Management of β-Adrenergic Blocker and Calcium Channel Antagonist Toxicity

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This review intends to update the management portion of a comprehensive description of β-adrenergic blocker (BB) and calcium channel antagonist (CCA) toxicity that appeared in the 1994 Emergency Medicine Clinics of North America [1]. Over the last 13 years, these two classes of drugs remain invaluable treatments for various cardiovascular and other medical conditions. Unfortunately, they also remain common causes of cardiovascular collapse following accidental or intentional overdose. Toxicity is associated with significant mortality. According to American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC TESS) data, deaths amongst cardiovascular agents like BBs and CCAs are only exceeded by abused sympathomimetics such as cocaine (Fig. 1) [2–6].

The most significant changes with BB and CCA toxicity occurring in the last 13 years deal with the search for improved treatment. New therapies have evolved and continue to evolve. Once a novel therapy, investigation with insulin-euglycemia yielded insight into metabolic abnormalities that occur with drug-induced shock and now provides a valuable treatment. There are new formulations of standard antidotes such as recombinant glucagon. There is additional experience with efficacy and safety of calcium supplements. Emphasis on early and aggressive goal-directed therapy of shock has brought more critical care skills into the emergency department, including more rapid diagnosis of cardiogenic shock with the advent of emergency department ultrasound [7,8].

A review of the mechanism of BB- and CCA-induced toxicity will facilitate understanding various antidotal strategies. Calcium is critical for physiologic signaling. Calcium enters cells by way of specific channels and once
in the cell, participates in multiple processes. In myocardial cells, calcium entry by way of L-type or voltage-gated calcium channels initiates calcium release from intracellular storage organelles that is necessary to affect excitation–contraction coupling [9]. It is also critical for action potential generation in sinoatrial tissue [9]. In vascular smooth muscle, calcium influx maintains tone [9]. Adrenergic stimulation can modulate the effects of calcium. For example, β1-adrenergic receptor stimulation facilitates calcium entry into cardiac myocytes by increasing the number of open calcium channels. β-adrenergic–facilitated calcium entry involves activation of adenyl cyclase, a membrane-bound enzyme that catalyzes cyclic adenosine monophosphate (cAMP) formation. Formation of cAMP leads to phosphorylation of the L-type channel with subsequent opening and calcium influx [10]. Although they act through differing mechanisms, both BBs and CCAs inhibit calcium entry. β-adrenergic–blocking drugs inhibit facilitated L-type calcium channel opening, and CCAs maintain the channel in the closed state [11]. Excessive inhibition of calcium entry results in hallmark toxicity of bradycardia, conduction abnormalities, hypotension, and, if severe, hypodynamic shock [1,12].

Calcium signaling is critical to other processes that are affected by cardiac drug toxicity including carbohydrate metabolism. During drug-induced shock due to either BBs or CCAs, the heart switches its preferred source of energy substrate from free fatty acids to carbohydrates [13,14]. In response, the liver increases glucose availability by way of glycogenolysis. Even though circulating glucose is sufficient enough to support the heart during stress, CCAs block calcium-mediated insulin release by pancreatic β-islet cells that is necessary for myocardial cells to use the additional glucose [15]. The resulting metabolic manifestations resemble diabetic ketoacidosis with insulin deficiency, hyperglycemia, and acidemia [16].

Beyond general supportive care, the goals for both new and established therapies for management of BB and CCA drug toxicity are to achieve
improved perfusion by increasing blood pressure and reversing myocardial dysfunction.

Supportive care

Initial resuscitation

Attention to airway, breathing, and circulation is paramount in improving patient survival following BB and CCA overdose. Although some patients maintain surprising alertness despite significant cardiovascular compromise, many will have abrupt central nervous system depression with loss of airway protective reflexes and require intubation and mechanical ventilation. For patients that present with hallmark bradycardia and hypotension, atropine and normal saline fluid bolus are reasonable initial therapies. In cases of mild toxicity, these measures may suffice. However, atropine and fluid bolus more often fail to improve heart rate and blood pressure in significant overdose, and the health care provider should anticipate quickly moving on to other resuscitation measures [17,18].

Critically ill patients who have shock require prompt evaluation of the source(s) of hypotension to guide therapy. Emergency department bedside cardiac ultrasound is increasingly available and serves as a rapid, noninvasive screening tool to assess myocardial function [8]. If ultrasound identifies a hypodynamic myocardium, then pharmacologic therapy can focus on cardioactive drugs to improve contractility and output (see later discussion). Emergent formal echocardiography is useful if screening ultrasonography is not readily available. If ultrasonography demonstrates adequate contractility, then placement of a more invasive device such as an arterial blood pressure monitor and/or pulmonary artery catheter may be necessary. If lowered peripheral resistance is identified, then pharmacologic therapy can be directed to vasoactive agents such as norepinephrine to improve blood pressure. If the patient requires more resuscitation than a simple fluid bolus, then a Foley catheter is indicated to monitor urine output.

