






# Calcium Channel Blocker Toxicity: A Practical Approach

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**Abstract:** Calcium channel blockers (CCBs) are widely prescribed medications for various clinical indications in adults and children. They are available in both immediate and long-acting formulations and are generally classified into dihydropyridines and nondihydropyridines, with nondihydropyridines having more cardioselectivity. CCB toxicity is common given the widespread use which leads to serious adverse clinical outcomes, especially in children. Severe CCB toxicities may present with life-threatening bradycardia, hypotension, hyperglycemia, and renal insufficiency. Dihydropyridine toxicity, however, may present with reflex tachycardia instead of bradycardia. Initial patient evaluation and assessment are crucial to identify the severity of CCB toxicity and design the best management strategy. There are different strategies to overcome CCB toxicity that requires precise dosing and close monitoring in various patient populations. These strategies may include large volumes of IV fluids, calcium salts, high insulin euglycemia therapy (HIET), and vasopressors. We hereby summarize the evidence behind the management of CCB toxicity and present a practical guide for clinicians to overcome this common drug toxicity.

**Keywords:** calcium channel blockers, drug overdose, poisoning, emergency medicine, toxicity

## Introduction

Calcium channel blockers (CCBs) are commonly prescribed medications to treat various medical conditions, including hypertension, supraventricular tachycardia, vasospasm, and migraine headaches.<sup>1,2</sup> The widespread use of CCBs has contributed to the increase in intentional and accidental overdoses that are linked to lethal consequences as a result of cardiovascular collapse.<sup>3</sup> The lack of standardized guidelines to manage CCB toxicity and the unfamiliarity of CCB toxicity management among health care providers, cases of CCB toxicity can go unrecognized. This can lead to delays in life-saving treatments and an increased risk of mortality.<sup>3</sup> This review paper aims to provide a practical comprehensive management approach to guide providers caring for patients with CCB overdose.

## Epidemiology

According to a 2020 report by the American Association of Poison Control Centers' National Poison Data System (NPDS), 6132 CCBs single exposures were reported in the United States (US), 1159 of which occurred in children five years or younger.<sup>3</sup> This has resulted in 101 major adverse outcomes and 45 cases of death. Unintentional ingestion was the most common cause of exposure and accounted for almost 84% of all overdose cases, whereas intentional ingestion accounted for 12.5%. According to the Danish Poison Information Center (DPIC) data from 2009 to 2014, the age distribution of CCB exposure suggests increased exposure in young preschool children (20%) as well as in adults 40–80 years.<sup>4</sup> The majority of CCB exposures happened in females in the >16 years age group (61%), whereas more males were exposed in the children <16 years age group (56%). The

majority of the cases (81%) required hospital admission, with a 2% 30-day mortality rate mainly occurring in adults with suicidal exposure.<sup>4</sup>

## Overview of CCBs

CCBs are classified into two main clinical categories based on their physiological effects: *dihydropyridines* (eg, amlodipine, nifedipine, felodipine, nicardipine) and *non-dihydropyridines* (eg, verapamil and diltiazem).<sup>5</sup> *Dihydropyridines* have a greater affinity for peripheral vascular smooth muscle cells, while *nondihydropyridines* have a greater affinity for cardiomyocytes.<sup>5</sup> CCBs exert their pharmacological effect by inhibiting the alpha-1 subunit of L-type voltage-gated calcium channels leading to the prevention of calcium influx intracellularly required for myocardial, vascular, and GI smooth muscle contraction.<sup>5</sup> This, in turn, results in the relaxation of vascular smooth muscles leading to vasodilation and hypotension, myocardial depression resulting from excessive negative inotropy, bradycardia resulting from negative chronotropy, and atrioventricular node blockade due to negative dromotropy.<sup>5</sup> In addition, CCBs also inhibit L-type calcium channels in pancreas Islet cells, leading to a reduction in insulin secretion, hyperglycemia, and reduced cardiac glucose utilization.<sup>6,7</sup> The drop in blood pressure due to CCB toxicity is a result of a combination of factors such as negative myocardial inotropy and chronotropy as well as peripheral vasodilation.<sup>6–9</sup>

At therapeutic doses, CCBs maintain selectivity to certain tissues.<sup>10</sup> However, at toxic doses, CCBs lose their degree of selectivity resulting in potentially life-threatening bradycardia, hypotension, hyperglycemia, and renal insufficiency.<sup>10</sup> Unique hemodynamic outcomes have been observed with nifedipine and other dihydropyridine overdoses resulting in reflex tachycardia.<sup>11</sup> In an animal study, nifedipine at moderate levels of toxicity exerted less effect on the atrioventricular conduction than diltiazem and verapamil, resulting in tachycardia with preserved cardiac output.<sup>12</sup> Reflex tachycardia with dihydropyridines is common but may still exist concomitantly with cardiogenic shock.<sup>13</sup>

