Management of Calcium Channel Blocker Toxicity in the Pediatric Patient

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Calcium channel blockers (CCBs) are commonly prescribed cardiovascular medications used in several disease states including hypertension, coronary artery disease, and atrial fibrillation. Inadvertent exposure or intentional overdose of CCBs may result in hypotension, bradycardia, dysrhythmias, conduction disturbances, and hyperglycemia. In the most severe cases, CCB toxicity can lead to rapid cardiovascular collapse. Given the risk of significant morbidity and mortality associated with CCB toxicity, it is important that health care professionals are able to recognize and treat patients who present with a potentially toxic ingestion. Due to the paucity of literature in managing pediatric patients with severe CCB toxicity, treatment strategies for pediatric patients are mostly limited to case reports and extrapolation from expert consensus recommendations for adults. All pediatric patients with a potentially toxic CCB ingestion should be evaluated in the emergency department. Activated charcoal may be considered for asymptomatic patients presenting within an hour of ingestion. Symptomatic patients should be placed under cardiac monitoring and treatments to stabilize the patient's hemodynamics should not be delayed. Traditional first-line IV therapies include small boluses of fluids, calcium, and vasopressors. High-dose insulin has been proposed to independently increase inotropy and improve CCB-induced hypoinsulinemia and insulin resistance that results from CCB inhibition of insulin release from pancreatic β -islet cells. High-dose insulin is recommended as first-line therapy for adults and shows promising efficacy and safety in several pediatric case reports. Intravenous lipid emulsion may be considered in patients who are refractory to first-line therapies, although the data for pediatric patients are extremely limited.

ABBREVIATIONS BB, β -adrenergic blocker; CCB, calcium channel blocker; ECMO, extracorporeal membrane oxygenation

KEYWORDS antidotes; calcium channel blockers; drug overdose; fat emulsions; intravenous; poisoning; toxicity

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Introduction

The National Poison Data System of the American Association of Poison Control Centers reported approximately 2.2 million human exposures to potentially toxic substances in 2016, 46% of which involved children ≤ 5 years old. Cardiovascular medications are among the top 25 substance categories most frequently involved in pediatric and adult exposures, and are the third most common substance resulting in death of children ≤ 5 years of age. In 2016, of the 5493 reports of single exposures to calcium channel blockers (CCB), 26 patients died from their ingestion and 72 patients had life-threatening or significant disability. Calcium channel blockers specifically ranked as the top sixth overall substance category associated with the most reported fatalities, behind miscellaneous sedative/hypnotics/antipsychotics, opioids, miscellaneous stimulants and street drugs, miscellaneous alcohols, and acetaminophen.¹

Poisonings in pediatric patients may be the result of exploratory/unintentional ingestions, intentional overdoses, malicious intent, or medication errors. Overall,

unintentional ingestions are the most common cause of exposure in children < 6 years old, whereas intentional ingestions are more common in those aged 13 to 19 years of age.¹ Although most unintentional CCB ingestions of small amounts of medication present little or no risk, significant toxicity after the ingestion of 1 or 2 tablets have been reported.² For example, a case of a 14-month-old female ingesting a single 10-mg nifedipine capsule reportedly led to rapid and fatal cardiovascular collapse.³ Ingestion of sustained or extended-release products add a layer of complexity due to the potential delay in a child showing signs of toxicity.⁴

Medication errors at the hospital or at home can also lead to a serious CCB overdose. Nimbalkar and Patel⁵ reported on a nearly fatal amlodipine overdose in an 11-month-old infant who was erroneously dispensed and administered 6 doses of amlodipine 15 mg instead of the prescribed amoxicillin for a respiratory tract infection. The initial presentation of vomiting and lethargy led to a progressive loss of consciousness, respiratory distress, and hypotensive shock for which

he underwent mechanical ventilation and successful management with calcium gluconate, vasopressors, and a high-dose insulin and dextrose infusion.

Given the risk of morbidity and mortality associated with CCB toxicity, it is important that health care professionals can recognize and treat pediatric patients who present with a potentially toxic CCB ingestion. This paper reviews the most updated recommendations and evidence for the management of acute CCB toxicity in the pediatric patient, with a focus on high-dose insulin and lipid emulsion therapies.