Determination of acid-base status is important because acidemia can worsen myocardial dysfunction due to CCAs. The mechanism of enhanced myocardial depression with acidosis is not fully elucidated but may be due to increased drug-binding at the calcium channel [19]. Acidemia can be treated by using appropriate ventilator settings or administering bicarbonate with a target of maintaining blood pH of at least 7.4. Bicarbonate therapy can improve hemodynamics. Bicarbonate administration increased mean arterial pressure and cardiac output in a toxic verapamil model [20].

Continuous cardiac monitoring and a 12-lead electrocardiogram are essential to identify cardiac conduction abnormalities. Because several BBs and CCAs can antagonize myocardial fast sodium channel function similar to that of tricyclic antidepressants, the 12-lead electrocardiogram will also assess QRS duration and act as a treatment indicator [21,22].
to 2 mEq/kg sodium bicarbonate bolus for QRS duration greater than 120 milliseconds.

**Diagnostic studies**

In addition to bedside cardiac ultrasound, invasive monitors, electrocardiogram, and arterial blood gas analysis, other important studies specific to BB and CCA toxicity include analysis of blood lactate, glucose, and renal function as well as chest radiography.

Assessment of glucose and lactate is necessary because significant CCA overdose can induce a diabetogenic state with hyperglycemia and lactate accumulation [23–25]. This is due to altered glucose metabolism, insulin deficiency, and insulin resistance [16]. The extent of hyperglycemia and lactic acidosis serves as a marker of the degree of calcium channel poisoning [16].

Hypoglycemia has often been associated with BB overdose, but it is actually extremely rare [1,12]. Like serious CCA toxicity, BB overdose can occasionally present with hyperglycemia [26–28]. Insulin is indicated for hyperglycemia and hyperlactatemia (see later discussion).

A plain chest radiograph serves as an adjunct to the physical examination looking for pulmonary edema that may limit fluid and solute administration during resuscitation [29,30].

Specific serum BB and CCA drug levels may be obtained for later confirmation of exposure, but will not be available in a timely fashion to guide therapy.

**Gastrointestinal decontamination**

When considering the cumulative poisoning literature, there is insufficient evidence that gastrointestinal decontamination improves overall outcome. For this reason, airway, ventilation, and cardiovascular resuscitation take precedence over gastrointestinal decontamination following overdose. However, if the patient is stable and there is a suspicion of BB and CCA overdose, decontamination may be appropriate because of the potential mortality from these cardiovascular drugs.

Gastric lavage is not routinely indicated but may be useful if the patient presents within 1 to 2 hours of a “life-threatening ingestion” according to consensus review by toxicologists [31]. What constitutes a life-threatening ingestion can be determined on a case-by-case basis, weighing potential morbidity and mortality due to cardiac drug overdose versus risks of the lavage procedure itself.

It is reasonable to administer 1 gm/kg activated charcoal within 1 to 2 hours of ingestion to decrease systemic drug absorption [32]. The first 2 hours postingestion are considered the greatest window of opportunity to decrease drug absorption. However, many BBs and CCAs are available as sustained release preparations with delayed systemic absorption leading to onset of toxicity greater than 12 hours [18,33]. Thus, there is additional time to institute effective gastrointestinal decontamination compared with
regular release formulations. For example, charcoal given 4 hours after sustained release verapamil reduced bioavailability by nearly one third in a controlled volunteer study [34]. Whole bowel irrigation is a plausible adjunct to activated charcoal in the case of sustained release drug ingestion [35]. Whole bowel irrigation has been used in several cases of CCA ingestion [36,37]. A cooperative patient who does not have evidence of gut dysfunction is prerequisite for whole bowel irrigation.

Specific pharmacologic therapy

*Calcium*

Calcium is a logical therapy for CCA toxicity. In theory, augmentation of extracellular calcium may overcome competitive antagonism of the calcium channel or maximize calcium entry through unblocked channels. From animal investigations, calcium is expected to increase inotropy and improve blood pressure, but have little effect on conduction blocks and heart rate [38–40]. Calcium affords some survival effect in these studies [14,40].

Clinical experience is mixed. Calcium infusion alone has improved blood pressure in some instances [33,37,41]. In a large series of CCA overdoses (n = 139), 23 patients were treated with calcium. Blood pressure increased in 16 (70%) of these patients [18]. However, calcium failed in many cases [25,42–45].

Calcium has been used to treat BB toxicity as well, but evidence to support its use is less substantial than for CCA toxicity. In rodent and canine models, calcium reversed negative inotropy induced by various beta-blockers, but did not reverse bradycardia or conduction abnormalities [46–48]. These studies did not test for survival. Inotropic benefit without chronotropic effect has been observed in limited human application, although no case report used calcium alone to treat BB toxicity [49–52]. In one unusual case, a patient demonstrated dramatic restoration of pulse and conduction in addition to blood pressure in temporal relationship to calcium boluses when other agents failed [53]. Calcium often failed to improve hemodynamics [51].

