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Clinical Reviews

Pearls and Pitfalls for the Emergency Clinician: Beta Blocker and Calcium Channel Blocker Toxicity

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□ **Abstract—Background: Beta blocker or calcium channel blocker toxicity is a serious condition that carries with it a high rate of morbidity and mortality. Objective: This review highlights the pearls and pitfalls of beta blocker and calcium channel blocker toxicity, including presentation, diagnosis, and management in the emergency department (ED) based on current evidence. Discussion: Beta blocker and calcium channel blocker toxicity is a life-threatening emergency that requires prompt identification and management. Patients commonly present with both hypotension and bradycardia. The rare exception to this involves overdoses with dihydropyridines such as amlodipine which can initially present with hypotension and tachycardia before eventually developing bradycardia. Beta blockers such as propranolol can present with altered mentation, seizures, and ventricular dysrhythmias resulting from their ability to block sodium channels. Sotalol can cause significant QT prolongation in addition to hypotension and bradycardia. While laboratory evaluation does not confirm the diagnosis of beta blocker or calcium channel blocker toxicity, laboratory testing such as renal function and lactate can be used to evaluate for end organ perfusion, while acetaminophen, salicylate, and digoxin concentrations can be sent to evaluate for possible concomitant ingestions. Initial treatment should focus on fluids, atropine, calcium, and in select patients, gastrointestinal (GI) decontamination with activated charcoal. For more significant toxicity that does not respond to initial treatments, vasopressors and high-dose insulin should be considered, while intralipid and extracorporeal membrane oxygenation should be considered in the cases of refractory toxicity despite maximal therapy. Patients should be admitted to the intensive care unit for close hemodynamic monitoring. Conclusion: An understanding of beta blocker and calcium channel blocker toxicity can assist emergency clinicians in diagnosing and managing this potentially deadly disease. © 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.**

□ **Keywords—Calcium channel blocker; Beta blocker; Vasopressors; Insulin; Extracorporeal membrane oxygenation; Toxicology; Hemodialysis; Intralipid**

Introduction

Definition

Beta blockers (BB) and calcium channel blockers (CCB) are two classes of cardioactive medications that are primarily used for the treatment of various cardiovascular disorders such as tachydysrhythmias, angina, coronary artery disease, and hypertension. These medications are also used for a variety of noncardiovascular disorders such as migraine prophylaxis, essential tremor, and performance anxiety (1,2,3). BBs can be further subdivided based on certain pharmacological properties such as receptor selectivity, while calcium channel blockers are typically divided into two main clinical groups: dihydropyridines and nondihydropyridines (4,5). Toxicity from these two groups of cardioactive medications most commonly occurs after overdose but can also occur in the setting of therapeutic use or through drug-drug in-

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teractions. This review will focus on the pathophysiology, emergency department evaluation, and management strategies of BB and CCB toxicity.

Pathophysiology

The electrical and mechanical activity of the heart relies on the movement and concentration of various ions including calcium, sodium, and potassium. Heart rate is largely determined by rate of spontaneous depolarization of pacemaker cells in the sinoatrial node. The spontaneous depolarization of pacemaker cells involves several mechanisms including inward cation currents through pacemaker cells and the rhythmic release of calcium from the sarcoplasmic reticulum which is termed the "calcium clock." (6).

During normal systole, cellular depolarization causes the opening of L-type calcium channels on the myocyte membrane. The influx of calcium into the cardiac myocyte causes an increase in the concentration of calcium in the myocyte, which triggers the opening of ryanodine receptors on the sarcoplasmic reticulum (SR) and causes a large efflux of calcium from the SR. This is known as "calcium induced calcium release." (7). Calcium within the myocyte then binds to troponin C which allows actin and myosin interaction which causes a subsequent contraction. The strength of the myocyte contraction is dependent on the amount of calcium released from the SR (8).

In diastole, several mechanisms help to remove calcium from the myocyte cytoplasm. These mechanisms include the SR calcium ATPase which pumps calcium back into the SR and the calcium-sodium transporter that exchanges one intracellular calcium ion for three sodium ions from the extracellular fluid (9). The drop in calcium concentrations within the cytosol causes the dissociation of calcium from troponin and relaxation occurs.

Beta receptors, mainly beta 1, are found in the cardiac myocyte and help to increase inotropy. Beta 1 receptors are coupled to Gs proteins that activate adenylate cyclase which causes the increased formation of cyclic adenosine monophosphate (cAMP). cAMP then activates protein kinase A (PKA) which then phosphorylates several key proteins in the myocyte that all help to promote increased inotropy (10).

While both BB and CCBs decrease cardiac output and heart rate and cause peripheral vasodilation, the mechanisms of action differ. Toxicity from BBs largely results from their competitive antagonism of catecholamines at beta receptors located in the cardiac myocyte. Toxicity from CCBs comes from the blockade of L-type calcium channels located in the cardiac myocyte and smooth muscle (11). Nondihydropyridines such as verapamil and diltiazem bind to cardiac L-type channels due to their preferential binding at more negative membrane potentials (−90 mv) while the dihydropyridines such as amlodipine bind to calcium channels located in the peripheral smooth muscle due to their preferential binding at less negative membrane potentials (−70 mV) (12).

Epidemiology

According to the 2023 American Associated of Poison Control Centers (AAPCC) annual report, deaths from CCBs and BBs were the 6th and 7th most common causes of fatalities from overdose with 193 and 125 fatalities involving CCBs and BBs respectively. Within the BB class, propranolol accounts for a large number of cases in both overall exposures and fatalities with a total of 29 cases resulting in fatalities that involved propranolol (13). The remainder of this review will discuss key tenets of the presentation, evaluation, and management of patients with BB and CCB toxicity.

Discussion

Are Certain Beta Blockers Associated with Greater Risk of Toxicity?

