to reverse hypotension and bradycardia. There is evidence that hyperinsulinemia-euglycemia (HIE) therapy is superior to other therapies for CCB poisoning, and the potential mechanism is thought to be the insulin-mediated active transport of glucose into the cells that counters the CCB-induced intra-cellular carbohydrate-deficient state. Conventional decontamination measures are ineffective in accelerating clearance of CCB. Experience with intravenous lipid emulsion for lipophilic drug overdose, such as verapamil, is limited but has been proposed as a rescue therapy with improvements in cardiac inotropy through intravascular sequestration of the lipophilic CCB.

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Introduction

Calcium channel blockers (CCB) are antihypertensive and atrioventricular nodal blocking agents that are widely available and commonly prescribed. Taken in large doses, these drugs can lead to catastrophic cardiovascular collapse. Verapamil and diltiazem are a lipophilic, non-dihydropyridine calcium channel blockers that have particular cardioselectivity, and are more toxic than dihydropyridine antagonists (such as amlodipine and nifedipine).While CCB overdose is rare, it is often lethal and optimal therapy remains unclear. In 2008, the American Association of Poison Control Centers (AAPCC) reported 2,491,049 human overdosecases. CCB were responsible for 10,398 of such cases (0.4%), resulting in 12 deaths and 63 major outcomes defined as life-threatening or resulted in significant residual disability or disfigurement[1].Potential complications of overdose include stroke, hyperglycemia, bowel ischemia, non-cardiogenic pulmonary edema, and cardiovascular collapse.

Traditionally, treatment of CCB overdose has been primarily supportive; however, more recently intravenous lipid emulsion (ILE) therapy has been used. Lipid infusions have been postulated to sequester lipophilic drugs such as verapamil and subsequently reduce their volume of distribution in the tissues.Additionally, hyperinsulinemia-euglycemia (HIE) therapy and glucagon infusions have been used in these cases in an effort to improve cardiac utilization of glucose and myocardial contractility in the presence of profound and refractory shock[2-5].

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We describe a case of massive intentional overdose of multiple medications, including sustained-release verapamil, which proved resistant to conventional support including fluid replacement, vasopressor and inotropicagents, and required mechanical ventilation for non-cardiogenic pulmonary edema. Our patient was successfully treated with institution of mechanical ventilation for non-cardiogenic pulmonary edema, and with initiation of HIE, glucagon, intravenous calcium and bicarbonate, activated charcoal, and intravenous lipid therapy.

Case Summary

A 40 year-old male with history of obesity (body mass index 38.5kg/m^2), polysubstance abuse, major depression, and hypertension was brought to the emergency department (ED) by paramedics after a suicide attempt that involved multiple drug overdoses of unclear nature and amount. Patient was found to be unconscious on the floor when the paramedics responded to the spouse's call at a remote rural home approximately 3 hours post-ingestion.In the ED, the patient was intoxicated but hemodynamically stable with a blood pressure of 110/70mm Hg and heart rate of 97 beats per minute. Physical examination was unremarkable and patient was sedated, yet easily arousable and oriented. Initial EKG revealed normal sinus rhythm without PR or QTc prolongation and no changes suggestive of ischemia.Laboratory investigations included serum chemistry, complete blood count, and liver function tests which were all normal with the exception of bicarbonate level. Other laboratory examination values are provided in **Table 1**. Initial chest radiography showed bibasilar atelectasis.