There are no clear guidelines as to what form or dose of calcium to use. Animal models of CCA toxicity demonstrate that large doses are needed. A twofold to threefold increase in serum calcium was associated with improved inotropy in two models [14,38]. Little can be inferred from human case reports regarding the necessary dose because most refer to the total dose in terms of grams rather than milliequivalents. The largest case series of CCA toxicity reported doses ranging from 4.5 to 95 mEq [18].

Calcium is available in two forms: chloride and gluconate. Calcium chloride contains more calcium in terms of milliequivalents than calcium gluconate. A 10 mL vial of 10% calcium chloride solution contains 13.5 mEq of calcium, whereas a similar volume and concentration of calcium gluconate
provides 4.5 mEq. However, when given as equivalent doses, the chloride and gluconate form provide similar increases in ionized calcium [54,55].

Most patients tolerate the necessary large doses of calcium without problems, including one patient whose total serum calcium peaked at 23.8 mg/dL (5.9 mmol/L) following 30 gm of calcium [56]. However, calcium administration has potential adverse cardiac effects (albeit rare) including hypotension, conduction blockade, bradycardia, and, asystole if given too rapidly [57]. There is also the theoretic risk of inadvertently giving calcium to a digitalis-intoxicated patient who has resultant excessive cardiac myocyte calcium overload and asystole. Tissue injury due to extravasation of calcium preparations is more of a concern, especially due to the chloride form. Thus, central intravenous administration is recommended when using calcium chloride. Given the greater risk of tissue injury with calcium chloride and similar ability of the various forms to raise calcium levels, it seems prudent to use the gluconate form during cardiac drug resuscitation.

A reasonable approach to calcium therapy is to give a 0.6-mL/kg bolus of 10% calcium gluconate (0.2 mL/kg 10% calcium chloride) over 5 to 10 minutes. After the bolus, initiate a continuous calcium gluconate infusion at 0.6 to 1.5 mL/kg/hour (0.2–0.5 mL/kg/hour 10% calcium chloride), because bolus administration only briefly increases ionized calcium (5–10 minutes) [54,55]. Titrate the infusion to affect either improved blood pressure or contractility. Follow serial ionized calcium levels every 30 minutes initially and then every 2 hours with a goal of maintaining ionized calcium at approximately twice normal.

In summary, although calcium is a logical agent to resuscitate cardiac drug toxicity, clinical experience is mixed and disappointing at times. When beneficial, it appears to provide primarily inotropic effect. The calcium gluconate form is the safest of the available preparations to use.

**Glucagon**

Glucagon is produced in pancreatic α-cells from cleavage of proglucagon. It is a regulatory hormone that opposes the hypoglycemic action of insulin, hence its first clinical application for treatment of hypoglycemia. During stress states, including shock, glucagon stimulates hepatic glycogenolysis resulting in increased circulating glucose. Glucagon also has direct myocardial action and has been investigated as an inotrope in both ischemic and non-ischemic heart failure [58]. Thus, it is an attractive antidote for drug-induced myocardial failure.

Since 1998, pharmaceutic glucagon has been produced by way of recombinant technology. Before that time, glucagon consisted of a purified bovine or porcine pancreatic extract. This is important to understand because virtually all research and published clinical experience regarding antidotal glucagon use used the older bovine or porcine-derived form. The animal-derived glucagon product also contains insulin [14]. Because pure glucagon has not been
used in cardiac drug toxicity models until recently [59], it is unclear what contribution the insulin contaminant plays in the apparent efficacy of glucagon. Lastly, unlike bovine and porcine glucagon, recombinant glucagon does not contain phenol, so concerns with secondary toxicity due to excessive administration of this preservative are no longer necessary.

Glucagon pharmacokinetics are well characterized. The onset of action is rapid and the duration of effect is short. Increased cardiodynamic changes occur in 1 to 3 minutes in nonpoisoned individuals, peak at 5 to 7 minutes, and persist for 10 to 15 minutes [58]. The hyperglycemic effect peaks at 20 to 30 minutes after administration [60].

Glucagon exerts positive inotropic and chronotropic effects on the myocardium by stimulating adenyl cyclase similar to catecholamines, but through a separate receptor [61,62]. This property makes glucagon particularly attractive as an antidote for BB toxicity by providing cAMP necessary for myocardial cell performance in the face of β-adrenergic receptor blockade. Glucagon’s positive chronotropic and inotropic effects are demonstrated in several animal models of β-blockade, including isolated, perfused myocardial tissue and intact canine models [63,64].