While all beta blockers have the potential to cause depending on the amount ingested, there are two important groups of beta blockers to consider when performing an initial risk assessment. Sotalol toxicity can result in not only bradycardia and hypotension, but also significant QT interval prolongation leading to ventricular dysrhythmias including torsades de pointes (14). Specific management that may be required in cases of sotalol toxicity include treatment of hypokalemia and hypomagnesemia if present and general management of torsades de pointes which can include the use of chronotropic agents such as epinephrine or isoproterenol or overdrive pacing to increase heart rate (15).

Several beta blockers possess membrane stabilizing activity with propranolol having the strongest membrane stabilizing effect (16). In addition to bradycardia and hypotension, toxicity from beta blockers with membrane stabilizing effects can cause ventricular dysrhythmias from their ability to antagonize sodium channels which leads to a prolonged QRS interval (17). The evidence on the use of sodium bicarbonate in the case of beta blocker poisoning is mixed. Sodium bicarbonate therapy did slightly decrease the QRS interval in propranolol poisoned canines, although the decrease was not statistically significant (18). A case report of acebutolol induced ventricular tachycardia was rapidly corrected with the administration of sodium bicarbonate (19). While the evidence is mixed, in patients who overdose on membrane stabilizing beta blockers with evidence of QRS interval prolongation or

Table 1. Comparing Calcium Channel Blocker (CCB) and Beta Blocker (BB) Toxicity.

Component	Beta Blockers	Calcium Channel Blockers
Blood pressure	↓	↓
Heart rate	↓	↓ (Dihydropyridines may cause a reflex tachycardia)
Central nervous system effects (seizure, delirium)	Yes (seen with lipophilic BBs like propranolol)	Not typically seen
QRS prolongation	Yes (seen with the membrane stabilizing BBs such as propranolol)	Not typically seen
QTc prolongation	Yes (seen with the potassium channel blocking BBs such as sotalol)	Mild prolongation
Blood glucose concentrations	Normal/↓	Normal/↑

ventricular dysrhythmias, 1–2 mEq/kg of sodium bicarbonate IV should be administered.

Are Certain Calcium Channel Blockers Associated with Greater Risk of Toxicity?

The most commonly encountered CCBs that result in toxicity include verapamil, diltiazem, and amlodipine. In the 2023 AAPCC annual report, the CCB that was involved with the most fatalities was amlodipine, followed by verapamil and then diltiazem. There was a total of 275 fatalities reported involving cardiovascular drugs, with 109 of these cases involving amlodipine, reflecting the severity of amlodipine toxicity (13).

How Can the Presentations Differ between Beta Blocker and Calcium Channel Blocker Toxicity?

While both BBs and CCBs overdose typically presents with bradycardia and hypotension, there are important differences (Table 1). While altered mentation can result from significant decrease in cardiac output, due to its lipophilicity and ability to penetrate the blood-brain-barrier, patients who overdose on propranolol can present with seizures and coma even in the absence of significant hypotension (20). While most patients with CCB toxicity present with bradycardia, patients who present with toxicity from the dihydropyridines such as amlodipine can initially present with tachycardia before developing bradycardia (21,22).

Determination of blood glucose concentrations can be helpful in differentiating patients who present with concern for toxicity from either a BB or CCB. While hypoglycemia is thought to be commonplace in patients presenting with BB toxicity, this association is mostly seen in the pediatric patient population and is rare in adults (23). The BBs most commonly associated with the development of hypoglycemia include the nonselective BBs and long acting BBs (24). The mechanism of the development of hypoglycemia is thought to be secondary to the inhibition of the beta 2 receptor. Normally, beta 2 receptor agonism results in a net increase in glucose due to the increase in glycogenolysis, hepatic gluconeogenesis, and the release of glucagon from pancreatitis alpha cells which can help increase glucose levels during hypoglycemic events. Therefore, beta blockade may help blunt the corrective process of increasing glucose concentrations but can also mask the sympathetic effects that may occur during hypoglycemic events (24).

In patients presenting with CCB toxicity, the presence and degree of hyperglycemia has been used as a prognostic factor in predicting severity of illness. The mechanism of hyperglycemia in the context of CCB toxicity is through the inhibition of L-type calcium channels on the pancreas, as well as the development of insulin resistance. Calcium influx through calcium channels on the pancreas is responsible for the release of insulin from the pancreas, and blockade of these channels results in the decrease of insulin secretion resulting in hyperglycemia (25). A retrospective study of CCB poisoning showed that patients who presented with a mean serum glucose concentration of 188 mg/dL went on to have higher rates of vasopressor use, pacemaker use, and death compared to those patients who presented with a serum blood glucose of 122 mg/dL (26).

What Are the Key Tenets of Management?

The hallmark of both BB and CCB toxicity is hypotension and bradycardia. Vital sign abnormalities generally

occur within the first several hours following ingestion. Multiple dysrhythmias can be encountered including idioventricular rhythms, junctional escape rhythms, and complete heart block (12). Signs and symptoms of toxicity can vary depending on the degree of hypoperfusion, ranging from dizziness and lightheadedness to altered mental status and coma. Acute respiratory distress syndrome has been described in some cases of severe calcium channel blocker poisoning and is believed to be caused by capillary vasodilation which leads to increased capillary transudates and interstitial edema (27,28).

As with all critically ill patients, attention should be made initially to airway, breathing, circulation, and decontamination. Patients with severe BB and CCB toxicity will likely need multiple points of intravenous access with multiple medications being given simultaneously, and thus ensuring adequate intravenous access is critical. A 12-lead electrocardiogram (ECG) should be performed, and patients should be placed on continuous cardiac monitoring. Critically ill patients secondary to a toxicological exposure should have a brief toxicological risk assessment performed which includes determining the type of medication, dose, preparation, and timeline of ingestion. While BB and CCB toxicity most commonly results after intentional ingestion, toxicity can also result from proper use of these medications due to accumulation of the parent compound or metabolites due to altered metabolism or poor clearance (29,30). Close attention should be drawn to both the type of preparation and the type of medication as the different pharmacological properties between specific BBs and CCBs can be crucial and can alter which management strategies are chosen. The initial treatment of bradycardia and hypotension should consist of both intravenous fluids and atropine. While atropine may have some benefit in mild cases of toxicity, in severe cases of BB and CBB toxicity, atropine may be insufficient (31,32).