Pathophysiology of CCB Overdose

CCBs block the opening of voltage-gated calcium channels found in myocardial cells, smooth muscle cells, and β -islet cells of the pancreas. Dihydropyridine CCBs, such as amlodipine and nifedipine, act predominantly on vascular smooth muscle cells, resulting in reduced systemic vascular resistance and blood pressure. Conversely, non-dihydropyridines, such as verapamil and diltiazem, are more selective for myocardial cells, decreasing cardiac conduction and contractility. In overdose, however, selectivity is decreased. Thus, the clinical features and subsequent treatment strategies are similar for toxicity caused by both classes of CCBs.^{4,6}

Decreased calcium entry into myocardial cells reduces electromechanical conduction, slows pacemaker activity in the sinoatrial and atrioventricular nodes, and decreases atrioventricular node conduction. Blocking calcium channels in the vascular smooth muscle results in vasodilation, while blocking calcium influx into pancreatic β -islet cells inhibits insulin release and alters tissue insulin sensitivity, leading to a hypoinsulinemic state. Overdose with CCBs results in an amplification of these physiological effects, which can lead to an unstable cardiovascular state of profound bradycardia, hypotension, metabolic acidosis, and shock. In a state of shock, myocytes switch from free fatty acids to glucose as their main fuel for energy. The hypoinsulinemic state results in decreased glucose uptake by the myocardium and vascular smooth muscle, which may result in further hemodynamic compromise.^{4,7}

In CCB overdose, medication pharmacokinetics may be altered. In general, CCBs are highly protein bound and have large volumes of distribution, making them poor candidates for removal by hemodialysis. Half-life in overdose may be increased as a result of saturated hepatic enzymes responsible for the metabolism of CCBs. Sustained-release products may have prolonged toxicity and a variable delay in onset of symptoms due to slower absorption.⁴ Bezoar formation, although uncommon, could also result in delayed or extended toxic effects.⁸

Clinical Manifestations

Clinical manifestations of pediatric CCB ingestions

range from asymptomatic to cardiovascular shock, depending on a variety of factors including age and weight of the child, dose and formulation of the specific agent ingested, underlying organ dysfunction, and coingested medications. In a dose-response analysis of unintentional amlodipine ingestions in children < 6 years old, a “clinically important response” was defined as bradycardia, hypotension, dysrhythmia, conduction disturbances, or hyperglycemia.⁹ Of the 678 cases of amlodipine ingestions analyzed, approximately 4% of patients developed a clinically important response. Hypotension was the most common concerning symptom, occurring in approximately 80% of patients developing clinically important responses. The lowest amlodipine dose to produce hypotension was 2.5 mg in 2 children aged 21 months and 2 years. The percentage of patients exhibiting clinical effects in this analysis was significantly lower than other published case series (8% vs 32%–60%), likely as a result of differences in study inclusion criteria.^{9–11} Other case reports have shown that seemingly small up to large pediatric ingestions can result in rapid cardiovascular collapse.^{2,3,12} Signs and symptoms of cardiovascular instability include hypotension, conduction abnormalities of the sinoatrial or atrioventricular node, dysrhythmias, and bradycardia. Other reported clinical effects of CCB ingestions in children < 6 years of age include hyperglycemia, vomiting, tachycardia, drowsiness, pallor, nausea, and fever.^{9,13}

Emergency Department Evaluation

Children or adolescents with an unwitnessed, unintentional ingestion or with a suspected intent of self-harm by overdose should be immediately evaluated in the emergency department. Important information to collect for a possible CCB ingestion includes the time and cause of the ingestion, an estimation of the maximum possible dose ingested, product formulation, possible coingestants, patient medical conditions, home medications, and symptoms.¹⁴

Asymptomatic patients are unlikely to subsequently develop symptoms 6 hours after the ingestion of solely immediate-release CCB products, 18 hours after modified-release CCB products other than verapamil, or 24 hours after modified-release verapamil.¹⁴ However, toxicokinetics of medications in overdose can create quite variable clinical presentations, particularly with polysubstance ingestions. Therefore, providers must take into account all patient-specific factors and information about the current ingestion to determine whether to observe the patient for a longer period of time. Current expert consensus recommendations suggest 24 hours as the preferable observing and monitoring period of asymptomatic patients with potentially toxic CCB ingestions (excluding polysubstance ingestions). Toxic CCB ingestions are defined as any amount that exceeds the usual maximum single therapeutic dose or equal to or greater than the lowest reported toxic

dose.^{14,15} Olson et al¹⁴ details potentially toxic CCB doses for both adults and children in their expert consensus guideline intended to assist poison center personnel in the appropriate triage and management of suspected CCB ingestions. In all CCB ingestion cases presenting to the emergency department, the poison control center can offer expert guidance on observation and monitoring.¹⁴

Children who develop symptoms should be placed under cardiac monitoring and undergo assessment of cardiac function.¹⁵ Conduction abnormalities found on electrocardiogram evaluation may be an early sign of significant toxicity.¹³

Treatment

Gastrointestinal decontamination with activated charcoal is a reasonable option for asymptomatic patients who have ingested a potentially toxic amount of CCB within an hour of presentation. However, for patients with signs and symptoms of CCB toxicity, treatments to stabilize the patient's hemodynamics should not be delayed. First-line measures recommended by an expert workgroup for the in-hospital management of CCB poisoning in adults include IV calcium, vasopressors, and/or high-dose insulin therapy. Lipid emulsion therapy is a potential second-line treatment for refractory patients.¹⁵ The following sections aim to explore the utility of these treatments in pediatric patients for the management of CCB toxicity, with a focus on the available evidence for high-dose insulin and lipid emulsion therapies. The Figure provides a proposed algorithm for the treatment of pediatric CCB ingestion.