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He was treated with one liter of normal saline in the ED.The patient became more awake and less inebriated. He appeared to be sufficiently stable to be evaluated by Psychiatry and was awaiting placement in a hospital bed while being closely monitored in the ED. Nine hours after admission (12 hours post ingestion) the patient became hypotensive and lethargic.Information received from his wife indicated that he may have consumed sustained-release verapamil 3.6 gm, fluoxetine 400 mg, sustained-release carbamazepine 1800 mg, and unknown quantity of alcohol.Other possible co-ingestionsincluded: sustained release oxycodone, amlodipine, valsartan, simvastatin, metformin, and trazodone (all of unknown amount). The intensive care team was immediately notified and Toxicology was consulted.Patient's blood pressure was 65/32 mmHg, heart rate 76 beats per minute, respiratory rate 22 per minute, and oxygen saturation 95% on 100% inspired oxygen. He received fiveliters of normal saline over a thirty-minute period without improvement. Norepinephrine and epinephrine intravenous infusions were initiatedat a rate of 10 mcg/min and 5mcg/min respectively. Despite such counter-measures, the patient remained in shock with worsening respiratory distress and hypoxemia.A 200 mL intravenous bolus of 20% Intralipid solution, 5 mgintravenous bolus of glucagon, and a total of 4 gm of intravenous 10% calcium chloride were administered.Subsequently,10% calcium chloride infusion was started at a rate of 0.2 mL/kg/hr(2.7 gm/hr) and ionized calcium levels were monitored every hour.

Rapid sequence intubation for obtundation and apparent respiratory distress was performed using etomidate20mg and succinylcholine 100 mg. Patient suffered aspiration

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of some abdominal contents during intubation.Patient was placed on assist-control volume control mode of mechanical ventilation. His initial ventilator settings were tidal volume of 600 mL, positive end-expiratory pressure (PEEP) of 5 cm H2O and 100% fractional inspired oxygen concentration (FiO2).He was sedated using midazolam 2-10 mg/hr intravenous infusion along with fentanyl 25-100 mcg/hr intravenous infusion. His arterial blood gas revealed PaO2/FiO2 ratio of 85and chest radiography was consistent with early pulmonary edema (**Figure 1**). A bedside echocardiography revealed a hyperdynamic left ventricle with an ejection fraction of 70% and no regional wall motion abnormalities. Ventilator settings were adjusted to tidal volume of 500 (6 mL/kg ideal body weight) and PEEP was increased to 10 cm H2O based on lung protective strategy for severe acute respiratory distress syndrome (ARDS). Plateau pressure decreased to 30 cm H2O and we were able to bring down FiO2 at 60%.

He was then transferred to the medical intensive care unit (MICU) where he continued to be hypotensive and required additional vasopressor agents including vasopressinintravenous infusion at a rate of 0.03 U/min,and phenylephrineintravenous infusion with a maximum titration upto a rate of 225 mcg/min.Norepinephrine and epinephrine intravenous infusions were titrated upto 120 mcg/min and30 mcg/min respectively.Allvasopressors were required at maximum doses despite continuous saline boluses for refractory hypotension.Patient received another dose of 200 mL of 20% Intralipid solution.Glucose and insulin therapy was initiated with 25% dextrose infusion at 7.5gm/hr(30 mL/hr) and regular insulin infusion at 140U/hr(1 U/kg/hr) after 80 unitsof regular insulin loading dose. Glucagon infusion was alsoinitiated at 5 mg/hr.Insulin

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infusion was titrated up to 220 U/hr (1.6 U/kg/hr) to account for hyperglycemia and to target hemodynamic stability.Plasma glucose was checked on an hourly basis to maintain blood sugar level around 150 mg/dL. Activated charcoal therapy was initiated at 50 gmevery 4 hours and whole bowel irrigation with polyethylene glycol was commenced as 2 L/hr through nasogastric tube (12 hours post ingestion).

Over the next 24 hours, the patient developed acute oliguric kidney injury and combined anion gap and normal anion gap metabolic acidosis. Consequently a bicarbonate intravenous infusion was initiated.Creatine Kinase level peaked at 387 IU/lit.Repeat EKG demonstrated first-degree atrioventricular block with a ventricular rate of 97 beats per minute, prolonged QTc of 456 msec, and ST segment depression and T wave inversions in inferior and lateral leads (**Figure 2**).Troponin-I peaked at 0.63 ng/mLover 24 hours and was attributed to a type II non-ST segment elevation myocardial infarction secondary to hypotension. Serum carbamazepine level peaked at 22.7 mcg/mL.