Laboratory testing evaluating for alternative etiologies of bradycardia should be obtained including thyroid function, electrolytes including potassium, renal and liver function, and troponin. Other etiologies of bradycardia and hypotension should be considered including myxedema coma and myocardial infarction, as well as other toxicological etiologies (Table 2). In cases of intentional overdoses, both salicylate and acetaminophen concentrations should be obtained. In patients who present with both hypotension and bradycardia and have access to digoxin or have features suggestive of cardioactive steroid poisoning such as nausea, vomiting, and abdominal pain, a digoxin concentration should be obtained. Serum concentrations of both BBs and CCBs are not typically readily available in the emergency department (ED) setting.

Gastrointestinal decontamination including activated charcoal (AC) should be considered in all patients who present within 1–2 hours after an ingestion of a CCB or BB. AC should still be considered in patients who present outside of this window in the case of massive ingestions or after an ingestion of an extended release formulation (33). In patients with intact mental status and who are cooperative, 50–100 g of AC should be administered. AC has been shown to decrease the absorption of various CCBs and BBs (34,35).

Table 2. Toxicological Causes of Bradycardia and Hypotension.

- Alpha-2 adrenergic agonists
- Antidysrhythmics (flecainide)
- Beta blockers
- Calcium channel blockers
- Cardiac glycosides (digoxin)
- Opioids
- Organophosphates
- Sedative hypnotics

Patients who present with bradycardia, hypotension, alteration in mental status, or ECG abnormalities including prolongation of the QRS interval or significant prolongation of the QTc should be admitted to an intensive care unit until these findings are resolved. In cases that involve immediate release preparations with the exception of sotalol (due to its long half-life) and the patient remains asymptomatic with normal vital signs for a period of 6–8 hours, discharge may be appropriate (34). In cases of toxicity resulting from either extended-release preparations, large ingestions, or from sotalol, patients should be observed for a period of at least 24 hours in an intensive care unit due to the risk of delayed toxicity (36).

While there are many pharmacological options that can be used in the treatment of BB and CCB toxicity, a stepwise and incremental approach should be used when treating critically ill patients. The following sections will go over the efficacy of different treatment options and when to consider a certain pharmacological intervention.

Is Calcium or Glucagon Effective?

Calcium salts have been shown to increase cardiac output and blood pressure in both animal models and human case series with little effect on heart rate (37,38). Limitations of calcium salt therapy are the short-lived effect and decreased efficacy in severely poisoned patients (39). Given its potential to give significant transient benefit and overall low side effect profile, the administration of calcium salts is recommended in both BB and CCB toxicity. While there is no established dosing protocol, an initial

starting dose 1 gram of 10% calcium chloride through a central line or 3 grams of 10% calcium gluconate IV given over 10 minutes is recommended, two repeat doses can be given 10 minutes apart after the initial dose. Subsequent doses can be given every 20–60 minutes as needed. Serum calcium concentrations should be monitored closely and a target ionized calcium of 1.5 times the upper limit of normal should be maintained.

Glucagon is an endogenous polypeptide that exerts its positive inotropic effects through its interaction with Gs proteins in the heart. The binding of glucagon to Gs proteins in the heart increases the activity of adenylate cyclase (40). The increase of activity of adenylate cyclase is independent of any binding to beta adrenergic receptors. Thus, glucagon is thought to exert its clinical effects on the cardiac myocyte by effectively "bypassing" the poisoned beta adrenergic G coupled receptor. Glucagon has also been shown to inhibit phosphodiesterase, therefore inhibiting the breakdown of cAMP, which provides an increase in inotropy (41).

Glucagon has been shown to be effective in BB toxicity in several animal models and in a human case series (42,43). The evidence supporting the use of glucagon in CCB toxicity is limited as animal models have shown transient improvement in heart with little change in mean arterial pressure and little effect on survival rate, while human data are limited to case reports (44). The side effects of glucagon include nausea, vomiting, hyperglycemia, and hypocalcemia (45] The initial starting dose of glucagon is 3–5 mg given as a slow bolus over 1–2 minutes. The initial starting dose in pediatric patients is 50 mcg/kg. The initial bolus dosing can be repeated for a cumulative bolus dose of up to 10 mg. Bolus dosing can be followed by an infusion of glucagon that is typically started at the "response dose," meaning if a patient received a cumulative bolus dose of 5 mg of glucagon that resulted in a response, an infusion can be started at 5 mg/h. Limitations to providing large amounts of glucagon include limitations in a hospital's supply of glucagon and the development of tachyphylaxis which is the need for significant increase in the dose of a drug to provide the same clinical effect.

Given the mixed clinical evidence for glucagon therapy in the setting of BB and CCB toxicity and adverse effects, it is reasonable to trial glucagon in the early stages of BB and CCB toxicity while preparing for the use of other more effective treatment modalities.

What Vasopressor(s) or Inotrope(s) Should be Utilized?

Several vasopressors and inotropes have been utilized for both BB and CCB toxicity with varying rates of success. The decision to use these pharmacological agents typically is made when initial treatments such as atropine, calcium, glucagon, and fluids are ineffective in maintaining cardiac output.

Epinephrine and Norepinephrine

Epinephrine and norepinephrine are two vasopressors commonly used in the setting of BB and CCB toxicity. In animal studies, data suggest a lower efficacy of the use of vasopressors when compared to the use of an inotrope like high dose insulin. In a porcine model of propranolol toxicity, survival was significantly higher in pigs treated with high dose insulin compared to pigs treated with vasopressin and epinephrine. Hemodynamic parameters of mean arterial pressure and systemic vascular resistance tended to be much higher earlier on in the vasopressin and epinephrine group but then decreased precipitously (46).