## CCBs Pharmacokinetic

Identifying the CCB type, dose, formulation, and time of ingestion is imperative in understanding their toxicokinetic and pharmacokinetic profiles, leading to early detection of CCB intoxication and planning a rapid proactive management plan. The oral route is the mainstay of CCB administration. They are available as immediate-release (IR), extended-release (ER), and sustained-release (SR) tablet and capsule formulations. Both types of CCBs are absorbed orally well and undergo extensive hepatic first-pass metabolism through Cytochrome P450 enzymes (CYPs).<sup>14</sup> Use of CYP inhibitors, such as macrolide antibiotics or grapefruit juice, increases diltiazem, felodipine, nicardipine, nifedipine, and nisoldipine bioavailability.<sup>15,16</sup> Table 1 provides some examples of drug–drug interactions with CCBs that are of clinical significance.<sup>17,18</sup> CCBs are lipophilic molecules, highly protein-bound, and utilize a large volume of distribution.<sup>19</sup> At higher doses, the rate of CCB clearance decreases, leading to a prolonged half-life due to hepatic clearance change from first-order to zero-order kinetics due to CYPs saturation.<sup>5</sup> The absorption rate and duration of toxicity are unpredictable with the use of ER formulations.<sup>20–22</sup>

The onset of action and elimination half-life varies between CCBs. For instance, nifedipine, verapamil, and diltiazem have shorter onset of action with IR formulations ranging between 0.5–2 hours. Furthermore, their elimination half-life ranges from 2–7 hours. On the other hand, as a second-generation CCB, amlodipine has a slower onset (6–12 hours) and longer half-life (30–50 hours). The variability in CCBs pharmacodynamics adds to the challenging nature of managing CCB toxicity. Table 2 summarizes the pharmacokinetics of most prescribed CCB agents.<sup>23–27</sup>

## Evaluation

Given the high risk of morbidity and mortality and the nonspecific presentations of CCB toxicity, healthcare providers are urged to suspect CCB toxicity in potential toxicity cases such as presentation with hypotension plus bradycardia that may be associated with unexpected hyperglycemia, particularly in patients prescribed CCBs for medical uses. The presentation may vary from asymptomatic to nonspecific symptoms such as dizziness, fatigue, and lightheadedness, with severe toxicities associated with a rapid decline in mental status, cardiac arrest, and death.<sup>10</sup> Healthcare providers must be familiar with the risk factors (eg, children and old patients, patients prescribed CCBs, history of suicidal attempts, alcohol abuse) and early signs of CCBs toxicity.<sup>3</sup> Clinicians must carefully evaluate the patient's history and be proactive to exclude any other potential differential diagnosis. Patient age, weight, past medical history, type of CCB ingested, time since CCB ingestion, and other co-ingested cardiovascular

**Table I** Examples of Common Drug–Drug Interactions with CCBs

<b>Mechanism of Interaction</b>	<b>Interacting Medications</b>
<b>Induction of CYP3A isoenzyme (Higher doses of CCBs maybe needed)</b>	Carbamazepine
	Oxcarbazepine
	Phenytoin
	Barbiturates
	Nevirapine
	Rifampicin
	Pioglitazone
<b>Inhibition of CYP3A isoenzyme (Lower doses of CCBs maybe needed)</b>	Cimetidine
	Erythromycin
	Clarithromycin
	Azole antifungals
	HIV-protease inhibitors
	Grapefruit juice
<b>CYP3A isoenzyme inhibition by verapamil and diltiazem (Lower doses of interacting medication maybe needed)</b>	Ciclosporin
	Statins
	Benzodiazepines
	Buspirone
	Sildenafil
<b>P-glycoprotein inhibition by verapamil and diltiazem (Lower doses of interacting medication maybe needed)</b>	Digoxin
	Ciclosporin
	Fexofenadine
	Daunorubicin
	Doxorubicin
	Etoposide
	Vinca alkaloids
<b>Added antihypertensive effects</b>	All antihypertensive medications
<b>Added negative chronotropic effects</b>	Digoxin
	Beta blockers
	Amiodarone
<b>Added negative inotropic effects</b>	Beta blockers
	Flecainide

**Abbreviation:** CCBs, calcium-channel blockers.

medications are essential to the diagnosis and management process. CCB toxicity can be suspected if the amount of CCB ingested exceeds the maximum therapeutic dose. Toxicity symptoms resulting from IR formulation ingestion are expected within 3 hours of ingestion, while ER formulation ingestions may take up to 16 hours.<sup>10</sup>