Gastrointestinal Decontamination. Gastrointestinal decontamination with activated charcoal may be considered in asymptomatic patients presenting within 1 hour of ingesting a potentially toxic amount of CCB, although the potential for benefit after 1 hour should not be ignored. The recommended dose is 10 to 25 grams or 0.5 to 1 g/kg for children up to 1 year of age and 25 to 50 grams or 0.5 to 1 g/kg for children 1 to 12 years of age.¹⁶ A single-dose of activated charcoal was found to be very effective and superior to gastric lavage in preventing the absorption of verapamil in healthy adult volunteers when given 5 minutes after ingestion of the medication.¹⁷ A position paper on gastric lavage published by the American Academy of Clinical Toxicology recommends that gastric lavage should not be used routinely, if at all, for the treatment of poisoned patients in general.¹⁸

Another study in healthy adult volunteers compared activated charcoal alone administered 1 hour after ingestion of sustained-release verapamil versus activated charcoal plus whole-bowel irrigation with polyethylene glycol (1 L/hr until stools were colored with activated charcoal). Activated charcoal plus whole-bowel irrigation reduced the exposure of verapamil by 85% compared with 63% when activated charcoal was

administered alone; however, this difference was not statistically significant.¹⁹ In an amlodipine study, activated charcoal reduced the exposure of the medication by 99% when administered immediately after ingestion and by 49% when administered 2 hours after medication ingestion.²⁰ This demonstrates that although early administration of activated charcoal is most effective for preventing absorption of medication, delayed administration may still have some benefit. Contraindications for the use of activated charcoal include an altered mental state or unprotected airway given the risks associated with aspirating gastric contents, although emesis following administration of aqueous activated charcoal is not common.¹⁶

Inducing vomiting with ipecac syrup is not recommended due to lack of evidence for its use and availability of more effective treatments, risk of pulmonary aspiration of gastric contents, and potential to further depress heart rate by vagal stimulation.¹⁴

Traditional Therapies for Cardiovascular Stabilization. Intravenous fluids, vasopressors, and/or IV calcium are common first-line measures in patients presenting with hemodynamic abnormalities from CCB toxicity with the goal to increase blood pressure, contractility, and heart rate. Although fluid resuscitation is commonly used, small boluses (5–10 mL/kg) of normal saline is recommended in order to not overload a patient with potential myocardial depression.²¹ Vasopressor selection is generally guided by the type of shock and desired effect, as there is no evidence that one agent is superior over another in CCB toxicity. Norepinephrine can be used to increase blood pressure in vasoplegic shock, and/or epinephrine can be used to increase contractility and heart rate. Dobutamine is also an option in the presence of cardiogenic shock, although rarely used in isolation. Dopamine and vasopressin as a single agent are not suggested based on inconsistent evidence for hemodynamic improvement.¹⁵ Atropine may be given in the presence of symptomatic bradycardia if due to increased vagal tone or primary AV conduction block, as part of routine advanced cardiac life support measures.²¹

Intravenous calcium is also often administered as a first-line agent for its inotropic effects. Although calcium has been shown to improve hemodynamics and decrease mortality in animal studies, its clinical benefits in humans are variable.²² However, IV calcium is generally readily available, and adverse effects such as hypercalcemia are rare, so it remains a reasonable first-line strategy.²² Calcium chloride is preferred over calcium gluconate in the critically ill child as it results in a more rapid increase in ionized calcium. Pediatric dosing is 20 mg/kg (0.2 mL/kg) of 10% calcium chloride intravenously over 5 to 10 minutes (maximum single dose is 2 g).²¹ If effective, IV calcium may be repeated after 10 to 15 minutes or followed by an infusion of 20 to 50 mg/kg/hr.^{13,21} Calcium gluconate (60 mg/kg over

Figure. Proposed algorithm for the treatment of pediatric CCB ingestion.

IO, intraosseous infusion; VA-ECMO, venoarterial extracorporeal membrane oxygenation

30–60 minutes) may be considered if calcium chloride is not available or in the non-arrest setting to minimize peripheral vein irritation.²¹

Glucagon, although occasionally used for CCB toxicity, is not suggested due to variable benefit observed in case series, more effective interventions available, and adverse effects of hyperglycemia and vomiting.¹⁵ Glucagon is still recommended in β -adrenergic blocker (BB) toxicity and may be a useful antidote when a BB is a coingestant in a CCB overdose.^{13,21}

High-Dose Insulin. High-dose insulin is an antidote for CCB poisoning that is supported by the strongest,

albeit low quality, evidence for improving hemodynamic parameters and mortality in adults.²² It is recommended as first-line therapy in patients with signs of myocardial dysfunction.¹⁵ It is also suggested as first-line in combination with IV fluids, calcium, and vasopressors therapy even in the absence of myocardial dysfunction.¹⁵