Two other separate studies of propranolol poisoned pigs showed that the use of high dose insulin had a significant increase in cardiac output and survival benefit compared to the use of vasopressors, although in one of these studies, the use of high dose insulin combined with norepinephrine was superior in terms of survival time compared to the use of high dose insulin alone (47,48). A retrospective chart review of patients admitted with either verapamil or diltiazem toxicity highlighted the successful use of vasopressors in a majority of cases without the use of high dose insulin and low rates of complications despite the high doses of vasopressors used (49). Vasopressors used in this study included dobutamine, isoproterenol, epinephrine, and norepinephrine. The median infusion rate for norepinephrine and epinephrine was 15 ug/min and 20 ug/min, respectively. Max infusion doses of norepinephrine and epinephrine were 100 ug/min and 150 ug/min, respectively. The study highlighted the low rates of ischemic complications with eight ischemic events reported and five of those events were deemed to have occurred before vasopressor therapy.

Despite no clear consensus on the efficacy of the use of vasopressors, it is reasonable to begin with either epinephrine or norepinephrine depending on the clinical context and in the setting where initial therapies have failed to maintain cardiac output. Typical dosing range for norepinephrine and epinephrine is 5–40 mcg/min and 5–20 mcg/min IV, respectively, and in the setting of CCB and BB toxicity, doses above this dose range may be needed.

Dobutamine

Dobutamine is another beta 1 agonist with little effect on the peripheral vasculature. Experience in human cases of BB and CCB toxicity are quite limited, and the effi-

cacy of dobutamine is mixed (50). The starting dose of dobutamine is 3–5 mcg/kg/min followed by an infusion of 5–15 mcg/kg/min IV.

Nonselective Beta Agonists

Nonselective beta agonists such as isoproterenol have been used for BB toxicity with varying success. High doses of isoproterenol are typically required and can cause vasodilation due to the stimulation of beta 2 receptors (51,52). While some animal models show positive results when using isoproterenol (53), many clinical cases show that isoproterenol is largely ineffective in raising blood pressure and increasing heart rate. Literature suggests, epinephrine is a superior vasopressor when compared to isoproterenol (54). Typical loading dose of isoproterenol is 0.02–0.06 mg IV followed by an infusion at 2–20 mcg/min.

Methylene Blue

Methylene blue is the antidote of choice for the treatment of methemoglobinemia but has also been used successfully in the treatment of refractory hypotension, particularly in cases involving amlodipine toxicity (55). Dihydropyridines, particularly amlodipine, are thought to increase nitric oxide in the peripheral smooth muscle which causes vasodilation and vasoplegia (56). Methylene blue theoretically counteracts the vasodilation and vasoplegia caused by dihydropyridines by inhibiting guanylyl cyclase which blocks the release of cyclic guanosine monophosphate, an important mediator in the nitric oxide signaling pathway (57). Methylene blue has also been shown to inhibit nitric oxide synthase, therefore directly reducing the amount of nitric oxide (58).

While the evidence supporting the use of methylene blue in the setting of CCB toxicity, particularly with amlodipine toxicity, is limited to case reports, it is reasonable to trial a dose of 1–2 mg/kg of methylene blue if significant hypotension persists despite initial treatment with vasopressors.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors have also been used in the setting of BB toxicity with varying degrees of success. These drugs inhibit the breakdown of cAMP by the enzyme phosphodiesterase, and therefore, increase cAMP without the need for beta receptor stimulation. Animal models have shown mixed results, and there are a limited amount of studies showing benefit in humans (59,60). In addition, phosphodiesterase inhibitors can cause significant hypotension due to peripheral vasodilation, and many of the agents have long half-lives making titration quite difficult. Thus, these agents are not routinely used in the setting of BB or CCB toxicity.

What Are the Pearls Regarding High-Dose Insulin and Glucose Therapy?

High-dose insulin (HDI) is an inotropic agent that has been used as an adjunctive treatment for BB and CCB toxicity. The heart primarily relies on free fatty acids for its energy needs, but during periods of stress such as overdose involving CCBs and BBs, the heart switches to carbohydrates as its primary energy source (61). HDI is thought to increase myocardial inotropy by helping to facilitate the utilization of carbohydrates for metabolism (62). In addition to the increasing glucose utilization during times of myocardial stress, HDI has been shown to increase the uptake and utilization of lactate in the myocardium by restoring pyruvate dehydrogenase activity in the setting of verapamil toxicity involving canines (62). HDI also results in the increase of intracellular calcium through the inhibition of the sodium-calcium antiporter, which helps increase calcium release from the sarcoplasmic reticulum causing increased myocardial contractility (63).

Most of the data showing positive results with HDI are from animal models that were previously mentioned in the discussion regarding the use of vasopressors (48,50,60). One of the earliest reports on the use of HDI therapy was from a case series in 1999 that involved five patients with either verapamil or amlodipine and atenolol overdoses. All patients failed the initial antidotal therapy, and all subsequently responded to insulin therapy (64). Because of the strong, positive inotropic effects on the myocardium, HDI therapy should be considered in the setting of patients with CCB or BB toxicity with evidence of myocardial depression. The presence of myocardial depression can be assessed with the use of cardiac ultrasonography.

HDI is typically initiated with a 1 unit/kg bolus of regular insulin IV alongside a 0.5 g/kg bolus of dextrose if blood glucose concentrations are below 300 mg/dL. Clinical responses to insulin typically occur within 15–60 minutes (65). Following the bolus dose, an infusion of 1 unit/kg/h of regular insulin should be started. A dextrose infusion beginning at 0.5 g/kg/h can be started to maintain a blood glucose concentration between 100 and 250 mg/dL. Common adverse events associated with HDI include hypoglycemia and hypokalemia (66). It should be noted that HDI causes vasodilation through the release of nitric oxide which can potentially amplify the vasodilatory effects of amlodipine, especially in overdose (58).