On second day of admission to MICU, oxygen requirements increasedacutely and repeat chest radiograph demonstrated four quadrant air-space filling shadows suggestive of non-cardiogenic pulmonary edema with superimposed bibasilar infiltrates. The patient was diuresed with intravenous furosemide and treated with intravenous piperacillin/tazobactam for aspiration pneumonia. By the morning of second day, the patient was successfully weaned off all vasopressors and the glucagon infusion was discontinued. The calcium chloride infusion was discontinued once ionized calcium reached 2 mmol/lit.The insulin infusion was discontinued on third day of admission. The patient did not require hemodialysis for carbamazepine intoxication as the druglevel

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gradually declined following the activated charcoal administration and prolonged QTc normalized.Serum electrolytes were closely monitored and replaced and by the third daykidney function normalized.

The hospital course was complicated by manifestation of acute alcohol and opiate withdrawal on third day warranting propofol infusion with dose upto 70 mcg/kg/min, benzodiazepines, and methadone. Anti-hypertensives, including lisinopril, metoprolol, and hydralazine werere-initiated in order to adequately control elevated blood pressure. Ventilator settings were adjusted based on plateau pressures, lung compliance and oxygenation. Patient was then liberated from the ventilator on seventh day of hospitalization and subsequently discharged to an inpatient psychiatric facility.Comprehensive toxicology analysis of blood by gas chromatography and urine by thin layer chromatography returned positive for verapamil, ethanol, carbamazepine, oxycodone,another opiate metabolizing via morphineand nicotine. Interestingly, although there was report of possible amlodipine ingestion, there was no other CCB identified.

Discussion

Calcium plays a central role in cardiovascular function. Cardiac function including conduction and contraction, as well as maintenance of vascular tone in the peripheral vasculature requires the flow of calciumacross cell membranes. CCBblocksthe flow of calcium through L-type calcium channels found in the myocardium, vascular smooth muscle and pancreatic β-cells. Interruption of calcium fluxes leads to decreased

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intracellular calcium producing hypoinsulinemia, negative inotropic and chronotropic actions and in severe poisoning may lead to profound bradycardia and cardiovascular shock[6-8].

Very few cases of non-cardiogenic pulmonary edema related to overdose of verapamil, a non-dihydropyridineCCB, have been reported in literature[2, 9, 10]. The mechanism of non-cardiogenic pulmonary edema is not well known. Possible mechanism of non-cardiogenic pulmonary edema include pre-capillary vasodilatation resulting in excessive pulmonary capillary transudation[3]. Concomitant administration of crystalloids for the refractory shock may conceivably aggravate such increased transudation and lead to worsening non-cardiogenic pulmonary edema. The prompt institution of mechanical ventilation in addition to aggressive management of shock is vital as is the recognition of CCB overdose as a cause of non-cardiogenic pulmonary edema when adequate history is unavailable.

ARDS is a syndrome of diffuse alveolar inflammation and damage leading to increased pulmonary vascular permeability. The Berlin definition proposed mild, moderate and severe stages of ARDS based on degree of hypoxemia (PaO2/FiO2 ratio at less than 100, 200 and 300 respectively). Increasing severity was associated with increasing mortality and higher number of ventilator days among survivors [11]. ARDS Network study has shown mortality benefits with lower tidal volume of 6 mL/kg of ideal body weight to keep plateau pressure below 30 cm H2O. PEEP should be adjusted to optimize alveolar recruitment without causing over-distention [12]. Lung protective ventilation has been

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shown to improve short-term and long-term mortality[13]. Our patient developed severe ARDS related to non-cardiogenic pulmonary edema and aspiration pneumonitis. He was promptly treated with mechanical ventilation using lung protective strategy leading to improved outcome and successful liberation from ventilator in 7 days.

CCBcan be divided in to two major classes, dihydropyridines and non-dihydropyridines.Dihydropyridineclass includes amlodipine and nifedipine. They havea high vascular selectivity and their powerful systemic vasodilator effect can lead to reflex tachycardia and increased inotropy. Non-dihydropyridineclass includesphenylalkylamine, verapamil and benzothiazepine,diltiazem. They have selectivity for both vascular and myocardium calcium channels and they tend to produce hypotension, bradycardia, and conduction disturbances.The lack of significant bradycardia or conduction abnormalities with occasional tachycardia early in the presentation of our patient was thought to be potentially explained by the concomitant overdose with dihydropyridines.CCB toxicity is often associated with significant hyperglycemia and acidosis. The underlying mechanisms for CCB-induced hyperglycemia may be due to decreased insulin release from pancreatic β-cells and decreased insulin sensitivity and glucose uptake by tissues including myocardium and vascular smooth-muscles.Such decreased glucose uptake by myocardium and vascular smooth muscles may perpetuatereductions in cardiac inotropyand peripheral vascular resistance.The consequent shock due to the afore-mentioned mechanisms can contribute to profound metabolic acidosis[7-9].

