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REVIEWS

Management of Calcium Channel Blocker Overdoses

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Calcium channel blockers (CCBs) are some of the most commonly used medications in clinical practice to treat hypertension, angina, cardiac arrhythmias, and some cases of heart failure. Recent data show that CCBs are the most common of the cardiovascular medications noted in intentional or unintentional overdoses.[1] Novel treatment approaches in the form of glucagon, high-dose insulin therapy, and intravenous lipid emulsion therapies have been tried and have been successful. However, the evidence for these are limited to case reports and case series. We take this opportunity to review the various treatment options in the management of CCB overdoses with a special focus on high-dose insulin therapy as the emerging choice for initial therapy in severe overdoses. *Journal of Hospital Medicine* 2014;9:663–668. © 2014 Society of Hospital Medicine

The 2011 National Poison Data System (NPDS) of the American Association of Poison Control Centers reported that among the top 25 categories associated with mortality, cardiovascular medications were second to sedatives/hypnotics/antipsychotics in terms of the number of deaths resulting from overdose. Moreover, of cardiovascular medications, Calcium channel blockers (CCBs) were the most common agents associated with mortality.[1,2] The 2012 NPDS report showed a similar trend, with cardiovascular drugs ranking among the top causes of overdoses, with an additional approximately 4614 cases in comparison to 2011.[3] In light of emerging strategies for the management of CCB overdoses, we sought to review the pathophysiology of CCB overdose and its management.

PATHOPHYSIOLOGY OF CCB OVERDOSE

CCBs are widely used in the management of various conditions such as hypertension, angina pectoris, atrial fibrillation, and other cardiac arrhythmias. CCBs block L-type receptors on the cell surface.[4] Based on their predominant physiological effect, CCBs have been classified as dihydropyridines and nondihydropyridines (Table 1). Dihydropyridine overdose generally results in vasodilation with resultant hypotension and reflex tachycardia.[5] In comparison, nondihydropyridine overdose generally results in bradycardia and decreased cardiac contractility.[6] With high serum concentrations of either CCB class, however, selectivity is lost, and patients may presents with bradycardia, hypotension, and decreased cardiac contractility.[7,8]

CCBs show good oral bioavailability and undergo first-pass metabolism. During an overdose, the enzymes involved in hepatic oxidation can become oversaturated, which reduces the effects of first-pass metabolism, resulting in increased quantities of the active drug reaching the systemic circulation and a prolonged half-life.[7] In addition, CCBs are highly protein bound and have large volumes of distribution.[9]

Calcium enters cells through specific channels and regulates various cell processes. In myocardial cells, calcium affects excitation-contraction coupling and potential action generation in the sinoatrial node. Similarly, in the pancreas, calcium facilitates the release of insulin. CCB overdose can result in inhibition of insulin secretion from the pancreas and a state of hypoinsulinemia and insulin resistance.[10] Mtabolic acidosis is a common presentation noted in several published case reports.[11] Metabolic acidosis represents a combination of insulin dysregulation with ketoacidosis and hypoperfusion with lactic acidosis. In addition, because CCBs block the entry of calcium into the mitochondria,[12,13] and because calcium is required for the normal enzymatic activity of the Krebs cycle, CCB overdose leads to lactic acid build-up from its direct effects on aerobic metabolism.[14]

The clinical picture of CCB overdose is further complicated by the switch in the mechanism of adenosine triphosphate (ATP) generation in the myocardium from free fatty acid oxidation to carbohydrate metabolism.[15] In response to this stress, the liver increases glucose production via glycogenolysis. With concomitant hypoinsulinemia[10] and relative insulin resistance, intracellular glucose transport is disturbed, with a resultant decrease in ATP production that quickly leads to myocardial dysfunction and cardiogenic

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TABLE 1. The Most Commonly Used Calcium Channel Blockers

Dihydropyridine
Short-acting agents: nifedipine
Longer-acting formulations: felodipine, isradipine, nicardipine, nifedipine, nisoldipine, amlodipine*
Nondihydropyridine
Verampamil and diltiazem

NOTE:
*Longer-acting agents generally have little cardio depressant activity, with amlodipine having the least.[6]

shock. The resultant clinical state of acidosis, hyperglycemia, and insulin deficiency is similar to diabetic ketoacidosis.[11,14] A presentation of symptomatic bradycardia, hyperglycemia, and persistent hypotension, with signs of hypoperfusion usually manifested as altered mental status, clinically defines a severe overdose.