High-dose insulin has been proposed to independently increase inotropy that is compromised by CCB inhibition of calcium influx in myocardium cells.⁶ High-dose insulin also overcomes the CCB-induced hypoinsulinemia and insulin resistance, thereby improving the hyperglycemic acidotic state and myocardial

use of carbohydrates. The degree of hyperglycemia in a patient has been correlated with severity of CCB overdose.²³ By improving glucose uptake by myocardial cells, insulin may improve their function and break the cycle of hemodynamic decline.^{7,24}

Observational studies and case series have shown potential improvement in hemodynamic parameters and survival with the use of high-dose insulin in adults with CCB toxicity.²² A prospective observational study found that blood pressure was significantly increased in 3 patients who received a bolus of 1 unit/kg of regular insulin prior to a maintenance infusion of 0.5 to 2 units/kg/hr versus 4 patients who did not receive the bolus loading dose. Only 1 patient experienced hypoglycemia, but this event was deemed clinically insignificant and quickly corrected.²⁵ Based on the available evidence for adult patients, the expert workgroup proposes a loading dose of 1 unit/kg of regular insulin followed by a continuous infusion of 1 unit/kg/hr.¹⁵

Overall, less is known regarding the safety and efficacy of high-dose insulin for CCB-poisoned pediatric patients. Several case reports have been published documenting its use (Table 1) with mostly positive results.^{5,12,26–34} Hypotension resolved in 5 cases following the administration of high-dose insulin after no response to various prior therapies.^{5,26–28,32} The other 6 pediatric cases exhibited either partial or no response to high-dose insulin. Five patients fully recovered in response to other measures including temporary pacemaker, IV lipid emulsion therapy, or extracorporeal membrane oxygenation (ECMO).^{29–31,33,45} Only 1 patient failed all resuscitation efforts.¹²

Delay in high-dose insulin administration may be a reason for its failure in some cases. Spiller et al¹² reports the only documented fatality after high-dose insulin in which an 11-month-old ingested 10 to 45 mg amlodipine with 40 to 180 mg benazepril. Less than an hour after presentation to the emergency department, the patient quickly deteriorated and underwent resuscitation efforts including chest compressions and boluses of epinephrine, atropine, sodium bicarbonate, and calcium gluconate. High-dose insulin was initiated 30 minutes into the code without benefit. It is unclear if earlier administration of high-dose insulin would have produced a better outcome.

Inadequate dosing could also be a reason for failure of high-dose insulin. Dogan et al²⁹ reported a case of accidental verapamil/trandolapril ingestion by a 3.5-year-old. High-dose insulin was reported to be initiated at least 5 hours after hospitalization, but the dose and duration of insulin was not specified. The patient's hemodynamic parameters improved after implantation of a temporary pacemaker. Gökyay et al³¹ reported a case of a 17-year-old female admitted unconscious and hypotensive after ingestion of 8 tablets of diltiazem 90 mg and 5 tablets of acetaminophen 500 mg/caffeine 30 mg. She received gastric lavage, activated charcoal,

calcium, dopamine, atropine, norepinephrine, and dobutamine prior to high-dose insulin was reported to be initiated at least 5 hours after hospitalization, but the dose and duration were not specified. The dose of insulin was 0.5 unit/kg without mention of a continuous infusion. Hypotension and metabolic acidosis persisted despite high-dose insulin and vasopressor therapies, but the patient eventually improved after IV lipid emulsion therapy.

Still, for other cases documenting relative failure of high-dose insulin and success of subsequent therapies, the potential delayed impact of high-dose insulin on the outcome cannot be excluded. Montiel et al³⁰ reported no immediate improvement following high-dose insulin other than a decrease in blood glucose, which had peaked at 393 mg/dL. Hemodynamic improvement was noted after administration of IV lipid emulsion therapy 3 hours later. Although the authors reported eventual recovery following IV lipid emulsion therapy, it is highly possible that the traditional therapies and high-dose insulin could have also influenced the outcome as well.

The dosing and duration of high-dose insulin varies widely in the published pediatric case reports. Although the current recommendation is a 1 unit/kg bolus of regular insulin followed by an insulin infusion of 1 unit/kg/hr, the evidence for this bolus and infusion dosing in pediatric literature is lacking.¹⁵ Four of the 7 patients received loading doses, with the largest dose administered being a 0.8 unit/kg bolus of insulin. Maintenance infusion rates ranged from 0.1 to 3 units/kg/hr. Based on the observational studies and case series in adults, a bolus is beneficial and does not result in additional clinically significant adverse effects.²⁵