**Table 2** Summary of the Pharmacokinetics of Commonly Prescribed CCB Agents

Medication	Usual Adult Daily Dose (mg)	Absorption (%)	Bioavailability (%)	Protein Binding (%)	Terminal Half-Life (hr)
Verapamil	120–480	90	20–35	90	2.8–7.4
Diltiazem	120–540	95	40	70–80	3–4.5
Amlodipine	2.5–10	100	64–90	93	30–50
Nicardipine	20–40	100	35	>95	8.6
Felodipine	2.5–10	100	20	>99	11–16

Children may present with non-specific signs such as vomiting, lethargy, hypotension followed by an altered level of consciousness (LOC), respiratory distress, and hypovolemic shock.<sup>28</sup> Although the case presentation of CCB ingestion is rarely specific to the type of CCB ingested, non-dihydropyridines overdose usually presents with more severe symptoms, such as hypotension, bradycardia, jugular vein distention (JVD), altered LOC, electrocardiogram (ECG) changes, and worsening hyperglycemia.<sup>29,30</sup> Distributive shock can be suspected in patients with early signs of shock such as bounding pulses and warm extremities; thus, these signs should not be underestimated. Signs of pulmonary edema might be present, especially in delayed cases where patients delay seeking medical help. Anticipatory guidance should cover measures and precautions to prevent future accidental ingestions, such as using childproof medication caps and keeping medication in safe cabinets. Counseling on early signs of toxicity, medication safety, and best medication storage practices for patients taking CCBs is a logical preventative step, especially in high-risk areas.

## Initial Work-Up

All patients with suspected CCB toxicity need to be monitored by cardiopulmonary monitors. Two peripheral intravenous lines are to be established, followed by preparation for central-line insertion when indicated.<sup>31</sup> Asymptomatic patients who ingested a toxic amount of CCB (greater than the therapeutic range listed in Table 2) need to be observed and monitored for 24 hours before hospital discharge.<sup>32</sup> To determine the severity of toxicity and monitor response to therapy, blood gases, serum lactate, electrolytes, blood glucose, and renal function will need to be checked and monitored regularly.<sup>32</sup> Serum levels of specific CCB agents are not widely reported. Hyperglycemia, secondary to inhibition of insulin release, is expected to occur more with diltiazem and verapamil than with amlodipine, and can be helpful in determining the severity of CCB toxicity.<sup>32–34</sup> Serum electrolytes such as potassium and calcium are expected to be low. Arterial blood gases will indicate the degree of metabolic acidosis and determine the need for sodium bicarbonate supplements in severe cases.<sup>35</sup> Paracetamol is a common co-ingested medication for intentional CCB toxicity; hence obtaining serum paracetamol levels is recommended.<sup>36</sup> Monitoring the Mean Arterial Pressure (MAP) to determine the response to fluid resuscitation (>65 mmHg, PH <6.7) is also recommended.<sup>37</sup> Assessment of cardiac functions using Echocardiogram (Echo) and ECG is indicated for symptomatic patients since the toxicokinetic of CCB can be unpredictable.<sup>32</sup> CCB toxicity is associated with common ECG findings, such as sinus bradycardia, atrioventricular blocks, QT prolongation, and junctional rhythms. Therefore, 12-lead ECG monitoring is required to identify arrhythmias and conduction disturbances.<sup>5</sup> For example, toxicity due to non-dihydropyridines such as verapamil presents with hypotension, bradycardia, AV and bundle branch block, QT prolongation, and junctional rhythm, while toxicity with dihydropyridine CCBs such as nifedipine may present with reflex sinus tachycardia. Referral to cardiology and toxicology services is necessary as soon as the patient has been initially stabilized. A poison control center may also be contacted if available.

## Management of CCBs Toxicity

Although multiple treatment approaches have been utilized to reverse CCB toxicity, there is no consensus on a gold-standard treatment approach (Table 3). Traditionally, healthcare professionals treat based on basic findings, such as