Several canine studies directly compare glucagon with other purported BB antidotes. Glucagon was superior to isoproterenol in reversing β-blockade with 2 mg/kg propranolol [65]. Another investigation compared glucagon with amrinone, a phosphodiesterase inhibitor. Although both agents reversed depressed myocardial contractility induced by 10 mg/kg propranolol, glucagon was superior in reversing bradycardia [66]. In a study that compared survival after propranolol intoxication, glucagon was superior to epinephrine but inferior to insulin-euglycemia [67]. In a rodent model of beta-blocker toxicity, glucagon alone did not alter survival but worsened survival when used in combination with dopamine [68].

The first published human case of BB overdose treated with glucagon appeared in 1973 [65]. The patient developed coma, bradycardia, and hypotension following an overdose of propranolol, imipramine, and valium. After 90 minutes of failed isoproterenol infusion, 10 mg glucagon increased heart rate from 52 to 70 beats per minute (bpm) and blood pressure from 60 to 95 mm Hg. Unfortunately, the patient later died from urosepsis. From this modest start, antidotal glucagon use increased, and many subsequent reports described good clinical response often after conventional therapy failed [17,28,69–77]. Despite the abundance of cases promoting glucagon’s efficacy, there are only a few reports whereby glucagon was the sole pharmacologic agent used to treat BB poisoning [76–78]. Glucagon failed in several other instances [27,79–82]. There are no human controlled trials of glucagon for BB toxicity.

Laboratory and clinical experience also support the use of glucagon for CCA toxicity. In isolated heart preparations, glucagon reversed bradycardia and hypotension induced by diltiazem, nifedipine, and verapamil [83]. In intact rat and canine studies, glucagon consistently increased
heart rate and contractility following verapamil infusion [77,84–87]. In addition to cardiodynamic effects, glucagon reversed conduction blocks due to diltiazem and verapamil [87–89]. Only one animal study directly compared glucagon with other standard antidotes for survival effect following severe verapamil toxicity [87]. In this study, glucagon provided similar survival compared with epinephrine but was inferior to insulin-euglycemia.

As in the case of glucagon use in human BB toxicity, there are no clinical trials to assess efficacy in CCA overdose. There are published cases demonstrating glucagon’s efficacy [25,77,90–94]. Glucagon failed to improve heart rate and blood pressure in several cases as well [18,25,95].

The recommended initial dose of glucagon is 50 to 150 μg/kg, roughly 3 to 10 mg in a 70-kg patient. Smaller initial doses frequently fail to produce adequate cardiodynamic responses [72,75]. Glucagon works rapidly. Responses in heart rate and blood pressure often occur within minutes [65,75,76]. Bolus therapy may be repeated again in 3 to 5 minutes. There is no established ceiling dose to bolus therapy with up to 30 mg cumulative dose in one case [71]. Rather than give repeated bolus doses, it makes more kinetic sense to initiate a glucagon infusion following the initial bolus because of the short duration of cardiac effects [58]. A reasonable guideline for determining the infusion dose is to give the effective bolus dose each hour. For example, if heart rate increased after two successive 5-mg boluses, then administer 10 mg/hour. The infusion rate can then be titrated to the desired effect. There is no established maximum dose for continuous infusion. One patient required 411 mg given over 41 hours following propranolol overdose [75].

The adverse effects of glucagon are well described. Nausea and vomiting are common and the occurrence is dose related [58,60,72,96,97]. Emesis may pose a substantial problem in the patient who has depressed mentation and tenuous airway status. Transient hyperglycemia may also occur [58,60]. Hyperglycemia is expected based on glucagon’s stimulation of glycogenolysis and typically does not require intervention. Hypoglycemia is infrequently reported during glucagon therapy for noncardiac drug–related conditions, possibly because of pre-existing poor hepatic glycogen stores [98]. Relevance during resuscitation of cardiac drug toxicity is unknown. In experimental verapamil poisoning, glucagon-treated animals develop hypoglycemia following initial hyperglycemia [14,87]. However, to the author’s best knowledge, there are no human reports of hypoglycemia following antidotal glucagon use in the setting of cardiac drug toxicity. Lastly, glucagon availability is a common shortcoming because many hospitals do not have sufficient pharmacy stock to provide adequate resuscitation [76,99,100].

All in all, the available animal data, human clinical experience, and minimal adverse effect profile support the use of glucagon early in the course of both BB and CCA toxicity. It seems to be most effective in increasing heart rate.
Adrenergic receptor agonists—catecholamines

Adrenergic receptor agonists are a rational therapeutic choice in drug-induced shock for their cardiotonic and vasoactive effects. All of the available catecholamines, including dopamine, dobutamine, epinephrine, isoproterenol, and norepinephrine, have been used to resuscitate BB and CCA toxicity [17,18,22,101,102]. In general, there is no single agent that is predictably successful for all cases. In theory, the choice of adrenergic agonist could be based upon the pharmacologic activity of the offending agent. For example, in the case of β-receptor blockade with hemodynamically significant bradycardia, predominant β-stimulation with isoproterenol is reasonable. However, this has not borne out in clinical application. In one series of 39 BB overdoses, isoproterenol faired poorly compared with other catecholamines, raising heart rate in only 11% and blood pressure in 22% of cases compared with epinephrine (67% and 50%) or dopamine (25% each) [17]. A better approach is to select an agent based upon specific hemodynamic and cardiodynamic monitoring. For example, the patient who has depressed contractility and decreased peripheral resistance may benefit from norepinephrine or epinephrine, because these drugs possess both β- and α-agonist properties.