Based on the available case reports for pediatric patients, high-dose insulin should be considered first-line in combination with other traditional first-line therapies for symptomatic CCB toxicity. High-dose insulin may be administered as a bolus of 0.5 to 1 units/kg regular insulin followed by an infusion of 0.5 to 1 unit/kg/hr. The onset of action is approximately 15 minutes, so the infusion can be titrated every 15 to 20 minutes until hemodynamic parameters have satisfactorily improved (i.e., to a blood pressure that is appropriate for the child's age). For refractory patients, the expert workgroup recommends titration of high-dose insulin up to 10 units/kg/hr.¹⁵ Although titration of high dose insulin to >10 units/kg/hr has been documented in adults; to date, there is no documented maintenance infusion beyond 3 units/kg/hr in children or adolescents.³⁵

The higher insulin dose necessary for treatment of CCB toxicity may require creation of a specialized entry in the infusion pump library to be able to administer the correct dose without reaching maximum limits of standard insulin infusion rates. Order sets with suggested insulin infusion rates, as well as pharmacy education that the high insulin dose for CCB toxicity is not a 10-fold error, may also help to prevent delays.

Table 1. Pediatric Case Reports for the Use of High-Dose Insulin Therapy for CCB Toxicity

Reference	Age, Sex	CCB Ingested (Coingested Medications)	Therapies Prior to High-Dose Insulin	High-Dose Insulin Therapy		
				Dose	Duration	Response Outcome
Yuan ²⁶	14 yr, F	Verapamil SR 30 mg/kg	Calcium, atropine, AC	10 units bolus, followed by infusion of 12 units/hr, titrated up to 0.5 unit/kg/hr	9 hr	Hypotension resolved Survived
Morris-Kukoski ²⁷	5 mo, F	Nifedipine 3.6 mg/kg	MV, calcium, glucagon, dopamine, epinephrine, phenylephrine, milrinone	Infusion of 1 unit/kg/hr	96 hr	Hypotension resolved Survived
Meyer ²⁸	13 yr, F	Verapamil SR 120–140 mg/kg	Lavage, AC, intubation, glucagon, NE, epinephrine	Infusion of 0.1 unit/kg/hr	26 hr	Hypotension resolved Survived
Aaronson ^{33*}	15 yr, F	Verapamil SR 4200 mg	Calcium, vasopressors, ILE	Infusion titrated to 3 units/kg/hr	Not specified	Improvement in heart rate Survived
Dogan ²⁹	3.5 yr, F	Verapamil 103 mg/kg (trandolapril)	Lavage, AC, dopamine, epinephrine	Not specified	Not specified	None Survived
Montiel ³⁰	18 yr, F	Diltiazem SR 3600 mg	Calcium, intubation, NE	0.8 units/kg bolus, followed by infusion up to 1 unit/kg/hr	9 hr	Hemodynamic improvement in combination with ILE Survived
Spiller ²	11 mo, M	Amlodipine 0.9–4.1 mg/kg (benazepril)	Intubation, epinephrine, atropine, sodium bicarbonate, calcium	0.4 units/kg bolus, followed by infusion of 0.9 unit/kg/hr	<1 hr	None Died
Nimbalkar ⁵	11 mo, M	Amlodipine 7.5 mg/kg/day × 2 days	MV, calcium, dopamine, epinephrine	Infusion of 0.5 to 1 unit/kg/hr	15 hr	Hypotension resolved Survived
Maskell ³⁴	17 yr, M	Amlodipine, unknown amount (metoprolol)	Calcium, glucagon, epinephrine, sodium bicarbonate	1 unit/kg bolus, followed by infusion of 1 unit/kg/hr	Not specified	Intermittent response Survived
Gökay ³¹	17 yr, F	Diltiazem 720 mg (APAP/caffeine)	Lavage, AC, calcium, dopamine, atropine, NE, dobutamine, MV	0.5 units/kg	N/A	None Survived
Raj ³²	18 yr, F	Amlodipine 150 mg	Decontamination, dobutamine, NE, calcium, glucagon	1 unit/kg bolus, followed by infusion of 0.5 unit/kg/hr titrated to 1 unit/kg/hr	62 hr	Hypotension resolved Survived

AC, activated charcoal; APAP, acetaminophen; CCB, calcium channel blocker; F, female; ILE, intravenous lipid emulsion therapy; M, male; MV, mechanical ventilation; N/A, not available; NE, norepinephrine; SR, sustained release

* Abstract available only.

Duration of high-dose insulin therapy varied widely in the pediatric case reports (<1–96 hours).^{5,12,26–33} Although there is no consensus regarding duration of high-dose insulin therapy, many clinicians continue administration until hemodynamic stability is achieved.³⁶

Potential adverse effects of high-dose insulin include hypoglycemia and hypokalemia.³⁶ In the documented pediatric case reports using high-dose insulin, only Yuan et al²⁶ reported hypoglycemia during the high-dose insulin infusion, but this event was asymptomatic and easily corrected with a dextrose bolus. Hypoglycemia can be avoided by monitoring blood glucose at least every 30 minutes for the first 4 hours and then hourly, administering dextrose boluses (0.5–1 g/kg with a maximum of 25 g/dose), and/or titrating infusions of dextrose (initiated at 0.5–1 g/kg/hr, which is equivalent to 8.3–16.7 mg/kg/min) during insulin therapy as needed to maintain euglycemia. Children who are markedly hyperglycemic at presentation may not need the dextrose supplementation despite the high dose of insulin administered.³⁶