TABLE 2. Treatment Options of Calcium Channel Blocker Overdose

Initial resuscitation measures
Intravenous hydration with crystalloids, colloids.
Gastrointestinal decontamination
Activated charcoal 1 g/kg body weight in hemodynamically stable patients who can protect their airways.[1] Best administered within 2 hours. However, in poisoning from extended release preparations, it can be used beyond the 2-hour window. Anecdotally, WBI has been utilized in calcium channel blocker overdose. However, it is not the recommended approach, especially in patients who are hemodynamically unstable.
Atropine
Reserved for bradycardia; 0.5 mg every 3–5 minutes, not to exceed a total of 3 mg or 0.04 mg/kg (per ACLS protocol).
Sodium bicarbonate
1–2 mEq/kg boluses of hypertonic sodium bicarbonate when QRS widening is noted on the ECG.[46] For severe acidosis or persistent ECG changes, a sodium bicarbonate drip can be initiated with 150 mEq sodium bicarbonate in 1 L D_5W to run at about 100–125 mL per hour.[46]
Following intravenous hydration and GI decontamination (hyperinsulinemia-euglycemia therapy) or vasopressors are usually initiated as resuscitation measures.
Agents used to reverse the calcium channel blocker poisoning
Hyperinsulinemia-euglycemia therapy (refer to Table 33).
Glucagon
Initiated at 0.05–0.15 mg/kg as bolus dosing, with a repeat dosing in 3–5 minutes. An intravenous infusion can be initiated following this.[1]
Calcium salts
A bolus of 0.3 mEq/kg of calcium can be administered as intravenously over 5–10 minutes (0.6 mL/kg of 10% calcium gluconate solution or 0.2 mL/kg of 10% calcium chloride solution). If beneficial response noted, an infusion of 0.3 mEq/kg per hour. Titrate the infusion to obtain an adequate hemodynamic response. Serum ionized calcium levels should be monitored, and target ionized calcium levels should be less than twice the upper limit of normal.[2]
Adrenergic agents
Norepinephrine, dopamine, vasopressin.
Intravenous lipid emulsion therapy
20% fat emulsion is what is usually used with 1 mL/kg given as a bolus followed by a continuous infusion of 0.25–0.5 mL/kg per hour.
Phosphodiesterase inhibitors
Amrinone, milrinone.
Invasive therapy
Transvenous and transcutaneous pacing for high-grade atrioventricular dissociation. Intra-aortic balloon pump. Extra corporeal membrane oxygenation.

NOTE: **Abbreviations:** ACLS, advanced cardiovascular life support; ECG, electrocardiogram; GI, gastrointestinal; WBI, whole bowel irrigation.

MANAGEMENT APPROACH

Maintenance of the airway and circulation is of primary importance in CCB overdose cases (Table 2). Hypotension and bradyarrhythmias are noted in cases of severe overdose, and some patients might require endotracheal intubation and mechanical ventilation very early in their management. The initial treatment strategy typically consists of the use of intravenous crystalloids and gastrointestinal (GI) decontamination; atropine is reserved for symptomatic bradycardia. Some patients may also require transcutaneous and transvenous pacing early and emergently due to complete cardiovascular collapse. Therefore, having a medical toxicologist or a regional poison control expert involved from the time of initial management is advised, especially for cases of severe overdose or consumption of extended-release preparations.

GI Decontamination

In cases of severe overdose, patients may present with lethargy from hypotension and poor cerebral flow, and the risk for aspiration and pneumonitis should be strongly considered in these patients if GI decontamination is considered. GI decontamination is best in cases where the patient is hemodynamically stable and presents early to the emergency department (ED), preferably within 2 hours[7,9]; early use might decrease drug absorption and enterohepatic circulation, thus lowering the drug levels.[16] However, in cases in which the drug consumed was an extended-release preparation, GI decontamination is beneficial even when the patient presents late to the ED.[17] GI decontamination is typically achieved using activated charcoal (1 g/kg body weight) or by performing whole bowel irrigation (WBI) with polyethylene glycol.[9] However, there is very little evidence that either approach changes the overall outcome, and WBI can be potentially harmful for patients with hemodynamic instability.[18] Therefore, airway and circulation maintenance is preferable to this approach.

Catecholamines

Catecholamines, such as dopamine, dobutamine, and norepinephrine, appear to be obvious choices in the management of cases of CCB overdose, because most patients present with hypotension and bradyarrhythmias.[19] However, there is no evidence to show the superiority of 1 agent over another in the management of CCB drug toxicity. Catecholamines increase the heart rate and blood pressure and increase systemic vascular resistance, which can potentially decrease the cardiac output by increasing the afterload.