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Initial management of critically ill patients involves supportive care to ensure airway protection, adequate breathing and circulation. However, maintenance of adequate circulation in patients withCCB overdose may often require a multitude of simultaneous therapies that include intravenous fluids, vasopressors, inotropes, calcium, glucagon, high-dose insulin with supplemental glucose therapy, phosphodiesterase inhibitors, and mechanical devices such as pacemakers (for refractory bradycardia and heart block) and even extracorporeal membrane oxygenation in refractory shock (**Figure 3 and Table 1**)[4, 5, 7]. In our patient, we did not have to resort to such mechanical device therapies.

There are currently no controlled clinical studies demonstrating that gastrointestinal decontamination can reduce morbidity or mortality, although case series and retrospective studies suggest that decontamination is beneficialin some patients with CCBoverdose. A recent meta-analysis of 64 controlled studies to estimate the effect of activated charcoal administered during the first 6 hours after drug ingestion found that activated charcoal is most effective when given immediately after drug ingestion, although theremay be beneficial effects even when given as long as 24hours after drug intake[14]. The recommended dose of activated charcoal is 1 gm/kg up to 100 gm. Effectiveness of single dose versus multiple dose therapy is not established. A randomized controlled trial comparing no dose to multiple dose activated charcoal therapy found that fewer patients receiving multiple-dose activated charcoal died than those receiving no charcoal, although difference was not statistically significant [15]. Volunteer studies suggest consideration of whole bowel irrigation for patients presenting more than two hours after toxic ingestions of sustained-release or enteric-coated drugs[16].

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Our patient reportedly did ingest sustained-release preparations of verapamil and carbamazepine and was treated with both activated charcoal and whole bowel irrigation.

Initial treatment for hypotension is primarily supportive and includes fluid resuscitation to correct vasodilation and low cardiac filling pressures.In severely poisoned patients, conventional therapies such as atropine, glucagon and calcium often fail to improve hemodynamic status and vasopressors are usually required to improve mean arterial pressures. Our patient needed up to four vasopressor agents in the first 24 hours of MICU admission to maintain adequate mean arterial pressure.Catecholamineshelp by increasing blood pressure and heart rate, but they also increase systemic vascular resistance which may result in decrease in cardiac output and perfusion of vascular beds.The resultant increase in myocardial oxygen demand may prove deleterious in the setting of hypotension and decreased coronary perfusion[17].

Unfortunately, conventional decontamination measures,such as urinary alkalization, hemodialysis or hemofiltration,are ineffective in accelerating blood clearance of CCB and there have been few efforts to develop antidotes. Injectable long-circulating liposomes bearing a transmembrane pH-gradient have been postulated to sequester lipophilic drugs and hampertheir pharmacological effect[18].Intravenous lipid emulsion (ILE) has been proposed as a rescue therapy for severe local anesthetic drugs toxicity, although experience with other lipophilic drugs including CCB is limited[19].The definitive mechanism of action is not known, although 'lipid sink' theory is most prevailing. ILE is an oil-in-water emulsion. It creates an intravenous lipid phase within the plasma that

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pulls the lipid-soluble drug into the lipid partition in the blood[20]. Initial bolus of 1.5 mL/kgof 20% lipid emulsion followed by 0.25-0.5mL/kg/min (not to exceed 10 mL/kg) over 30 minutes is the recommended protocol from American Society of Regional Anesthesia (ASRA).Verapamil is a lipophilic cardiotoxic drug, which could sequester in an expanded plasma lipid phase. Therefore, ILE has been proposedas efficient detoxifying agents of CCB poisoning[21]. Hypertriglyceridemia and marked interference in analysis of glucose and magnesium seem to be some of very few adverse effects due to ILE treatment. In order to avoid potentially harmful interventions, blood samples should be collected prior to initiating lipid therapy and triglyceride level should be monitored[22].