One aspect of treating with a catecholamine that is clear from experimental models and clinical reports of severe cardiac drug toxicity is that large doses may be necessary for successful resuscitation. The doses of isoproterenol and dopamine had to be increased 15 fold and 5 fold, respectively, to reverse propranolol-induced hemodynamic changes in canines [103]. After labetolol infusion in volunteers, isoproterenol at 26 times the control dose was needed to restore blood pressure [104]. Following combined diltiazem and metoprolol overdose, epinephrine at 30 to 100 μg/minute raised blood pressure [105]. Epinephrine at 0.8 μg/kg/minute raised blood pressure following verapamil overdose [42]. Even with extraordinary doses and combining multiple catecholamines, this class of agents often fails to restore adequate perfusion [27,86,106].

Adverse effects of catecholamine administration include tissue injury, hypotension, and detrimental metabolic consequences. Extravasation of potent α-agonists from peripheral intravenous sites may lead to skin and local tissue necrosis. Thus, central intravenous administration is preferable to peripheral administration whenever possible. Catecholamines, such as isoproterenol and dobutamine, that possess predominant β-receptor activity and little α-agonist activity may decrease peripheral resistance and worsen hypotension [107]. Lastly, adrenergic agonists enhance free fatty acid use by the heart, and this may be detrimental during shock (see insulin-euglycemia discussion) [14].

A reasonable approach to catecholamine use is based on cardiodynamic and hemodynamic monitoring, using norepinephrine as a first line agent for hypotension due to low systemic resistance. Because of potential detrimental metabolic effects on the heart from catecholamines and marginal efficacy in
animal studies, other cardiotonic agents are better initial choices for improving depressed myocardial function. In summary, there is no one catecholamine that is superior for cardiovascular drug toxicity. Large doses of multiple adrenergic agents may be required.

**Insulin-euglycemia**

Insulin is a pancreatic polypeptide that plays an essential role in glucose homeostasis. It is secreted by β-islet cells primarily in response to elevated circulating glucose. Insulin promotes glucose use and storage and inhibits glucose release, gluconeogenesis, and lipolysis. Insulin is necessary for glucose uptake by most tissues, including the heart. Insulin also possesses inotropic properties, improving myocardial function in depressed hearts due to ischemic and nonischemic causes [108–112]. Interest in insulin as a treatment for cardiovascular drug overdose arose from insulin’s inotropic property. The beneficial effect in drug-induced shock may be due to its role in carbohydrate metabolism.

Insulin was first used specifically for cardiac drug toxicity in an anesthetized canine model of verapamil poisoning in 1993 [87]. In this model, 4 IU/minute insulin infused with dextrose to maintain euglycemia (HIE) improved contractility and coronary blood flow compared with calcium, epinephrine, and glucagon. Most importantly, HIE provided superior survival compared with standard treatments; all HIE animals survived. Similar findings were observed in a subsequent study using nonanesthetized, verapamil-toxic animals [113]. HIE treatment was also tested in a model of propranolol toxicity [67]. As in the verapamil investigations, HIE reversed myocardial failure, increased coronary blood flow, and improved survival compared with standard antidotes.

The mechanism of insulin’s beneficial effect is not fully understood. Initially the inotropic effect was thought due to catecholamine release [109]. This is unlikely because β-receptor blockade does not impair the increased inotropy afforded by insulin [110]. Additionally, catecholamine levels did not increase after insulin administration in the verapamil canine study [16]. The best explanation lies in metabolic rescue.

The metabolic consequences of drug-induced shock provide a milieu that is ideal for insulin treatment—namely hyperglycemia and insulin deficiency. During nonstress conditions, the heart prefers free fatty acid as its primary substrate from which to generate energy molecules. During drug-induced shock, the preferred myocardial energy substrate shifts from free fatty acids to carbohydrates [13,14,110]. Glucose release occurs by way of hepatic glycogenolysis to meet increased carbohydrate demand. Both animal models and human cases of CCAs, especially verapamil, show marked hyperglycemia [16,23,114]. Although not as common, hyperglycemia can be seen during severe BB toxicity as well [26–28,115]. As an added insult, CCA toxicity is associated with insulin deficiency. Insulin release by the pancreatic β-islet cells is calcium channel–mediated and CCAs inhibit insulin release [15,16].
Cellular glucose uptake becomes concentration-dependent rather than insulin-mediated [116]. Critical tissues such as the myocardium may not efficiently or adequately use needed glucose during shock. Impaired substrate use—metabolic starvation—worsens depressed contractility already present from direct myocardial calcium channel antagonism.