High-dose insulin may also cause hypokalemia by shifting extracellular potassium into the intracellular space, although no reports of this adverse effect were documented in the pediatric case reports using high-dose insulin. Yuan et al²⁶ suggests a serum potassium range of 2.8 to 3.2 mEq/L be maintained during high-dose insulin and only supplementing if the potassium falls below approximately 2.5 mEq/L. It is hypothesized that mild hypokalemia is beneficial during high-dose insulin because it may facilitate calcium entry during systole by prolonging the action potential, thereby augmenting insulin's inotropic action.²⁶

Intravenous Lipid Emulsion. Intravenous lipid emulsion is both a component of parenteral nutrition and a widely accepted antidote for acute local anesthetic toxicity.³⁷ More recently, the use of IV lipid emulsion as an antidote has expanded to overdoses of other highly lipophilic medications, including CCBs. As an antidote, it is commonly administered as a bolus of 1.5 mL/kg lipid emulsion 20% followed by an infusion of 0.25 mL/kg/min for 30 to 60 minutes.¹⁵ A proposed mechanism of action for lipid emulsion for the acute toxicity of lipophilic medications is that it forms a “lipid sink,” or a lipid phase in the plasma. This phase creates a concentration gradient for the medication in the tissues, sequestering the medication from tissue into the plasma and thus reducing toxicity.³⁶ Another proposed mechanism is that the fatty acids from the lipid emulsion provide an energy source for the myocardium, thereby, improving cardiac function.³⁸

Animal studies have shown that IV lipid emulsion, both alone and in combination with standard therapies, improves hemodynamics and survival in severe IV verapamil toxicity.^{39,40} Conversely, other animal studies using an oral verapamil toxicity model did not find significant benefit.²²

Presley and Chyka⁴¹ identified 14 pediatric cases of anesthetic or non-anesthetic medication toxicity using IV lipid emulsion for treatment. Thirteen cases in this series demonstrated beneficial responses. Of the cases with sufficient weight-based dosage information for Intralipid 20%, patients typically received 1 or 2 bolus doses of 0.8 to 1.6 mL/kg with or without a continuous infusion of 0.25 mL/kg/min for 30 to 60 minutes. One patient from this series developed significant adverse events from the IV lipid emulsion. This was a 13-year-old female with amitriptyline toxicity who developed hypertriglyceridemia and pancreatitis after successful resuscitation with 2 boluses of 1.5 mL/kg of Intralipid 20% and a continuous infusion of 0.25 mL/kg/min for 30 minutes. Triglycerides peaked at 8611 mg/dL 18 hours after IV lipid emulsion administration, and serum lipase peaked at 1849 U/L 5 days after lipid emulsion administration.

Case reports documenting the use of IV lipid emulsion specifically for CCB toxicity in pediatric patients are rare. No cases reports were found using IV lipid emulsion for CCB toxicity in patients <15 years of age (Table 2). Montiel et al³⁰ described a case in which an 18-year-old female intentionally ingested 3600 mg of sustained-release diltiazem. She was admitted to the intensive care unit and was administered calcium chloride, fluids, and a norepinephrine continuous infusion. A few hours later, mechanical ventilation was initiated for respiratory failure. A bolus and continuous infusion of high-dose insulin with concomitant dextrose infusion was initiated. Three hours later, after no significant hemodynamic improvement with insulin, Intralipid 20% was given as a 1.5 mL/kg bolus followed by an infusion of 0.25 mL/kg over 1 hour. As a result, there was a modest increase in mean arterial pressure, decrease in blood lactate level, and improvement in urine output. The high-dose insulin infusion was subsequently discontinued 4 hours later, the norepinephrine infusion was stopped on day 4, and the patient was discharged from the intensive care unit on day 9 with a full recovery.

The case of refractory CCB toxicity reported by Gökay et al,³¹ described previously, used IV lipid emulsion when the patient did not respond to a variety of therapies including vasopressors, high-dose insulin, and hemodiafiltration. ClinOleic 20% lipid emulsion was given as a 100-mL bolus followed by a 1-hour infusion of 200 mL, then subsequently another 1-hour infusion of 500 mL lipid emulsion. The patient's weight was not specified, so the precise weight-based dosing is unknown. Within 1 hour of the initial bolus, the patient's heart rate, blood pressure, and metabolic acidosis showed improvement. Over the next few days, inotropes were weaned, and she was extubated. She was discharged on day 9 with a full recovery.