A recent review of the experimental and clinical data suggests high-dose insulin (Hyperinsulinemia-euglycemia) therapy is superior to conventional therapies for CCBtoxicity[17].HIE therapy is proposed to correct CCB overdose related hypoinsulinemia and insulin resistance by increasing the uptake of glucose by myocardium and vascular smooth muscle. The net effect is improved cardiac function and peripheral vascular resistance[23].The optimal dose of insulin in HIE therapy is not known.Insulin dosing recommendationscautiously included0.5U/kgregular insulin intravenous bolus followed by a 0.5-1 U/kg/hrcontinuous infusion[24]. Clinical experience with high dose insulin revealed improved outcomes and acceptable safety profile. Therefore, current insulin dosing recommendationsare 1 U/kgregular insulin intravenousbolus followed by a 1-10 U/kg/hrcontinuous infusion.Higher intravenous bolus doses up to 10 U/kg and continuous infusions up to 22 U/kg/hr have been reported in literature[17].High-dose insulin therapy is associated with hypoglycemia and hypokalemiaby causing a shift from the extracellular

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to intracellular space. Therefore, glucose and potassium concentrations must be closely monitored every hour, and supplementationis usually required throughout therapy and for up to 24 h after discontinuation of high-dose insulin[25].

Supratherapeutic doses of calcium saltshave a limited effect but can be given to conceivably reverse hypotension and bradycardia[6]. Calcium chloride, 10 mL of a 10% solution (1 gm), can be administered over 10 minutes. If no effect is noted, dose may be repeatedup to four times every 15 to 20 minutes. Calcium gluconatecanalso be used, although the dose must be adjusted to 30 mLof 10% solution (3 gm), as calcium gluconate has only one third of elemental calcium compared with calcium chloride. This can be followed by a continuous infusion of calcium at 0.5 mEq/kg/hr with close monitoring of ionized calcium and serial EKG.

Intravenous infusions of inotropicagents like dobutamine or phospohdiestrase inhibitors are used for signs of heart failure or cardiogenic shock. High-dosecatecholamines lead to increase in afterload, further impairingleft ventricular function. Phosphodiesteraseinhibitors, like milrinone and amrinone, improve cardiac function because of their inotropic and vasodilation effects(Amrinone is not available in the US) [26]. Levosimendan is an inotropic agent that enhances myofilament response to calcium, increases myocardial contraction and could therefore be beneficial in verapamil intoxication[27].The use of levosimendan in CCB overdose is not widely accepted(Levosimendan is also not available in the US).Dose varies between 3 and 36

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mcg/kg as intravenous bolus and between 0.05 and 0.6 mcg/kg/minas a continuous infusion[28].

In conclusion, treatment of CCB overdose requires a multi-faceted approach and may not respond to traditional supportive measures such as fluid replacement and vasopressor support alone.Less conventional modalities such as hyperinsulinemia-euglycemiatherapy and intralipid infusions need to be administered early in patients presenting with hemodynamic instability in order to produce favorable outcomes.

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Legends

Figure 1: Portable chest x-ray showing non-cardiogenic pulmonary edema and atelectasis.

Figure 2: EKG showing sinus rhythm with 1st degree AV block, prolonged QTc interval (456 msec) and extensive ST-T wave changes.