TABLE 3. Hyperinsulinemia-Euglycemia Therapy

Bolus dosing
Check finger stick blood glucose, and 25 g dextrose can be given as a bolus, provided the patient is not markedly hyperglycemic[1] (eg, blood glucose >400 mg/dL).
0.5 IU/kg of insulin given as bolus. An acceptable alternative would be to give 1 IU/kg as a bolus to saturate the receptors.[1,3,4]
Maintenance dose infusion
Short-acting insulin initiated at 0.5 IU/kg per hour, and this dose can be titrated up to 2 IU/kg per hour. Doses as high as 10 IU/kg per hour have been tried and have been successful.[1,4]
Continuous dextrose infusion might be required to maintain euglycemia (25 g per hour intravenous infusion would be a reasonable choice).[1]
Monitoring
Monitor blood glucose every 30 minutes for the first 4 hours and then hourly. Titrate dextrose infusion to maintain euglycemia.[1]
Dextrose containing fluid can be initiated at 0.5–1 g/kg per hour and titrated to maintain euglycemia.[10,15]
Monitor potassium levels every 60 minutes and replace as needed to maintain at lower limits of normal (2.8–3.2 mEq/L).
Titration of the insulin infusion is usually to the resolution of hemodynamic parameters.
Discontinuation
No clear evidence to say if a weaning protocol is necessary. In several case reports, the protocol was discontinued after objective parameters of clinical resolution were achieved; however, continued dextrose infusion may be required despite the discontinuation of the insulin.[5]

Calcium Salts

In cases of severe overdose, the initial measures are typically not sufficient for stabilizing the patient. Intravenous (IV) calcium salts have been evaluated in animal models[20,21] and, anecdotally, in human case reports.[22–24] However, the response to treatment has been mixed, with improvement in hemodynamic parameters in some cases and treatment failures in other cases. Moreover, the effects of these treatments are typically short lived, and repeated dosing might be required. Calcium salts are typically administered with the theoretical scheme of reversing antagonism with a higher calcium load and increasing cardiac inotropy. Calcium gluconate and calcium chloride are 2 frequently used agents, although no clear guidelines exist regarding this approach and the required dosage.[22] There are also published case reports in which refractory hypotension was treated with continuous calcium infusion in an attempt to reach predefined serum calcium levels.[24] However, the fear of iatrogenic hypercalcemia and its consequences is constant.[25] Calcium chloride contains 3 times the calcium for the identical volume compared to calcium gluconate and is more corrosive to the blood vessels; therefore, it is best administered through a central intravenous access. Although the evidence is limited to a few case reports, continuous calcium infusion appears effective and safe as an adjunctive therapy for patients with severe hypotension resulting from CCB overdose.[21–24,26]

Glucagon

Although insulin and glucagon are physiologically counter-regulatory, they have a similar effect on heart stimulation. In animal models, the positive inotropic and chronotropic effects of glucagon have been clearly demonstrated.[27] Glucagon increases intracellular cyclic adenosine monophosphate (AMP) by stimulating adenylyl cyclase, a mechanism by which glucagon possibly exerts its inotropic effect.[7] Most studies conducted on the use of glucagon in the treatment of CCB overdose originated in an era in which bovine or porcine glucagon was used, and these animal glucagon products contained insulin.[9] Glucagon is typically initiated at 50 to 150 μg/kg as bolus dosing, with a repeat dosing after 3 to 5 minutes.[9] A continuous IV infusion can then be administered following the initial treatment, because glucagon has a very short half-life and works rapidly.[7,9] However, there is no established maximum infusion dose of glucagon, and it should be titrated to the desired clinical outcome. IV glucagon therapy also carries a risk for nausea and vomiting,[7,28] which in combination with lethargy may increase the risk for aspiration pneumonitis. The evidence for the use of glucagon in cases of CCB overdose is predominantly based on animal models[27]; evidence in human subjects is limited to case reports.[11,28,29] Some cases have demonstrated an improvement in hemodynamics with glucagon, whereas in a few cases, glucagon failed to result in such improvement.[30] In cases in which the ingestion history is unclear or there is polysubstance ingestion, as with β-blockers and CCBs, glucagon is an ideal treatment agent[9]; in contrast, in single CCB overdose, glucagon might not be as helpful as more recent treatment modalities.