Table 3. Summary of Pearls.

- Consider beta blocker and calcium blocker toxicity in patients presenting with bradycardia and hypotension.
- Dihydropyridines can present with tachycardia initially as these agents can cause profound vasoplegia with a compensatory increase in heart rate.
- Lipophilic beta blockers like propranolol can cause seizures and significant QRS widening.
- Potassium channel blocking beta blockers such as sotalol can cause significant QTc prolongation and torsade de pointes.
- Initial treatment for BB or CCB toxicity should include activated charcoal if the airway is intact, atropine for significant bradycardia, calcium salts, and in the setting of BB toxicity, glucagon can be considered if readily available.
- If initial interventions fail, vasopressors should be utilized with consideration for high dose insulin if there is evidence of diminished cardiac contractility on echocardiogram.
- Methylene blue can be used to treat refractory vasoplegic shock due to dihydropyridine toxicity.
- Intralipid therapy is reasonable if ECMO is not available or in cases or cardiac arrest from a presumed overdose of a CCB or BB.
- In the event of refractory hypotension and bradycardia, ECMO should be considered if feasible and available.

BB = beta blocker; CCB = calcium channel blocker; ECMO = extracorporeal membrane oxygenation.

When Should Intralipid Therapy Be Considered, and What Are the Components of Administration?

Intralipid is an antidote that has the most evidence for treatment of toxicity from local anesthetics (67). Intralipid has been used in many cases of toxicity from xenobiotics including cases involving CCBs and BBs with mixed results. Several mechanisms of action have been proposed for intralipid in the setting of CCB and BB toxicity. Intralipid is thought to favor the uptake of lipophilic medications such as verapamil and propranolol into lipid droplets which results in the redistribution of lipophilic compounds from the tissue to the blood stream. Intralipid has been shown to act as an inotropic agent and promote the use of fatty acids, the hearts preferred energy substrate, during times of cardiac stress where the heart preferentially utilizes carbohydrates (68).

Most of the evidence regarding the use of intralipid in cases of CCB and BB toxicity is from case reports. There are several case reports reporting the use of intralipid with positive outcomes (69,70,71). Intralipid may play a more important role in the setting of overdose from lipophilic medications such as propranolol or verapamil, although it is not considered first line treatment for either BB or CCB toxicity. The use of intralipid is reasonable in the setting of significant, refractory CCB or BB toxicity despite maximum therapies or in the setting of cardiac arrest from presumed CCB or BB overdose, especially when extracorporeal life support such as extracorporeal membrane oxygenation (ECMO) is not readily available (72).

The dosing for intralipid in the setting of CCB and BB toxicity follows the same dosing for local systemic anesthetic toxicity. A bolus dose of 1.5 cc/kg of intralipid is administered over two to 3 minutes. The bolus dose can be repeated every three to 5 minutes for a maximum total dose of 8 cc/kg.

When Should Hemodialysis and Extracorporeal Membrane Oxygenation Be Considered?

Hemodialysis is typically reserved for the removal of xenobiotics with a low volume of distribution and low degree of protein binding. Two beta blockers in particular that can cause severe toxicity that are readily dialyzable include atenolol and acebutolol (73,74). It is reasonable to consider hemodialysis in the setting of refractory hypotension, bradycardia, significant renal impairment, and in the case of sotalol toxicity, recurrent torsades de pointes (75). Due to high volume of distribution, high lipophilicity, and high degree of protein binding of propranolol, verapamil, diltiazem, and amlodipine, hemodialysis is not recommended.

ECMO has been used in cases of both CCB and BB toxicity that are refractory to advanced therapies. Two reviews show that timely initiation of ECMO in the setting of CCB or BB toxicity improves survival to discharge and results in lower mortality (76,77). Initiation of ECMO provides hemodynamic support and oxygen exchange while allowing time for the drug to metabolize. Veno-arterial ECMO is the form most commonly employed

in the setting of cardiovascular drug toxicity, as it provides both cardiac and respiratory support (77). The most common limitation in utilizing ECMO is its limited availability. Adverse effects associated with ECMO include bleeding, development of coagulopathy, sepsis, and limb ischemia (78). In patients who have failed standard and advanced therapies including vasopressors and HDI, it is reasonable to consider ECMO cannulation if readily available.

Table 3 presents pearls regarding the evaluation and management of patients with BB or CCB toxicity.

Conclusions

BB and CCB toxicity can result in significant morbidity and mortality if not recognized and treated in a timely manner. While many BBs and CCBs share similar characteristics, there are important differences within these two drug classes. While almost all BBs and CCBs cause significant bradycardia and hypotension, amlodipine can initially cause a reflex tachycardia due to its vasoplegic properties. Propranolol can cause significant toxicity related to its ability to block sodium channels, and sotalol has the ability to cause significant QTc prolongation and torsades de pointes. The primary components initial treatment include AC, fluids, atropine, and calcium salts. If these initial treatments fail, vasopressors, HDI, or methylene blue can be used depending on the agent and clinical context. If patients are refractory to initial and more advanced therapies, depending on resource availability, intralipid rescue therapy or ECMO should be considered.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Fermin Suarez: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Conceptualization. **Alex Koyfman:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Conceptualization. **Brit Long:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Conceptualization.