Supplemental insulin provides metabolic support to the heart during shock by promoting carbohydrate metabolism. Following beta-blockade, insulin increased myocardial glucose uptake and improved function [110]. In severe CCA toxicity, insulin increased both glucose and lactate uptake [14]. Further evaluation of metabolic changes during verapamil toxicity showed that HIE increased lactate extraction to a greater extent than glucose extraction [116]. Improved function following insulin treatment occurs without an increase in myocardial work [14,110]. In contrast, treatment with calcium, glucagon, or epinephrine promotes free fatty acid use with subsequent increased myocardial work [14]. This metabolic difference may explain why standard treatments often fail to resuscitate severe drug-induced myocardial depression.

Clinical experience with insulin is favorable. Insulin was first used to treat hyperglycemia associated with CCA toxicity with good outcome [23]. HIE was specifically used for its inotropic properties to resuscitate five patients who had hypodynamic shock due to cardiac drug overdose in 1999 [25]. Since the initial 1999 case series, HIE has been used at the author’s institution for five additional patients who had improved cardiovascular performance and all survived. Fifty-eight additional cases have been reported in the literature [117–128].

These 68 patients ingested CCAs [63], combined CCA–BB [4], and BB [1]. HIE was typically used as a rescue therapy after patients received varying doses of multiple pharmacologic antidotes. There are no cases whereby cardiotoxic drug overdose was managed with HIE alone. Given this framework for making clinical conclusions, most authors report good cardiodynamic and hemodynamic response to HIE, often when other therapies failed. Blood pressure and contractility typically increased within 15 to 60 minutes after initiating HIE [25]. This time course is similar to animal investigations [67,87]. Heart rate response is less dramatic and consistent with a lack of chronotropic effect in animal models [67,87]. In two cases managed at the author’s institution, patients converted from third degree heart block to normal sinus rhythm in temporal relationship to HIE, but restoration of normal conduction was not reported in other published cases. Three reports (5 total patients) found HIE unhelpful in managing hypotension, although the insulin dose may have been suboptimal in one case [125], was unreported in a second [120], and may have been started too late in 2 patients [121]. Overall survival in the 68 patients was 85%. However, no randomized clinical trial has formally studied mortality nor adverse events with HIE versus other antidotes.

The insulin regimens used to treat these 68 patients varied, and details were often incomplete. The maximum insulin infusion ranged from 0.1 to 319
2.5 IU/kg/hour with 0.5 IU/kg/hour (39/55 patients) as the most common dose and 1.0 IU/kg/hour as the next most used dose (15/55). Fifteen patients received an insulin bolus (range 10–90 IU) before continuous infusion. Three patients were managed with a single bolus only, including a patient that inadvertently received 1000 IU with good cardiovascular response and no adverse events [117]. The duration of insulin infusion varied widely as well with a mean of 31 hours and ranged from .75 to 96 hours (n = 20 patients). Euglycemia was maintained by way of exogenous dextrose. The average maximum dextrose requirement was 24 gm/hour, but ranged from 0.5 to 75 gm/hour (n = 14 patients). The mean duration of dextrose infusion was 47 hours and ranged from 9 to 100 hours (n = 10 patients). Dextrose was required after cessation of insulin in 7 of these 10 patients.

Adverse events with HIE were predictable and infrequent. Numeric hypoglycemia (blood glucose <60 mg/dL or 3.3 mmol/L) was reported in 9 of 55 patients. In most cases, additional dextrose was administered and HIE was continued without further hypoglycemia. However, in one series totaling 37 patients, 5 patients developed hypoglycemia that led to early cessation of insulin infusion [127]. These 5 patients had less hypotension on presentation than the remaining patients and thus may have been more insulin sensitive (communication with coauthor of Ref. [127]). HIE treatment lowers serum potassium. In the initial case series, serum potassium fell as low as 2.2 mEq/L (2.2 mmol/L) without sequelae [25]. Keep in mind that HIE does not deplete potassium; it simply shifts potassium from the extracellular to intracellular compartment. Potassium administration in these cases can theoretically result in potassium excess. Other asymptomatic electrolyte findings include hypophosphatemia and hypomagnesemia [25]. It is not clear if changes in magnesium and phosphate are due to the cardiac drug insult, general critical illness, or HIE. Similar changes are observed following insulin therapy for diabetic ketoacidosis [129,130].