**Table 3** Common Monitoring Parameters for Selected Reversal Agents

<b>Treatment</b>	<b>Monitoring Parameter</b>
<b>Atropine</b>	<ul style="list-style-type: none"> <li>- Heart rate</li> <li>- Blood pressure</li> <li>- Pulse oxygenation</li> <li>- Mental status</li> </ul>
<b>Calcium</b>	<ul style="list-style-type: none"> <li>- Vital signs</li> <li>- Electrocardiograph</li> <li>- Serum calcium</li> </ul>
<b>Insulin</b>	<ul style="list-style-type: none"> <li>- Electrolytes</li> <li>- Blood glucose</li> <li>- Mean arterial pressure</li> <li>- Hypersensitivity and allergic reactions</li> </ul>
<b>Norepinephrine</b>	<ul style="list-style-type: none"> <li>- Blood pressure every 2 minutes until desired hemodynamic effect, and every five minutes for duration of infusion after desired effect is achieved</li> <li>- Cardiac function</li> <li>- Changes to skin of extremities</li> <li>- Signs of extravasation</li> </ul>
<b>Epinephrine</b>	<ul style="list-style-type: none"> <li>- Blood pressure (or mean arterial pressure)</li> <li>- Heart rate</li> <li>- Cardiac output (as appropriate)</li> <li>- Intravascular volume status</li> <li>- Pulmonary capillary wedge pressure (as appropriate)</li> <li>- Urine output Peripheral perfusion Infusion site</li> </ul>
<b>Dobutamine</b>	<ul style="list-style-type: none"> <li>- Electrocardiograph</li> <li>- Blood pressure (or mean arterial pressure)</li> <li>- Heart rate</li> <li>- Pulmonary wedge pressure</li> <li>- Cardiac output</li> <li>- Electrolytes (ie, potassium)</li> </ul>
<b>Glucagon</b>	<ul style="list-style-type: none"> <li>- Blood glucose</li> </ul>
<b>Lipid emulsion</b>	<ul style="list-style-type: none"> <li>- Allergic reactions</li> <li>- Triglycerides levels</li> <li>- Monitor for pancreatitis</li> </ul>
<b>Methylene blue</b>	<ul style="list-style-type: none"> <li>- Electrocardiograph</li> <li>- Serotonin syndrome</li> <li>- Anaphylaxis</li> <li>- Vital signs</li> <li>- Toxicity in patients with renal/hepatic impairment</li> </ul>
<b>Dialysis</b>	<ul style="list-style-type: none"> <li>- Blood pressure</li> <li>- Electrolytes</li> <li>- Coagulopathy</li> <li>- Drug serum level</li> </ul>
<b>ECMO</b>	<ul style="list-style-type: none"> <li>- Heart rhythm</li> <li>- Mean arterial pressure</li> <li>- Blood flow</li> <li>- Gas exchange</li> </ul>

patients' specific hemodynamics and neurological status. Furthermore, literature is scarce and mostly based on case reports, recommendations from poison control centers, toxicologists, and published reports from concerned medical organizations. Overall, managing CCB toxicity is a resource-draining process due to patients being frequently ill and requiring close monitoring with resource-intensive therapies. Cardiopulmonary monitoring, adequate cardiopulmonary resuscitation, and preparing for advanced cardiac life support remain the mainstay of therapy for CCB toxicity.<sup>9,38</sup> However, there are some common recommendations that can be utilized to provide options to maximize hemodynamic outcomes for CCB toxicity victims. Figure 1 attempts to present a rational algorithm to aid healthcare providers in making the best decision. Dosing, desired effects, and adverse reactions are presented in (Table 1).

### Airway and Breathing

Clinicians are urged to maintain close monitoring of cardiac and respiratory functions in CCB-poisoned patients. Providers should also consider endotracheal intubation in high-risk patients with hemodynamic instability. Induction agents can change the positive ventilation and exacerbate the hemodynamic stability of the patient due to loss of sympathetic tone. As such, the treatment of hypotension should be addressed first before attempting rapid sequence intubation (RSI). Both etomidate (0.3 mg/kg) and ketamine (1 mg/kg) possess the same concern for hemodynamic compromise.<sup>39</sup> Succinylcholine (1.5 mg/kg) should be avoided in patients with hyperkalemia or at risk of hyperkalemia and malignant hyperthermia. Rocuronium is generally used when succinylcholine is not available or contraindicated. Due to the activation of the autonomic respiratory center, patient-ventilator asynchrony is a potential problem in mechanically