Figure 3: Schematic of medications used to counter the effect of calcium channel blocker poisoning shown at the interface of a blood vessel and cardiac mycocyte. Lipids (yellow) can bind the calcium channel blocker (CCB; orange symbols) and reduce the free drug concentration. Intravenous calcium administration (purple) can increase plasma concentration and try and overcome the blockage of the calcium channels (red cylinder) by CCBs. Intravenous crystalloids can be administered to combat hypotension. The β1 receptor (grey), G protein (G; blue), Adenylcyclase (A; orange) complex can increase intracellular cyclic adenosine monophosphate (cAMP) levels which can increase intracellular calcium concentration and promote myocardial contractility. Intravenous glucagon can also increase intracellular cAMP by activating adenylcyclase and bypassing the β-receptor (a mechanism that makes this agent useful in β-blocker poisoning as well). Phosphodiesterase inhibitors can increase cAMP concentration by reducing the breakdown by PDE4. It is unclear as to how insulin works in CCB poisoning, but it is thought that Insulin favors active transport of glucose intracellularly to make sufficient substrate available for myocardial metabolism, which is thought to suffer from a carbohydrate-deficient state during CCB poisoning. Levosimendan can in turn sensitize the contractile structures to calcium and thereby augment myocardial contractility.

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Table 1: Results of Laboratory Tests

Laboratory Study	Time of Presentation	12 Hours Post Presentation	24 Hours Post Presentation	Normal Range
Chemistries				
Sodium (mMol/L)	138	142	145	136-145
Potassium (mMol/L)	3.8	4.2	3.4	3.5-5.1
Chloride (mMol/L)	104	113	118	101-111
Carbon Dioxide (mMol/L)	18	9	19	20-29
Urea Nitrogen (mg/dL)	9	16	10	9-26
Creatinine (mg/dL)	0.9	2.0	1.3	0.7-1.3
Glucose (mg/dL)	233	285	76	70-105
Calcium (mg/dL)	10.1	9.9	13.6	8.6-10.6
Magnesium (mg/dL)		3.1	1.4	1.6-2.6
Phosphorus (mg/dL)		3.0	1.2	2.3-4.7
Carbamazepine Level (mcg/mL)	3.8	16.5	21.2	4-12
Salicylate Level (mcg/mL)	< 20			<20
Acetaminphen Level (mcg/mL)	<6			<6
Ethanol Level (mg/dL)	279			Undetected
Creatine Kinase (IU/L)		75	387	30-200
Troponin I (ng/mL)		0.03	0.63	0.00-0.02
Arterial Blood Gas				
pH		7.06	7.42	7.35-7.45
pCO2 (mmHg)		40	31	35-45
pO2 (mmHg)		85	84	70-95
SaO2 (%)		95.6	95	94-98
Calculated Bicarbonate (mMol/L)		11.3	20	22-26
Ionized Calcium (mMol/L)		1.35	1.98	1-1.18
Lactate (mMol/L)		7.6	3.8	0.5-2.2

- Complete Blood Count (CBC) remain within normal range except for increase in WBC in 12 hours of presentation that came down to normal range and dilutional drop in Hemoglobin/Hematocrit.
- Coagulation Profile (PT/PTT) remained within normal range.
- Liver Function Test (LFT) remained within normal range.

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Table 2: Treatment options in an Overdose of Calcium Channel Blockers
Volume replacement – Crystalloid or colloid intravenous infusion (as needed)
Circulatory Support – Atropine 0.5 to 1 mg every 2-3 min up to a total of 3 mg
Calcium Therapy – 10 mL of 10% Calcium Chloride (1 gm) or 30 mL of 10% Calcium Gluconate (3 gm) up to 4 doses every 15-20 minutes Infusion of 0.2-0.4 mL/kg/h of 10% Calcium Chloride or 0.6-1.2 mL/kg/h of 10% Calcium Gluconate
Glucagon – 50 mcg/kg or 5 mg up to 3 doses every 10 min Infusion of total dose at which response is noted
Inotropes and Vasopressors – intravenous infusions Catecholamines - Epinephrine, Norepinephrine, Phenylephrine, Isoproterenol, Dobutamine, Dopamine Phosphodiesterase Inhibitors – Amrinone, Milrinone Vasopressin Levosimendan
Hyperinsulinemia-Euglycemia Therapy – 1 U/kg regular insulin bolus, followed by a 1-10 U/kg/h continuous infusion 15 to 30 g of glucose per hour (as glucose 10% or more) to maintain euglycaemia (110 to 150 mg/dl)
Toxin Removal – Activated Charcoal 1 g/kg up to 100 g Whole Bowel Irrigation with Polyethylene Glycol at 2 L/hour
Intravenous lipid Emulsion – Intralipid 20%, 1.5 ml/kg as bolus, followed by 0.25-0.5 ml/kg/min over 30 minutes Boluses can be repeated if insufficient hemodynamic response
Mechanical Support – Transthoracic and intravenous Cardiac Pacer Intra-Aortic Balloon Pump Extra-Corporeal Membrane Oxygenation