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References

1. Shanker V. Essential tremor: diagnosis and management. BMJ 2019;366:l4485 *(Clinical research ed.)*. doi:10.1136/bmj.l4485.
2. Fumagalli C, Maurizi N, Marchionni N, Fornasari D. β-blockers: their new life from hypertension to cancer and migraine. Pharmacol Res 2020;151. doi:10.1016/j.phrs.2019.104587.
3. Fernholz I, Mumm JLM, Plag J, et al. Performance anxiety in professional musicians: a systematic review on prevalence, risk factors and clinical treatment effects. Psychol Med 2019;49:2287–306. doi:10.1017/S0033291719001910.
4. Frishman WH, Saunders E. β-adrenergic blockers. J Clin hypertens (Greenwich Conn,) 2011;13:649–53. doi:10.1111/j.1751-7176.2011.00515.x.
5. Elliott WJ, Ram CV. Calcium channel blockers. J Clin Hypertens (Greenwich Conn,) 2011;13:687–9. doi:10.1111/j.1751-7176.2011.00513.x.
6. Chen PS, Joung B, Shinohara T, Das M, Chen Z, Lin SF. The initiation of the heart beat. Circ J: Off J Jpn Circ Soc 2010;74:221–5.
7. Endo M. Calcium-induced release of calcium from the sarcoplasmic reticulum. Adv Exp Med Biol 2007;592:275–85. doi:10.1007/978-4-431-38453-3_23.
8. Eisner DA, Caldwell JL, Kistamás K, Trafford AW. Calcium and excitation-contraction coupling in the heart. Circ Res 2017;121:181–95. doi:10.1161/CIRCRESAHA.117.310230.
9. Barry WH, Bridge JH. Intracellular calcium homeostasis in cardiac myocytes. Circulation 1993;87:1806–15. doi:10.1161/01.cir.87.6.1806.
10. Levitzki A, Marbach I, Bar-Sinai A. The signal transduction between beta-receptors and adenylyl cyclase. Life Sci 1993;52:2093–100. doi:10.1016/0024-3205(93)90724-h.
11. Goldfine CE, Troger A, Erickson TB, Chai PR. Beta-blocker and calcium-channel blocker toxicity: current evidence on evaluation and management. Eur Heart J Acute Cardiovasc Care 2024;13:247–53. doi:10.1093/ehjacc/zuad138.
12. Pitt B. Diversity of calcium antagonists. Clin Ther 1997;19:3–17. doi:10.1016/s0149-2918(97)80033-1.
13. Gummin DD, Mowry JB, Beuhler MC, et al. 2023 Annual report of the National Poison Data System® (NPDS) from America's Poison Centers®: 41st Annual Report. Clin toxicol (Phila Pa,) 2024;62:793–1027. doi:10.1080/15563650.2024.2412423.
14. Weeke P, Delaney J, Mosley JD, et al. QT variability during initial exposure to sotalol: experience based on a large electronic medical record. Eur: Eur Pacing Arrhythm Card Electrophysiol 2013;15:1791–7. doi:10.1093/europace/eut153.
15. Thomas SH, Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. Br J Clin Pharmacol 2016;81:420–7. doi:10.1111/bcp.12726.
16. Doggrell SA. The membrane stabilizing and beta 1-adrenoceptor