Hyperinsulinemia-Euglycemia Therapy

In recent years, increasing evidence from multiple case reports and case series has shown the superiority of high-dose insulin therapy over other treatment modalities (Table 3). Insulin acts as a potent inotrope[31,32] and vasodilator. In their prospective observational series of 7 patients, Greene et al. report the successful use of hyperinsulinemia-euglycemia therapy (HIET) with no significant adverse events when combined with conventional measures in a critical-care setting.[33] Similarly, more than 50 cases have been reported in which HIET was used successfully in the management of CCB overdoses.[34]

Although there is wide variation in the insulin dosing regimens in published case reports, hyperinsulinemia therapy is typically initiated with a 0.5 IU/kg to 1 IU/kg bolus, followed by a continuous drip of 0.5 UI/kg per hour to 1 IU/kg per hour. This dose is titrated every 15 to 20 minutes until satisfactory hemodynamic and clinical stability is noted. Titrations are usually avoided for a shorter time interval because insulin must enter cells and initiate intracellular signaling and metabolic activation. However, the response to HIET might be delayed, and other therapeutic modalities could be required simultaneously until the clinical effects of insulin are observed.

Euglycemia should be maintained by checking the blood glucose levels every 30 minutes and using a dextrose solution to maintain the blood glucose

within the upper limits of normal.[35] Hyperglycemia noted in CCB overdose cases indicates the degree of insulin resistance and serves as a marker of the severity of the overdose.[14,15] In particular, patients who are hyperglycemic at presentation may not require supplemental dextrose infusion despite the high-dose insulin therapy. The blood glucose level should be checked every 30 minutes for the first 4 hours and then hourly to avoid overlooking hypoglycemia during the treatment regimen, especially in intubated and sedated patients. Fluids containing dextrose may be initiated at 0.5 to 1 g/kg per hour and titrated to maintain euglycemia.[9,11]

However, there is no consensus as to how long the infusion should be continued once initiated. Although insulin has not been shown to induce tachyphylaxis in experimental animal models, many clinicians prefer to discontinue the infusion once hemodynamic stability has been achieved. There is also no evidence indicating whether a weaning protocol would make any difference over abrupt discontinuation.[36] The physiological effects of insulin persist for hours after the discontinuation of the infusion and will gradually taper down with time. Therefore, theoretically, an abrupt cessation should seldom cause any deleterious effects.[11] Dextrose supplementation may be required to maintain euglycemia for up to 24 hours following discontinuation of the insulin drip due to the elevated insulin levels.[11,36]

Insulin is a potent vasodilator in the coronary and pulmonary vasculature but does not increase the requirement for myocardial oxygen. Instead, insulin facilitates endothelial nitric oxide activity through the phosphoinositide 3-kinase (PI3K) pathway, which translates into vasodilatation of the capillary microvasculature and better perfusion at the capillary junction. As a result, insulin corrects the capillary dysfunction that is the major pathology in cardiogenic shock and the ultimate presentation in severe CCB overdose.

Gradinac et al. reported that patients with cardiogenic shock, in the postoperative period of coronary artery bypass grafting, showed a better cardiac index with the use of IV insulin therapy.[37] In an experiment on explanted human myocardium, von Lewinski et al. demonstrated the positive inotropic effect of insulin through calcium-dependent pathways as well as PI3K pathways.[38] Moreover, Hsu et al. demonstrated with human myocardial cells that this inotropic property of insulin was dose dependent, with better responses observed after the use of higher doses of insulin; in addition, this effect was rapid (ie, as fast as 5 minutes after the infusion) and was sustained throughout the duration of insulin treatment.[39] The best clinical translation of this finding was demonstrated by Yuan et al.[11] in their case series of 5 patients with severe cardiogenic shock secondary to CCB overdoses.

There have also been cases of CCB overdoses in which insulin therapy has failed, which may be because the insulin protocol was initiated late as salvage therapy or because of the severity of the events.[35] Insulin therapy should be initiated early in the course of management rather than as salvage therapy.[7,35] Agarwal et al. reported their experience in treating an patient on 3 separate occasions of CCB overdose. These authors reported rapid improvement on the third occasion, in which insulin therapy was initiated early during the course of management.[40] In recent years, HIET has been shown to be a promising approach in the management of CCB overdose. Patients with third-degree heart blockage resulting from CCB overdose reverted to a normal sinus rhythm while on an insulin drip protocol without the intervention of a temporary pacemaker.[11]