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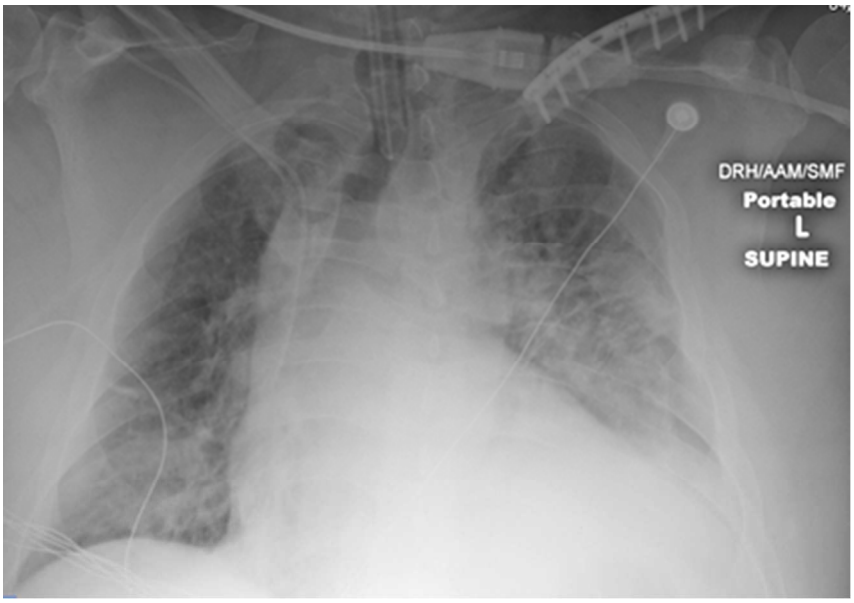

Portable chest x-ray showing non-cardiogenic pulmonary edema and atelectasis.
111x78mm (96 x 96 DPI)

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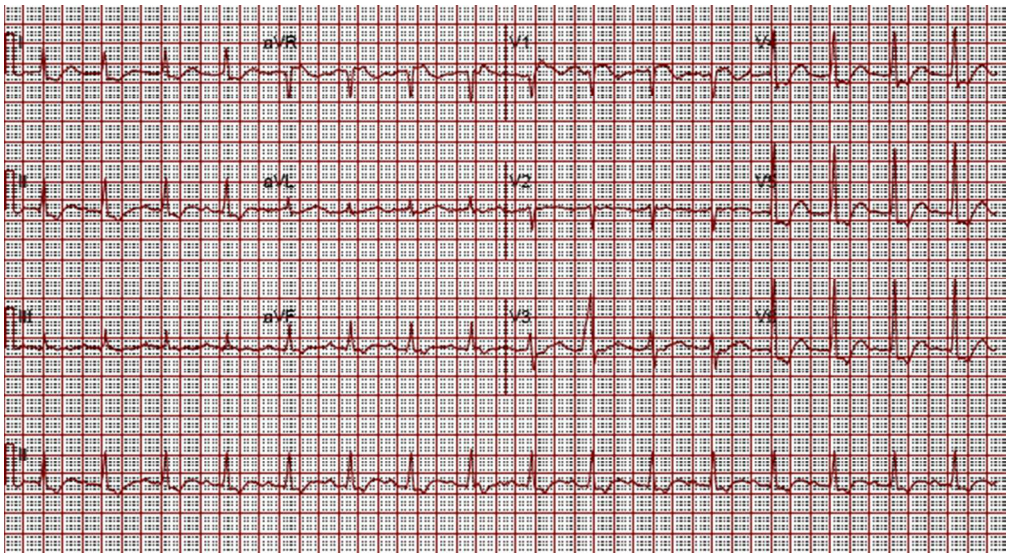