Based on the animal data and clinical experience to date, a reasonable HIE regimen consists of the following: 1 IU/kg regular insulin bolus to maximally saturate receptors followed by a regular insulin infusion starting at 0.5 IU/kg/hour. The infusion can be titrated upward every 30 minutes to achieve the desired effect on contractility or blood pressure. (Bedside echocardiography is an ideal, rapid, and noninvasive technique for measuring myocardial response.) Euglycemia is defined as blood glucose between 100 and 250 mg/dL (5.5–14 mmol/L) and is maintained by administering intravenous dextrose. Unless the patient is markedly hyperglycemic (>400 mg/dL or 22 mmol/L), a 25-gm dextrose bolus is given with the initial insulin bolus and is followed by dextrose infusion at 0.5 gm/kg/hour. Because this amount of dextrose is associated with a large volume of solute (25 gm/hour = 250 mL/hr of a 10% solution), establish central intravenous access so that smaller volume, more concentrated solutions can be given. The glucose infusion is titrated based on frequent bedside glucose monitoring—every 20 to 30 minutes until blood glucose is stable—and then at least every 1 to 2
hours. Potassium can be measured, but does not need to be replaced unless it falls below 2.5 mEq/dL (2.5 mmol/L) and there is a source of potassium loss.

In summary, HIE is a safe and effective therapy for significant CCA or BB toxicity. Animal and clinical data suggest that the best indication is when there is evidence of a hypodynamic myocardium. Additionally, the response to HIE is not immediate, so early detection of depressed contractility and early initiation of HIE therapy will increase the chance of benefit.

**Sodium bicarbonate therapy**

Sodium bicarbonate is used to treat acidemia and sodium channel blockade.

As discussed under supportive therapy, acidemia worsens CCA toxicity [19], and sodium bicarbonate treatment improves hemodynamics [20].

Both BB and CCA drugs appear to antagonize myocardial sodium channels. β-blockers with the so-called “membrane stabilizing effect” include acebutolol, betaxalol, carvedilol, metoprolol, oxprenolol, and propranolol [131]. Thus, toxicity from these drugs may include widened QRS in addition to bradycardia [53,132,133]. At high doses, CCAs impair myocardial sodium channels, although experimental evidence is mixed [134–137]. Patients who have wide complex QRS abnormalities are reported following CCA overdose [21,22].

Sodium bicarbonate is the traditional treatment for wide complex QRS conduction abnormalities due to sodium channel antagonism. Bicarbonate has been evaluated in animal studies of BB and CCA toxicity and has been used anecdotally in human poisoning. Bicarbonate therapy alone did not alter QRS duration or hemodynamics in a canine model of mild BB toxicity [138]. However, it reversed QRS widening following acebutolol overdose in one case report [100]. Diltiazem and verapamil overdoses resulted in QRS prolongation responsive to bicarbonate boluses [21].

Despite limited evidence to fully support bicarbonate use for BB and CCA toxicity, it may be a useful adjunct to other resuscitation measures in cases of either BB or CCA toxicity with QRS prolongation greater than 120 milliseconds.

**Nonpharmacologic modalities**

**Hemodialysis**

Extracorporeal drug removal has limited usefulness following BB and CCA overdose. All three classes of CCAs are lipophilic, highly protein bound, and primarily undergo hepatic metabolism [1,12]. Thus, one would predict little drug removal with dialysis. The same is true for most BBs, with a few exceptions. Atenolol, nadolol, and sotalol have properties that render them amenable to hemodialysis including: protein binding less than 25%,
volume of distribution less than 2 L/kg, and renal elimination [139]. Dialysis was used in three confirmed cases of atenolol toxicity [26,140,141].

**Cardiac pacing**

Transvenous or transthoracic electrical pacing may be required to maintain heart rate [17,18,22,142]. However, pacing often fails to achieve electrical capture, and if electrical capture occurs, blood pressure is not always restored [17,18,73]. The disconnect between electrical capture and lack of improved contractility or increased blood pressure lies in the lack of intracellular calcium necessary for contraction. This is especially true for CCAs whereby there is increased time required for calcium to enter myocytes during diastole [143]. For this reason, the optimal pacing rate is probably 50 to 60 bpm—lower than the target rate suggested to treat other causes of hemodynamically significant bradycardia. Attempts to pace at higher rates may not provide sufficient time for the myocardium to attain a forceful contraction.

**Extraordinary measures**

Extracorporeal circulatory support, aortic balloon pump, and prolonged cardiopulmonary resuscitation (CPR) have been employed in severe toxicity when standard pharmacologic measures failed. Following a massive propranolol overdose that resulted in a witnessed cardiac arrest and 4 hours of CPR, 6 hours of extracorporeal support resulted in full neurologic recovery [73]. Cardiopulmonary bypass has also been used for verapamil toxicity. Bypass was started after 2.5 hours of CPR and failed pharmacologic therapy. Return of spontaneous circulation occurred during bypass; the patient survived and fully recovered [144]. In another report, bypass failed to resuscitate a toddler after accidental verapamil ingestion [145]. Resuscitation of an atenolol overdose included extracorporeal membrane oxygenation before hemodialysis [26]. Placement of an intra-aortic balloon pump after 2.75 hours of CPR and pharmacologic resuscitation sustained a propranolol overdose through cardiogenic shock [146]. The patient survived without neurologic sequelae. Aortic balloon pump was used with multiple drugs to stabilize a combined atenolol and verapamil overdose [147]. In addition to demonstrating the utility of unusual resuscitation techniques, these cases also demonstrate that patients who have cardiac drug toxicity may survive prolonged cardiac arrest (2.5–4 hr) with good neurologic outcome.