High-dose insulin therapy can also result in hypokalemia, which theoretically may represent a beneficial response in the management of CCB overdose, because it provides a membrane stabilizing effect by prolonging repolarization and allowing more calcium to enter the cytoplasm during cardiac systole.[11] Yuan et al. suggested a serum potassium range of 2.8 to 3.2 mEq/L during insulin-glucose therapy.[11] Hypomagnesemia and hypophosphatemia are other electrolyte derangements reported during treatment that are similar to conditions observed in patients with diabetic ketoacidosis.[41,42]

Intravenous Lipid Emulsion Therapy

CCBs are naturally lipophilic, and intravenous lipid emulsion (ILE) therapy has been attempted with success in cases of severe CCB overdose.[43,44] A systematic review by Jamaty et al.[45] showed that, although the overall quality of the evidence for this modality was poor, ILE could be beneficial in the management of severe cases of CCB poisoning. ILE therapy was first described by Weinberg et al. for bupivacaine toxicity in the year 2003.[46] ILE is commonly utilized as part of total parenteral nutrition, and several case reports have shown the success of its use in the treatment of local anesthetic toxicity.[47] Although the mechanism remains to be clearly elucidated,[48] it is hypothesized that this emulsion in the circulation creates a lipid channel, which causes sequestration of lipophilic drugs, and stimulates the redistribution of lipophilic drugs from the tissues to this channel.[47] Recent data have further revealed the inotropic properties of lipid emulsion; when used for acute overdose, lipid emulsion improves ventricular contractility and diastolic relaxation, going beyond its role as a simple fuel for cardiac tissue or a "lipid sink."[49] Lipid emulsion in the circulation also stimulates insulin secretion, which is beneficial in reversing the antagonism caused by CCB on the β cells of the pancreas.[50] However, fat embolism, infection, and the development of acute respiratory distress syndrome have been reported as

complications associated with this therapy.[51] Thus, it is prudent to involve a medical toxicologist or the regional poison center to decide whether a patient would be a candidate for this treatment approach. In most cases, this is reserved as a last resort in the management of CCB overdose. Typically, a 20% fat emulsion is used, with 1 mL/kg given as a bolus followed by a continuous infusion of 0.25 to 0.5 mL/kg per hour.[7]

Sodium Bicarbonate

Metabolic acidosis resulting from CCB overdose facilitates the binding of CCB to L-type calcium channels; thus, correcting this acidemia might improve the hemodynamic profile. Sodium bicarbonate has been suggested as a useful adjunct because it decreases the affinity of the CCB for the calcium channel. In cases of severe toxicity, electrocardiogram (ECG) findings may show widening of the QRS complex; these ECG changes are mediated through the inhibitory action of CCB on fast sodium channels, similar to that observed in cases of overdose from tricyclic antidepressants.[9,52]

Although the evidence is limited to a few case reports, treatment with 1 to 2 mEq/kg boluses of hypertonic sodium bicarbonate is recommended in cases in which QRS widening is noted on an ECG.[52] In cases of severe toxicity with severe acidosis, dysrhythmia, or persistent QRS widening, a sodium bicarbonate drip could be initiated, with 150 mEq of sodium bicarbonate in 1 L D_5W to run at approximately 100 to 125 mL per hour.[52]

OTHER TREATMENT MODALITIES

Levosimendan has inotropic properties and is a calcium sensitizer to the myocardium. Although this drug has been used for CCB overdose,[53] it is not available in the United States. Temporary pacemakers and intra-aortic balloon pump counter pulsation therapy are reserved for severe heart blocks and cases of refractory cardiogenic shock. The use of these 2 modalities is recommended only on a case-by-case basis. Wolf et al. demonstrated treatment success in a case of severe verapamil toxicity following the use of glucagon and amrinone.[54] However, there is the potential for hypotension, and this therapy is not routinely recommended. Considering that all CCBs are highly protein bound, with large volumes of distribution, extracorporeal measures such as hemodialysis and charcoal hemoperfusion have very limited roles in the management of an overdose.

CONCLUSION

There is no standardized approach for the management of patients with CCB overdose, and most of the existing evidence consists of case reports and case series. Calcium salts, glucagon, and vasopressors are common first-line agents. In severe cases, HIET appears to be a promising treatment strategy, with several case reports reiterating its efficacy. However, euglycemia and a stable electrolyte panel should be maintained throughout the clinical course of management. Most of the benefits observed with HIET were noted in cases in which insulin therapy was initiated early in the course of management. ILE therapy, temporary pacemakers, and intra-aortic balloon pump counter pulsation therapy are used on a case-by-case basis and best applied in consultation with a medical toxicologist or the regional poison control center.

Disclosure

Nothing to report.

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