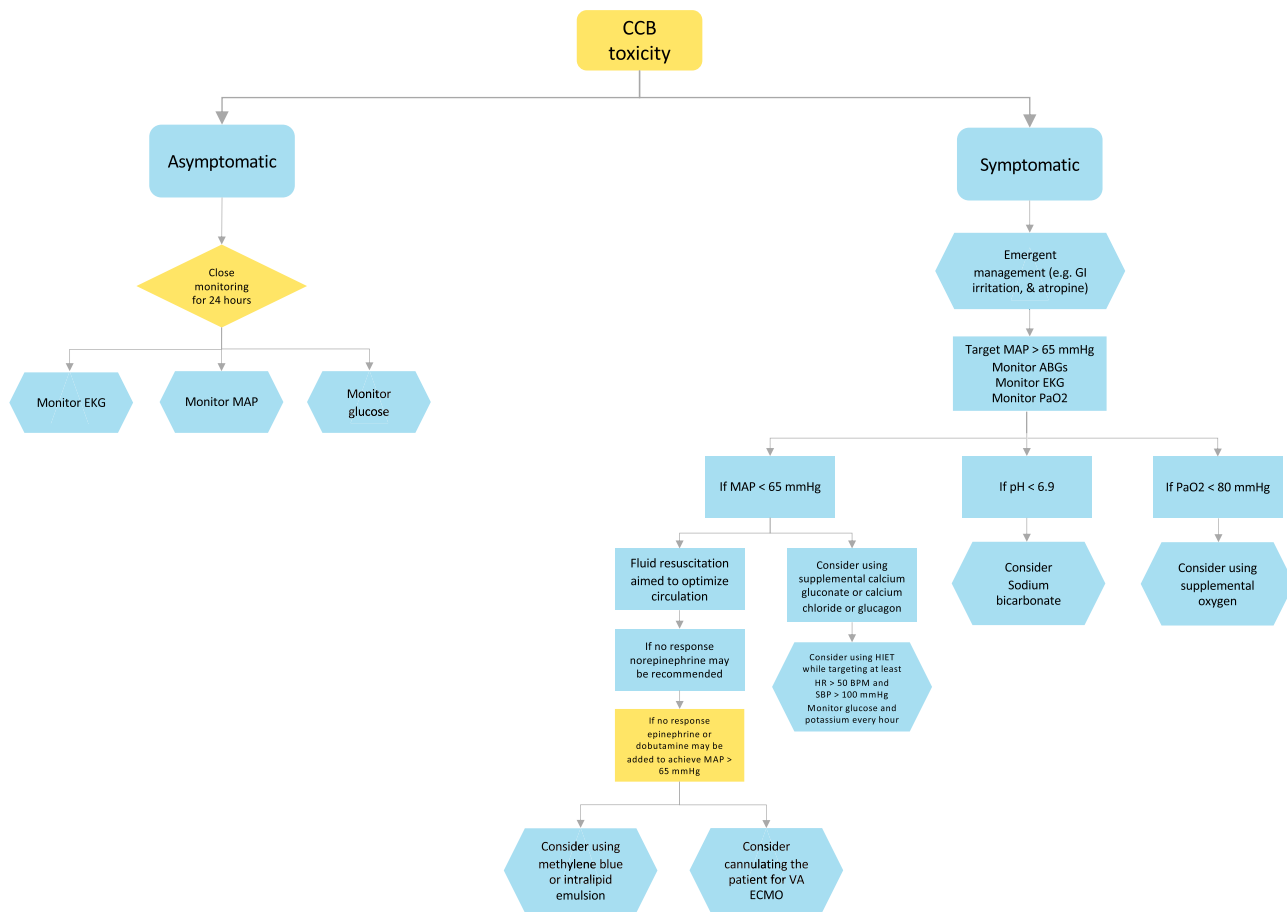


Figure 1 Algorithmic structure for managing patients with calcium channel blocker toxicity.

**Abbreviations:** CCB, calcium channel blocker; EKG, electrocardiogram; MAP, mean arterial pressure; GI, gastrointestinal; ABGs, arterial blood gases; PaO2, partial pressure of oxygen; HIET, high insulin euglycemia therapy; HR, heart rate; BPM, beat per minute; SBP, systolic blood pressure; VA, venous arterial; ECMO, extracorporeal membrane oxygenation.

ventilated patients with CCB toxicity.<sup>40</sup> Such factors need to be taken into consideration when setting the ventilator to a rate to achieve adequate oxygenation.

## Circulation

The use of intravenous crystalloid bolus (1–2 liters) is the mainstay treatment for hypotensive patients. Monitoring of fluid overload and pulmonary edema is encouraged.<sup>33</sup> If hypotension persists, the use of vasopressor agents is warranted.<sup>32</sup>