blocking activity of (+)- and (-)-propranolol on the rat left atria. Gen Pharmacol 1990;21:677–80. doi:10.1016/0306-3623(90)91016-k.
17. Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol 2016;81:453–61. doi:10.1111/bcp.12763.
18. J N, Howell JM, Newsome JT, Skibbie DF, Dickerson LW, Henderson KJ. The effect of sodium bicarbonate on propranolol-induced cardiovascular toxicity in a canine model. J Toxicol, Clin toxicol 2000;38:421–8. doi:10.1081/clt-100100952.
19. Donovan KD, Gerace RV, Dreyer JF. Acebutolol-induced ventricular tachycardia reversed with sodium bicarbonate. J Toxicol, Clin Toxicol 1999;37:481–4. doi:10.1081/clt-100102439.
20. Sharifpour A, Sadeghi M, Zakariae Z, Soleymani M. Seizures and irreversible cardiogenic shock following propranolol poisoning: report of 2 cases and literature review. Clin Med Insights, Case rep 2022;15. doi:10.1177/11795476221126981.
21. Spiller HA, Milliner BA, Bosse GM. Amlodipine fatality in an infant with postmortem blood levels. J Med Toxicol: Off J Am Coll Med Toxicol 2012;8:179–82. doi:10.1007/s13181-011-0207-x.
22. Miranda CH, Xavier L, Fiorante F, et al. Cardiac rhythm disturbances associated with amlodipine acute intoxication. Cardiovasc Toxicol 2012;12:359–62. doi:10.1007/s12012-012-9176-9.
23. Gokalp G, Nalbant T, Berksoy E, et al. Is hypoglycemia really observed in pediatric beta-blocker intoxications? A case-control study. Arch Pediatrie: Organe Off Soc Pediatrie 2022;29:56–60. doi:10.1016/j.arcped.2021.10.006.
24. Carnovale C, Gringeri M, Battini V, et al. Beta-blocker-associated hypoglycaemia: new insights from a real-world pharmacovigilance study. Br j Clin Pharmacol 2021;87:3320–31. doi:10.1111/bcp.14754.
25. Kline JA, Raymond RM, Schroeder JD, Watts JA. The diabetogenic effects of acute verapamil poisoning. Toxicol Appl Pharmacol 1997;145:357–62. doi:10.1006/taap.1997.8195.
26. Levine M, Boyer EW, Pozner CN, et al. Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. Crit Care Med 2007;35:2071–5. doi:10.1097/01.ccm.0000278916.04569.23.
27. Welsh LH, Bose JT, Sahhar HS. Calcium channel blocker overdose causes acute Respiratory distress syndrome and acute kidney injury in a 15-year-old female. Cureus 2023;15. doi:10.7759/cureus.43806.
28. 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:e15–21.
29. Majeed H, Khan U, Khan AM, et al. BRASH Syndrome: a systematic review of reported cases. Curr Probl Cardiol 2023;48. doi:10.1016/j.cpcardiol.2023.101663.
30. Farkas JD, Long B, Koyfman A, Menson K. BRASH syndrome: bradycardia, renal failure, AV blockade, shock, and hyperkalemia. J Emerg Med 2020;59:216–23. doi:10.1016/j.jemermed.2020.05.001.
31. Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. Am J Emerg Med 1995;13:444–50. doi:10.1016/0735-6757(95)90137-X.
32. Taboulet P, Cariou A, Berdeaux A, Bismuth C. Pathophysiology and management of self-poisoning with beta-blockers. J Toxicol, Clin Toxicol 1993;31:531–51. doi:10.3109/15563659309025759.
33. Hoegberg LCG, Shepherd G, Wood DM, et al. Systematic review on the use of activated charcoal for gastrointestinal decontamination following acute oral overdose. Clin Toxicol (Phila Pa,) 2021;59:1196–227. doi:10.1080/15563650.2021.1961144.
34. Wax PM, Erdman AR, Chyka PA, et al. beta-blocker ingestion: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila Pa,) 2005;43:131–46.
35. Laine K, Kivistö KT, Laakso I, Neuvonen PJ. Prevention of amlodipine absorption by activated charcoal: effect of delay in charcoal administration. Br J Clin Pharmacol 1997;43:29–33. doi:10.1111/j.1365-2125.1997.tb00029.x.
36. de la Cruz Seoane M, Kapil A, Morello P, Abdelmoneim SS, Gomez S. Triaging the clinical dilemma of a suicidal attempt with Sotalol overdose presenting with ventricular tachycardia, asystole, and Torsades de Pointes. Cureus 2025;17. doi:10.7759/cureus.79006.
37. Gay R, Algeo S, Lee R, Olajos M, Morkin E, Goldman S. Treatment of verapamil toxicity in intact dogs. J Clin Investig 1986;77:1805–11. doi:10.1172/JCI112505.
38. Lüscher TF, Noll G, Stürmer T, Huser B, Wenk M. Calcium gluconate in severe verapamil intoxication. N Engl J Med 1994;330:718–20. doi:10.1056/NEJM199403103301019.
39. Gay R, Algeo S, Lee R, Olajos M, Morkin E, Goldman S. Treatment of verapamil toxicity in intact dogs. J Clin Investig 1986;77:1805–11. doi:10.1172/JCI112505.
40. Yagami T. Differential coupling of glucagon and beta-adrenergic receptors with the small and large forms of the stimulatory G protein. Mol Pharmacol 1995;48:849–54.
41. Fadhlillah F, Patil S. Pharmacological and mechanical management of calcium channel blocker toxicity. BMJ Case Rep 2018;2018. doi:10.1136/bcr-2018-225324.
42. Love JN, Sachdeva DK, Bessman ES, Curtis LA, Howell JM. A potential role for glucagon in the treatment of drug-induced symptomatic bradycardia. Chest 1998;114:323–6. doi:10.1378/chest.114.1.323.
43. Glick G, Parmley WW, Wechsler AS, Sonnenblick EH. Glucagon. Its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta-receptor blockade with propranolol. Circ Res 1968;22:789–99. doi:10.1161/01.res.22.6.789.
44. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: a systematic review. J Toxicol, Clin Toxicol 2003;41:595–602. doi:10.1081/clt-120023761.
45. Sherman JJ, Lariccia JL. Glucagon Therapy: a comparison of current and novel treatments. Diabetes Spectr: Publ Am Diabetes Assoc 2020;33:347–51. doi:10.2337/ds19-0076.
46. Cole JB, Corcoran JN, Engebretsen KM, Stellpflug SJ. Use of a porcine model to evaluate the risks and benefits of vasopressors in propranolol poisoning. J Med Toxicol: Off J Am Coll Med Toxicol 2020;16:212–21. doi:10.1007/s13181-020-00758-8.
47. Holger JS, Engebretsen KM, Fritzlar SJ, Patten LC, Harris CR, Flottemesch TJ. Insulin versus vasopressin and epinephrine to treat beta-blocker toxicity. Clin Toxicol (Phila Pa,) 2007;45:396–401. doi:10.1080/15563650701285412.
48. Katzung KG, Leroy JM, Boley SP, Stellpflug SJ, Holger JS, Engebretsen KM. A randomized controlled study comparing high-dose insulin to vasopressors or combination therapy in a porcine model of refractory propranolol-induced cardiogenic shock. Clin Toxicol (Phila Pa,) 2019;57:1073–9. doi:10.1080/15563650.2019.1580372.
49. 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;62:252–8. doi:10.1016/j.annemergmed.2013.03.018.
50. Shore ET, Cepin D, Davidson MJ. Metoprolol overdose. Ann Emerg Med 1981;10:524–7. doi:10.1016/s0196-0644(81)80008-x.
51. Heath A. Beta-adrenoceptor blocker toxicity: clinical features and therapy. Am J Emerg Med 1984;2:518–25. doi:10.1016/0735-6757(84)90078-0.