A retrospective study at Çukurova University in Turkey reviewed 15 patients administered IV lipid emulsion to treat cardiogenic shock due to severe CCB or

Table 2. Pediatric Case Reports for the Use of IV Lipid Emulsion Therapy for CCB Toxicity

Reference	Age, Sex	CCB Ingested (Coingested Medications)	Therapies Prior to Lipid Emulsion			IV Lipid Emulsion		Outcome
				Regimen			Response	
Aaronson ^{33*}	15 yr, F	Verapamil SR 4200 mg	Calcium, vasopressors	Not specified	None			Survived after ECMO
Montiel ³⁰	18 yr, F	Diltiazem SR 3600 mg	Calcium, intubation, NE, high-dose insulin	Intralipid 20% 1.5 mL/kg bolus followed by infusion of 0.25 mL/kg over 1 hr	Improvement of MAP, blood lactate, and urine output			Survived
Sebe ⁴²	18 yr, F	Verapamil 2800 mg	Calcium, high-dose insulin, MV	Intralipid 20% 1.5 mL/kg bolus followed by infusion of 0.25 mL/kg over 1 hr; regimen repeated twice	Normo-tension			Survived
Gökay ³¹	17 yr, F	Diltiazem 720 mg (APAP/caffeine)	Lavage, AC, calcium, dopamine, atropine, NE, dobutamine, MV, epinephrine, milrinone, glucagon	ClinOleic 20% 100 mL bolus followed by 1-hr infusion of 200 mL then a 1-hr infusion of 500 mL	Improvement in heart rate, blood pressure, and metabolic acidosis			Survived
Maskell ³⁴	17 yr, M	Amlodipine, unknown amount (metoprolol)	Calcium, glucagon, epinephrine, sodium bicarbonate, high-dose insulin	1.5 mL/kg followed by 0.5 mL/kg/min	Intermittent response			Survived after ECMO

AC, activated charcoal; APAP, acetaminophen; CCB, calcium channel blocker; ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure; MV, mechanical ventilation; NE, norepinephrine; SR, sustained release

*Abstract available only

β -blocker overdose. IV lipid emulsion was found to be effective (defined as an increase in mean arterial pressure of at least 10 mm Hg and return to normal perfusion signs) in 7 of the 9 patients with CCB overdose. The study included 1 pediatric patient, an 18-year-old female, with ingestion of verapamil 2800 mg (41 mg/kg). She became normotensive after a total of 3 mL/kg of Intralipid 20%.⁴²

While the previous 3 pediatric cases of CCB toxicity reported successful intervention with IV lipid emulsion, Aaronson et al³³ and Maskell et al³⁴ reported a lack of significant hemodynamic response following IV lipid emulsion. Aaronson et al³³ reported a case of sustained-release verapamil overdose in a 15-year-old female that is only available as a published abstract, and the dose of IV lipid emulsion given was not specified. However, the authors stated that the lack of hemodynamic improvement to IV lipid emulsion was most likely due to “suboptimal dosing.” Maskell et al³⁴ reported on an amlodipine/metoprolol overdose in a 17-year-old male in which an IV lipid emulsion dose of 1.5 mL/kg followed by an infusion of 0.5 mL/kg/min was given for an unspecified duration. The patient had intermittent responses, but ultimately required ECMO for hemodynamic stabilization.

More recently, an observational study used data from the National Poison Data System analyzed fatal poisonings in which IV lipid emulsion was administered. Of the 459 cases included, 20 cases were of children younger than 18 years of age and 183 (40%) of the cases involved CCBs. The majority of patients had “no response” or an “unknown response” to IV lipid emulsion, whereas only 7% had “transient/minimal response” and 7.4% had transient return of spontaneous circulation. In the CCB toxicity cases specifically, 4.4% of patients had transient return of spontaneous circulation following IV lipid emulsion administration.⁴³ Because this study only evaluated cases resulting in fatality, it was not designed to find potential benefits of IV lipid emulsion. However, it does increase uncertainty regarding the efficacy of lipid emulsion and highlight the need for well-designed controlled trials.

Expert consensus recommendations place IV lipid emulsion as a refractory treatment option for patients unresponsive to first-line agents including calcium, vasopressors, and high-dose insulin.¹⁵ A separate lipid emulsion workgroup takes a neutral position for the use of IV lipid emulsion in the setting of cardiac arrest due to CCB toxicity. They also suggest not using a lipid emulsion as first-line therapy for life-threatening toxicity due to CCBs.⁴⁴ The reason for delaying lipid emulsion treatment is due to the limited and inconsistent data of its benefit, potential adverse effects, and concern that it may enhance absorption of medication still in the gastrointestinal tract by altering its distribution.⁴⁴