## Gastrointestinal (GI) Decontamination

GI decontamination as a modality is rarely done in the emergency department, given the clinical applicability and time for the administration. GI decontamination should be considered within the first 1–2 hours post-ingestion of CCBs. Patients who ingest extended-release formulations may benefit from late GI decontamination (>2 hours). Use of this method is not recommended for hemodynamically unstable patients.<sup>41,42</sup> Neurological and respiratory status should be assessed to prevent aspiration. GI decontamination can be done via orogastric lavage, whole-bowel irrigation (WBI), or administration of activated charcoal (AC). Orogastric lavage with a No. 36 to 40 French tube (24 to 28 for children) is a complex procedure that is rarely performed and may exacerbate the hemodynamic status of the patient due to vagal stimulation. Thus, clinicians should weigh the risk before proceeding with this approach.<sup>43</sup> WBI is done by administering a large volume of polyethylene glycol solution (2 L per hour for adults, up to 500 mL per hour in children) orally or via a nasogastric tube to flush drugs out of the gastrointestinal tract. Studies showed that WBI might be a good treatment option for ER CCB-related toxicity unless the patient is hemodynamically unstable or has an ileus.<sup>5,44,45</sup> AC prevents absorption of ingested CCB and is generally considered safe and effective if administered within 4 hours of ingestion.<sup>46</sup> Although AC is more effective if administered within 1–2 hours after CCB ingestion, late administration offers some benefits that should not be disregarded. Similar findings were reported with Amlodipine toxicity among 32 healthy adults.<sup>47</sup> When immediately taken following IR verapamil ingestion, AC was remarkably effective in preventing the absorption of verapamil in the GI tracts by 99%; however, when administered 2 hours later, no significant changes were observed. Following SR verapamil ingestion, immediate AC administration reduced verapamil absorption by 86%; however, when administered 4 hours later, only 32% of absorption was reduced.<sup>46</sup> AC is given as a single dose of 1 g/kg for children and up to 100 g in adults, and it should be given for asymptomatic and symptomatic CCB-poisoned patients. Flavored beverages can be used to enhance patient compliance. For intubated patients, dilution in 0.25 water: 1 activated charcoal is warranted with the use of a large bore nasogastric (NG) tube (eg, 10–14 French gauge). Monitoring the GI tract for bowel sounds, abdomen distention, tenderness, vomiting, and fever to rule out perforation or obstruction is imperative. AC should be held if bowel sounds disappear.

## Atropine

Atropine may be administered to patients with symptomatic bradycardia after significant CCB exposure.<sup>11</sup> Patients have various responses following the atropine administration. In a prospective case series among patients with CCB toxicity, two out of eight patients responded to atropine administration.<sup>8</sup> Atropine is given in 0.5 to 1 mg IV dose every two to three minutes for adults and 0.02 mg/kg for pediatric patients.

## Calcium Infusion

IV calcium administration increases blood pressure, either due to an increase in cardiac output or by increasing systemic vascular resistance. Alone, calcium has not been proven an effective first-line treatment for CCB toxicity in severe cases, but rather a temporary supportive measure until inotropic agents can be administered.<sup>9</sup> Calcium can be given as calcium chloride (CaCl) or calcium gluconate. IV calcium has a rapid onset of action, but the exact dose–response relationship remains unclear. CaCl has three times as much elemental calcium as calcium gluconate; however, its administration can cause tissue necrosis if extravasation occurs. Ideally, it should be administered via a central line. If calcium chloride is used, infusing through a central venous catheter may minimize irritation. Infusion over 5 minutes to prevent hypotension, ventricular fibrillation, and AV dissociation is recommended. If the patient did not experience cardiac arrest and access to the central line has not been established, calcium gluconate can be utilized as an alternative. The initial dose is typically 10 to 20 mL of 10% solution of CaCl or 30 mL of 10% solution calcium gluconate every 10 minutes. A repeated dose

every 20 minutes is recommended if the clinical response is inadequate.<sup>48</sup> Due to the transient nature of calcium administration, a high dose continuous infusion of calcium (0.5 mEq/kg/hr) titrated to the clinical effect has been reported in the literature with various degrees of success.<sup>13,49,50</sup> Target dose should be titrated to achieve serum ionized calcium levels of 1.5 the normal upper limit (13–15 mg/dl), or until hemodynamics such as blood pressure or contractility have improved.<sup>35</sup> With calcium being widely used to manage CCB toxicity, reports of various adverse effects urged clinicians to opt for other modes of intervention.<sup>5</sup> Thus, monitoring ECG before and after starting calcium is recommended. In addition, calcium needs to be monitored closely (every 20 minutes) during therapy. Fatal iatrogenic hypercalcemia was reported at a calcium level of 32.3 mg/dl.<sup>51</sup>