52. Richards DA, Prichard BN. Self-poisoning with beta-blockers. Br Med J 1978;1:1623–4. doi:10.1136/bmj.1.6127.1623-c.
53. Strubelt O. Evaluation of antidotes against the acute cardiovascular toxicity of propranolol. Toxicology 1984;31:261–70. doi:10.1016/0300-483x(84)90107-0.
54. Weinstein RS. Recognition and management of poisoning with beta-adrenergic blocking agents. Ann Emerg Med 1984;13:1123–31. doi:10.1016/s0196-0644(84)80337-6.
55. Jang DH, Nelson LS, Hoffman RS. Methylene blue in the treatment of refractory shock from an amlodipine overdose. Ann Emerg Med 2011;58:565–7. doi:10.1016/j.annemergmed.2011.02.025.
56. Cole JB, Lee SC, Prekker ME, Kunzler NM, Considine KA, Driver BE, Puskarich MA, Olives TD. Vasodilation in patients with calcium channel blocker poisoning treated with high-dose insulin: a comparison of amlodipine versus non-dihydropyridines. Clin Toxicol (Phila Pa,) 2022;60:1205–13. doi:10.1080/15563650.2022.2131565.
57. Saha BK, Burns SL. The story of nitric oxide, sepsis and methylene blue: a comprehensive pathophysiologic review. Am J Med Sci 2020;360:329–37. doi:10.1016/j.amjms.2020.06.007.
58. Mayer B, Brunner F, Schmidt K. Inhibition of nitric oxide synthesis by methylene blue. Biochem Pharmacol 1993;45:367–74. doi:10.1016/0006-2952(93)90072-5.
59. Lee KC, Canniff PC, Hamel DW, Pagani ED, Ezrin AM. Cardiovascular and renal effects of milrinone in beta-adrenoreceptor blocked and non-blocked anaesthetized dogs. Drugs Under Exp Clin Res 1991;17:145–58.
60. Travill CM, Pugh S, Noble MI. The inotropic and hemodynamic effects of intravenous milrinone when reflex adrenergic stimulation is suppressed by beta-adrenergic blockade. Clin Ther 1994;16:783–92.
61. Kline JA, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. Crit Care Med 1995;23:1251–63. doi:10.1097/00003246-199507000-00016.
62. Kline JA, Raymond RM, Leonova ED, Williams TC, Watts JA. Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. Cardiovasc Res 1997;34:289–98. doi:10.1016/s0008-6363(97)00022-9.
63. Hsu CH, Wei J, Chen YC, Yang SP, Tsai CS, Lin CI. Cellular mechanisms responsible for the inotropic action of insulin on failing human myocardium. J Heart Lung Transplant: Off Publ Int Soc Heart Transplant 2006;25:1126–34. doi:10.1016/j.healun.2006.05.010.
64. 2nd Yuan TH, Kerns WP, Tomaszewski CA, Ford MD, Kline JA. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol, Clin Toxicol 1999;37:463–74. doi:10.1081/clt-100102437.
65. Isoardi KZ, Chan B, Chiew AL. High dose insulin is an inodilator, not an antidote in the poisoned patient!. Emerg Med Australas: EMA 2025;37. doi:10.1111/1742-6723.70035.
66. Cole JB, Arens AM, Laes JR, Klein LR, Bangh SA, Olives TD. High dose insulin for beta-blocker and calcium channel-blocker poisoning. Am J Emerg Med 2018;36:1817–24. doi:10.1016/j.ajem.2018.02.004.
67. Ok SH, Hong JM, Lee SH, Sohn JT. Lipid emulsion for treating local anesthetic systemic toxicity. Int J Med Sci 2018;15:713–22. doi:10.7150/ijms.22643.
68. Walter E, McKinlay J, Corbett J, Kirk-Bayley J. Review of management in cardiotoxic overdose and efficacy of delayed intralipid use. J Intensive Care Soc 2018;19:50–5. doi:10.1177/1751143717705802.
69. Thompson AM, Franco Palacios CR, Henriksen MN. Intravenous lipid emulsion and high-dose insulin as adjunctive therapy for propranolol toxicity in a pediatric patient. Am J Health-Syst Pharm: AJHP: Off J Am Soc Health-Syst Pharm 2016;73:880–5. doi:10.2146/ajhp150594.
70. 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:e56–60. doi:10.1002/phar.1579.
71. French D, Armenian P, Ruan W, et al. Serum verapamil concentrations before and after Intralipid® therapy during treatment of an overdose. Clin Toxicol (Phila Pa,) 2011;49:340–4. doi:10.3109/15563650.2011.572556.
72. Gosselin S, Morris M, Miller-Nesbitt A, et al. Methodology for AACT evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. Clin Toxicol (Phila Pa,) 2015;53:557–64. doi:10.3109/15563650.2015.1052498.
73. Rooney M, Massey KL, Jamali F, Rosin M, Thomson D, Johnson DH. Acebutolol overdose treated with hemodialysis and extracorporeal membrane oxygenation. J Clin Pharmacol 1996;36:760–3. doi:10.1002/j.1552-4604.1996.tb04247.
74. Saitz R, Williams BW, Farber HW. Atenolol-induced cardiovascular collapse treated with hemodialysis. Crit Care Med 1991;19:116–18. doi:10.1097/00003246-199101000-00026.
75. Bouchard J, Shepherd G, Hoffman RS, et al. Extracorporeal treatment for poisoning to beta-adrenergic antagonists: systematic review and recommendations from the EXTRIP workgroup. Crit Care (Lond Engl) 2021;25:201. doi:10.1186/s13054-021-03585-7.
76. Masson R, Colas V, Parienti JJ, et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation 2012;83:1413–17. doi:10.1016/j.resuscitation.2012.03.028.
77. Finn D, Stevens J, Tolkacz M, Robinson J, Mangla J, Iacco A. Calcium channel blocker overdose: what role does extracorporeal membrane oxygenation have in support? A systematic review of the literature. ASAIO J (Am Soc Artif Intern Organs: 1992) 2024;70:404–8. doi:10.1097/MAT.0000000000002129.
78. Zangrillo A, Biondi-Zoccai G, Landoni G, et al. Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. Crit Care (Lond Engl) 2013;17:R30. doi:10.1186/cc12512.

Article Summary

1. Why is this topic important?

BB or CCB toxicity is associated with high rate of morbidity and mortality.

2. What does this review attempt to show?

This review provides an evidence-based overview of managing the patient with BB or CCB toxicity.

3. What are the key findings?

Patients with BB or CCB toxicity typically present with hypotension, though other findings may be present depending on the specific medication. Management includes fluids, atropine, calcium, and GI decontamination with activated charcoal in appropriate patients. However, those with more severe toxicity require vasopressors and high-dose insulin, and intralipid and extracorporeal membrane oxygenation may be necessary in cases of refractory toxicity despite maximal therapy.

4. How is patient care impacted?

Emergency clinicians should have an understanding of BB and CCB toxicity.