Currently, the data are insufficient to recommend a specific dose and duration of lipid emulsion for CCB

toxicity. The IV lipid emulsion regimens used in the case reports for CCB toxicity are highly variable and may even be inconsistent within the same report. For example, Sebe et al⁴² reports the IV lipid emulsion maintenance infusion rate as 0.25 mL/kg/hr lasting 1 hour in their Patients and Methods section, then subsequently reports the maintenance infusion as 0.25 mL/kg/min lasting 1 hour in their Discussion section. Therefore, if IV lipid emulsion is deemed appropriate, it seems reasonable to use the most common dose of IV lipid emulsion used for managing local anesthetic systemic toxicity. The American Society of Regional Anesthesia and Pain Medicine recommends a bolus of 1.5 mL/kg lipid emulsion 20% rapidly over 2 to 3 minutes followed by an infusion of approximately 0.25 mL/kg/min for patients < 70 kg. The total amount of lipid emulsion should not exceed 12 mL/kg. For all patients > 70 kg, the Society recommends a bolus of 100 mL lipid emulsion 20% over 2 to 3 minutes, followed by an infusion of 200 to 250 mL over 15 to 20 minutes. If a patient remains unstable, boluses can be repeated once or twice at the same dose, and the infusion rate may be doubled keeping in mind the total limit of 12 mL/kg.⁴⁵ The American College of Medical Toxicology has similar dosing recommendations for the use of IV lipid emulsion used in overdoses of lipid-soluble cardiotoxic medications. They also state that IV lipid emulsion should be terminated after 1 hour or less if the patient’s clinical status allows.⁴⁶ It may be necessary to create a specialized entry in the infusion pump library in order to infuse the lipid emulsion at the recommended rate accurately.

Adverse events due to IV lipid emulsion when used for parenteral nutrition have been associated with rapid infusion rates and extended duration of use.⁴¹ Intravenous lipid emulsion was apparently well tolerated in the case reports included in this review, other than 1 pediatric patient who developed hypertriglyceridemia and pancreatitis as previously described. In contrast, Smolinske et al⁴³ reported a high rate (10.7%) of possible adverse effects to IV lipid emulsion in their observational study, with the most common being acute respiratory distress syndrome with hypoxemia and/or fluid overload. Infrequent but potentially immediate or early adverse reactions include allergic reactions, hyperlipidemia, hypercoagulability, flushing, and hyperthermia. Delayed adverse effects with long-term therapy include hepatomegaly, splenomegaly, thrombocytopenia, leukopenia, an increase in liver function test values, and seizures. Monitoring parameters include serum triglycerides to determine if patients are clearing the infused fat from circulation. Liver function should also be monitored.⁴⁷

Other Treatment Modalities. In patients with refractory cardiac arrest and multiorgan failure, ECMO has demonstrated success in case report series.^{15,48} Both venovenous and venoarterial have been used in other massive ingestions as a means to provide respiratory

support. Venoarterial would provide more circulatory support and could be ideal in a massive CCB ingestion.⁴⁹ Successful outcomes with the use of venoarterial ECMO were associated with a more rapid anticipation and initiation of cardiopulmonary bypass. It is theorized that initiation prior to organ failure and cardiac arrest in a massive ingestion setting may improve patient outcomes.^{50,51} However, due to its invasive nature, ECMO can have many complications such as limb ischemia, massive hemorrhage requiring multiple transfusions, and venous thromboembolisms.^{48,50}

Transcutaneous pacemakers could be a consideration in those with unstable bradycardia with high nodal heart block. It may be a useful treatment modality when the pediatric patient is not responding to vasopressors, high-dose insulin, and/or IV lipid emulsion. If transcutaneous pacing is effective, it may be appropriate to switch to IV pacing.¹⁵

Methylene blue is another treatment modality that has been used in refractory vasodilatory adult cases with success. In a case report of a 69-year-old female with a combined β -blocker and CCB overdose, methylene blue was administered at a dose of 1 mg/kg over 10 minutes followed by a 10-hour infusion of 1 mg/kg/hr. It was reportedly used along with pacing with minimal side effects other than a transient bluish discoloration.⁵¹ To date, there are no case reports using this agent for a pediatric CCB ingestion. Because successful case reports are seen with other treatment modalities, such as ECMO, methylene blue may have limited utility, particularly at ECMO centers.

Conclusion

Ingestions of CCBs by children and adolescents can have serious, and even fatal, consequences. Symptoms of a severe CCB overdose include cardiovascular instability, metabolic acidosis, and hyperglycemia. Due to the lack of evidence-based recommendations for the treatment of pediatric CCB overdose, treatment strategies are mostly based on adult observational studies and case reports. For asymptomatic pediatric patients with a potentially toxic CCB ingestion, gastrointestinal decontamination may be considered, and patients should be monitored at a health care facility. First-line therapies for a symptomatic CCB ingestion include IV calcium, vasopressors, and high-dose insulin. High-dose insulin shows efficacy in several pediatric case reports with a relatively benign safety profile if appropriately monitored. Administration of high-dose insulin should not be delayed, and sufficient doses should be administered. IV lipid emulsion should be reserved for refractory patients as there are few pediatric cases reporting its efficacy and safety. Overall, there is a need for further case reporting, case series, and observational studies for the management of pediatric CCB toxicity in order to

determine the best treatments and regimens to reduce morbidity and mortality.

ARTICLE INFORMATION

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