## High-Dose Insulin Euglycemia Therapy (HIET)

HIET works by several mechanisms in the management of CCB toxicity.<sup>37</sup> When utilized at ten times that of a normal antidiabetic dose, HIET produces positive inotropic effects by enhancing vascular dilation, increasing cardiac output and blood pressure, and enhancing intracellular transport of glucose into myocardial cells.<sup>37</sup> In addition, HIET helps with reducing the infusion requirements of catecholamines and hemodynamic instability as it has no effect on heart rate.<sup>37</sup> Before starting HIET, finger stick blood glucose and basic metabolic panel (BMP) should be checked. Concomitant D-glucose infusion (50 mL of D50W solution for adults and 0.25 g/kg of D25W for children) may be required for patients with serum glucose greater than 200 mg/dL to prevent hypoglycemia. Dextrose 70% can also be utilized to concentrate fluids.<sup>52</sup> Thus, administration via a central line is required as vein irritation from dextrose infusion is common if infused peripherally. Serum electrolytes should be monitored hourly for hyponatremia (after a high dose of dextrose is given), hypokalemia, hypophosphatemia, and hypomagnesemia. It is suggested that mild hypokalemia may prolong action potential and facilitates calcium entry during systole. This can strengthen the inotropic effect of insulin. Supplemental potassium might not be added until potassium goes below 2.8–3.0 meq/l.<sup>37</sup> HIET starts with a bolus dose of 1 unit/kg of regular insulin followed by an infusion of 1 unit/kg/hr. Based on animal data, increased insulin doses were associated with increased cardiac output.<sup>53</sup> In addition, HIET was found to be more effective for mono and multi-drug toxicity (animal models) than using catecholamine or glucagon alone. HIET is also effective in dihydropyridine poisoning.<sup>54</sup> Serum glucose should be checked 30 minutes after HIET for the first 4 hours of therapy and hourly after that, while venous blood gas needs to be checked at least 4–6 times hourly during the initial 24–48 hours of therapy. Regardless of high doses of HIET, hyperglycemia can occur, which points to the severity of CCB poisoning. There is limited consensus in the literature on when HIET can be discontinued. The therapeutic target for treatment should be a heart rate of 50 bpm or higher and a systolic blood pressure of 100 mmHg.<sup>55</sup> In addition, HIET should be weaned slowly (up to multiple days after initiation) since abrupt withdrawal has been associated with a rebound CCB toxicity effect. Hemodynamic parameters should be evaluated every 15–20 minutes to monitor the response to therapy.

Despite the evidence supporting HIET utility in CCB toxicity in adults, less is known regarding HIET utility in CCB toxicity in pediatric patients.<sup>28</sup> Positive results from several case reports have been published.<sup>7,56</sup> For cases where HIET was not effective, treatment failure has been attributed to late administration of HIET, multi-drug toxicity, inadequate dosing, and lack of consistent dosing and duration in the pediatric population. Despite the expert recommendation of titration of insulin for doses up to 10 units/kg/hr for refractory patients, a stepwise approach is still being observed due to concerns of volume overload and worsening vasodilation. The rationale for HIET should be thoroughly explained to medical and nursing staff as the unprecedented high doses of insulin required might not be given under the suspicion of drug error by the staff, leading to hemodynamic deterioration and death. Order sets with suggested insulin rates can be utilized to prevent delays in therapy. Close monitoring of serum glucose is essential until the first 24 hours after HIET initiation passes, as serum insulin levels are expected to remain high after insulin withdrawal. Psychiatric referral may be indicated in cases of intentional CCB ingestion once the patient has been stabilized.

## Inotropes and Vasopressors

In patients with suspected CCB toxicity, peripheral vasodilation, cardiac depression, and conduction abnormalities are expected.<sup>32</sup> The use of vasopressors is recommended to restore hemodynamic stability. No specific vasopressor is superior to another, and the selection of the agent should be guided by the type of shock observed in the patient.



Epinephrine increases HR, contractility, and BP through stimulation of  $\beta_1$  and  $\alpha_1$  adrenergic receptors simultaneously. Norepinephrine increases BP by acting predominantly on the  $\alpha_1$  adrenergic receptors. Dobutamine, on the other hand, increases HR and contractility through the stimulation of  $\beta_1$  receptors.

Epinephrine and Dobutamine are recommended in the presence of cardiogenic shock, while norepinephrine is recommended in vasogenic shock. Neither dopamine nor vasopressors alone are generally recommended for CCB toxicity due to poor clinical outcomes.<sup>32</sup> Ideally, vasopressor and HIET should be started simultaneously with close monitoring of the patient's hemodynamic status. If there is only one access line available in the setting of hypotension, a vasopressor should be started first. Local protocols should be followed for the initial vasopressor rate. Despite their metabolic side effects, CCB toxicity may require higher doses of vasopressors with the goal of improving tissue perfusion. Finally, the outcome of inotrope therapy in CCB toxicity remains unpredictable.<sup>57</sup>

## Glucagon

The role of glucagon in the management of CCB toxicity is diminished and only based on low-quality evidence consisting of case reports and animal studies.<sup>5</sup> The 2017 Critical Care Medicine Experts Consensus recommends against the use of glucagon because of the variable effects and noticeable vomiting and hyperglycemia seen in several case reports.<sup>32</sup>