**Continued research**

There are several recent investigations of novel therapies for BBs and CCAs. Immunotherapy has been explored for CCA toxicity. In a model using rat ventricular tissue, verapamil-specific IgG attenuated decreases in
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<tr>
<th>Indication</th>
<th>Treatment</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Contractility</td>
<td>Insulin-euglycemia (HIE)</td>
<td>1 IU/kg regular insulin + 0.5 gm/kg dextrose IV bolus, then 0.5–1 IU/kg/hr regular insulin + 0.5 gm/kg/hr dextrose continuous IV infusion</td>
<td>1) Initiate HIE simultaneously with either calcium, glucagon, or norepinephrine 2) If blood glucose is &gt;400 mg/dL (22 mmol/L), omit dextrose bolus 3) Titrate dextrose infusion to maintain blood glucose 100–250 mg/dL (5.5–14 mmol/L) 4) Monitor blood glucose q 20–30 min until stable, then q 1–2 hr 5) K+ replacement not needed unless &lt;2.5 mEq/L</td>
</tr>
<tr>
<td>10% Calcium gluconate</td>
<td></td>
<td>0.6 mL/kg IV bolus, then 0.6–1.5 mL/kg/hr IV continuous infusion</td>
<td>1) Calcium chloride can be substituted but requires central IV access 2) Used primarily for CCA toxicity but can be considered for BB toxicity</td>
</tr>
<tr>
<td>Glucagon</td>
<td></td>
<td>50–150 mcg/kg (3–10 mg) IV bolus, then 50–150 mcg/kg/hr continuous IV infusion</td>
<td>Used primarily for BB toxicity, but can also be used for CCA toxicity</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td>Titrate to age-appropriate systolic blood pressure</td>
<td>Administered via central IV access</td>
</tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>↓ Peripheral resistance</td>
<td>Heart rate &lt;50 bpm</td>
<td>Glucagon</td>
<td>50–150 mcg/kg (3–10 mg) IV bolus, then 50–150 mcg/kg/hr continuous IV infusion</td>
</tr>
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<td>Norepinephrine</td>
<td></td>
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</tr>
<tr>
<td>Cardiac pacing</td>
<td></td>
<td>Cardiac pacing</td>
<td>Target heart rate is 60 bpm</td>
</tr>
<tr>
<td>QRS &gt;120 ms</td>
<td>Sodium bicarbonate</td>
<td>1–2 mEq/kg IV bolus</td>
<td>Can repeat for recurrent QRS widening</td>
</tr>
</tbody>
</table>

*Abbreviation: IV, intravenous.*
myocardial contractility [148]. Intralipid has also been evaluated for CCAs. In theory, administration of an exogenous lipid compound provides an additional pharmacologic compartment in which highly lipid-soluble drugs can partition, thus reducing drug burden at target tissues. In verapamil toxic rats, intralipid infusion attenuated bradycardia, doubled survival time, and increased the lethal dose [149]. Vasopressin has been studied for both β-adrenergic blockade and calcium channel antagonism. It is a hypothalamic hormone released in response to lowered blood pressure. It stimulates smooth muscle V1-receptors that increase vascular tone. Vasopressin is attractive for use in cardiac drug overdose, especially because it may increase the response to catecholamines [150]. It has been anecdotally used for caffeine, amitriptyline, milrinone, and amlodipine overdose [125,151–153]. In the amlodipine case report, vasopressin increased blood pressure after calcium, catecholamines, insulin, and charcoal hemoperfusion failed [125]. Three animal studies have evaluated vasopressin for treatment of cardiac drug toxicity: two investigating CCAs and one BB drug toxicity [59, 152,153]. Unfortunately, these studies did not demonstrate any hemodynamic benefit, although all studies administered vasopressin as a single agent, and coadministration of a catecholamine was not tested.

**Therapeutic goals**

The overall objective of therapy is to improve organ perfusion with subsequent increases in survival. Reasonable clinical and physiologic markers of the efficacy of therapy include improvement in myocardial ejection fraction (EF) (≥50% EF); increased blood pressure (≥90 mm Hg in adult); adequate heart rate (≥60 bpm); resolution of acidemia, euglycemia, adequate urine flow (1–2 mL/kg/hour); reversal of cardiac conduction abnormalities (QRS ≤120 milliseconds); and improved mentation. It is unlikely that any single therapeutic modality will accomplish these multisystem goals. Thus, health care providers can anticipate that successful resuscitation of BB and/or CCA toxicity will require combined use of the agents previously described. To facilitate management, treatment options, doses, and guidelines are summarized in Table 1.

**References**