EKG showing sinus rhythm with 1st degree AV block, prolonged QTc interval (456 msec) and extensive ST-T wave changes.
224x123mm (72 x 72 DPI)

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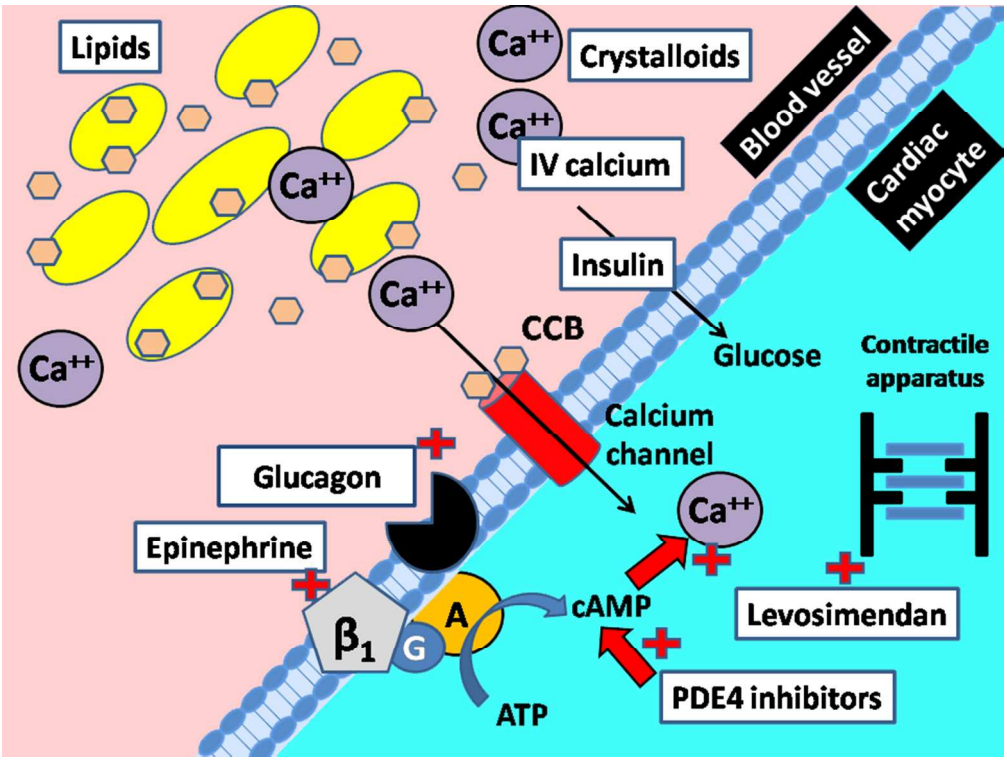

Schematic of medications used to counter the effect of calcium channel blocker poisoning shown at the interface of a blood vessel and cardiac mycocyte. Lipids (yellow) can bind the calcium channel blocker (CCB; orange symbols) and reduce the free drug concentration. Intravenous calcium administration (purple) can increase plasma concentration and try and overcome the blockage of the calcium channels (red cylinder) by CCBs. Intravenous crystalloids can be administered to combat hypotension. The β1 receptor (grey), G protein (G; blue), Adenyl cyclase (A; orange) complex can increase intracellular cyclic adenosine monophosphate (cAMP) levels which can increase intracellular calcium concentration and promote myocardial contractility. Intravenous glucagon can also increase intracellular cAMP by activating adenylcyclase and bypassing the β-receptor (a mechanism that makes this agent useful in β-blocker poisoning as well). Phosphodiesterase inhibitors (Amrinone) can increase cAMP concentration by reducing the breakdown by PDE4. It is unclear as to how insulin works in CCB poisoning, but it is thought that Insulin favors active transport of glucose intracellularly to make sufficient substrate available for myocardial metabolism, which is thought to suffer from a carbohydrate-deficient state during CCB poisoning. Levosimendan can in turn sensitize the contractile structures to calcium and thereby augment myocardial contractility.
254x190mm (96 x 96 DPI)

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