## Lipid Emulsions Therapy (LET)

LET has been used to reduce the toxicity of several lipophilic medications, including the non-dihydropyridine, Verapamil. However, LET should be reserved for patients unresponsive to first-line treatments, patients with refractory shock, and poly-drug toxicity.<sup>32</sup> Although the LET mechanism is not fully understood; it is thought to reverse the cardiovascular effects of lipophilic drugs by a lipid sink phenomenon, where the emulsion creates a lipid phase that draws the drug from blood – lower concentration – away from the heart and other tissues – higher concentration – by the concentration gradient, and by increasing intramyocyte calcium levels causing a positive inotropic effect.<sup>58</sup> The usual dose is an IV bolus of 100 mL (1.5 mL/kg) of intralipid 20%. The dose can be repeated every 5–10 minutes for at least three doses. The benefit-to-risk ratio should be assessed, especially in cases of patients with known severe egg allergies, since lipid-emulsion formulations may contain egg-derived phospholipids.<sup>59</sup> Lipid emulsions that only have long-chain fatty acids (Intralipid 20% and Lipovenoes 20%, for example) are preferred over the mixed medium-chain and long-chain fatty acids in terms of resuscitating the CCB toxicity.<sup>60</sup> LET is well studied in animal models; however, many case reports and case series showed benefits in patients with CCB toxicity.<sup>61,62</sup> In addition, reports of LET use in children <15 years of age are lacking. Caution should be taken to collect all blood samples before starting the infusion, as LET increases blood viscosity and results in difficulties in analyzing blood biochemistry. This is especially seen in serum magnesium and glucose laboratory values. In addition, monitoring of liver and kidney functions, as well as triglyceride levels is indicated. Finally, monitoring the response of LET should include signs of recurrent or delayed toxicity due to the possibility of enhanced absorption and delayed adverse effects.

## Methylene Blue (MB)

MB should be preserved for vasoplegic shock refractory to first-line therapies.<sup>63</sup> While amlodipine activates the endothelial nitric oxide synthase leading to increased nitric oxide production and vasodilation,<sup>64</sup> MB induces vasoconstriction through the inhibition of guanylate cyclase, which decreases cGMP resulting in nitric oxide inhibition.<sup>65</sup> A standard dose of MB for refractory vasoplegic shock has not been established.<sup>9,66,67</sup> MB results in a relatively rapid hemodynamics improvement as it reaches its peak effect within 5 minutes after infusion and reaches a steady state after 4 hours of administration.<sup>68,69</sup> Generally, MB is safe as adverse effects rarely happen with doses below 2mg/kg. Common adverse effects include dizziness, headache, nausea, and blue discoloration of the skin, urine, and saliva during the first 24 hours of therapy.<sup>70</sup> MB causes irritation to the vein in which the drug is being administered; therefore, the IV line should be flushed with normal saline. In addition, a history of antidepressant use has to be identified as drug–drug interactions resulting in serotonin toxicity might be expected. MB is not commonly used in children, and its use is contraindicated in patients with severe renal failure, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or

methemoglobin reductase deficiency. Due to the risk of hemolysis, it is recommended to check blood cell count if multiple doses are to be administered.

## Dialysis

CCBs are characterized by their high protein-binding capacity, which minimizes their ability to dialyze them in cases of severe CCB toxicity.<sup>71</sup> The EXTRIP workgroup has concluded that the risks and costs associated with extracorporeal treatments (ECTRs) in the management of CCB poisoning outweigh any potential benefits.<sup>71</sup> The ECTRs could increase the overall clearance of CCBs by 5–10%, which is unlikely to have any significant benefits in overcoming severe CCBs toxicity (ie, amlodipine, diltiazem, verapamil). Therefore, the use of ECTRs should be discouraged.

## Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation is an invasive hemodynamic rescue therapy that provides temporary mechanical support for circulation and gas exchange.<sup>32</sup> Despite the high risk of complications of ECMO, when used for cardiogenic shock and where all other modalities have failed, the benefits of ECMO outweigh its risk.<sup>9,32</sup> This approach is best reserved as a last-line modality in CCB toxicity.<sup>72,73</sup>

## Conclusion

CCB toxicity is a commonly encountered medical emergency that requires vigilant initial patient evaluation and assessment. Quick and comprehensive early management is recommended with close monitoring based on the most up-to-date clinical evidence. The first-line therapies mainly consist of IV calcium, HIET, and vasopressors. However, in refractory cases, incremental doses of HIET, LET, and ECMO may overcome severe toxicities.

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