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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

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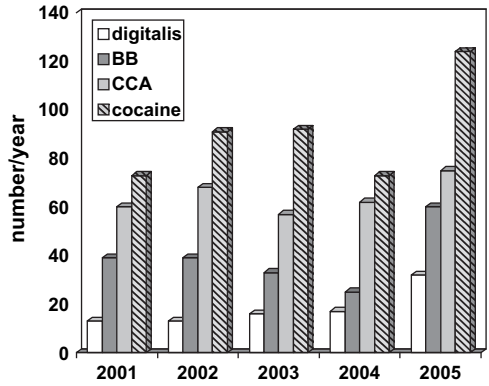

Fig. 1. Cardiovascular drug annual mortality from AAPCC TESS Data. (*Data from* Refs. [2–6].)

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, β_1-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 cardiotonic 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]. Consider 1

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 nonischemic 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

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, betoxalol, 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

Table 1
Treatment options for BB and CCA toxicity

Indication	Treatment	Dose	Comments
↓ Contractility	Insulin-euglycemia (HIE)	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	1) Initiate HIE simultaneously with either calcium, glucagon, or norepinephrine 2) If blood glucose is > 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 < 2.5 mEq/L
	10% Calcium gluconate	0.6 mL/kg IV bolus, then 0.6–1.5 mL/kg/hr IV continuous infusion	1) Calcium chloride can be substituted but requires central IV access 2) Used primarily for CCA toxicity but can be considered for BB toxicity
	Glucagon	50–150 mcg/kg (3–10 mg) IV bolus, then 50–150 mcg/kg/hr continuous IV infusion	Used primarily for BB toxicity, but can also be used for CCA toxicity
	Norepinephrine	Titrate to age-appropriate systolic blood pressure	Administered via central IV access
↓ Peripheral resistance	Norepinephrine	Titrate to age-appropriate systolic blood pressure	Administered via central IV access
Heart rate < 50 bpm	Glucagon	50–150 mcg/kg (3–10 mg) IV bolus, then 50–150 mcg/kg/hr continuous IV infusion	Used primarily for BB toxicity, but can also be used for CCA toxicity
	Norepinephrine	Titrate to age-appropriate systolic blood pressure	Administered via central IV access
	Cardiac pacing		Target heart rate is 60 bpm
QRS > 120 ms	Sodium bicarbonate	1–2 mEq/kg IV bolus	Can repeat for recurrent QRS widening

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 V_1-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) ($\geq$50% EF); increased blood pressure ($\geq$ 90 mm Hg in adult); adequate heart rate ($\geq$ 60 bpm); resolution of acidemia, euglycemia, adequate urine flow (1–2 mL/kg/hour); reversal of cardiac conduction abnormalities (QRS$\leq$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

[1] Kerns W, Kline J, Ford MD. Beta-blocker and calcium channel blocker toxicity. Emerg Med Clin North Am 1994;12:365–90.

[2] Watson WA, Litovitz TL, Rodgers GC, et al. 2002 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2003;21:353–421.

[3] Litovitz TL, Klein-Schwartz W, Rodgers GC, et al. 2001 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2002;20:391–452.

[4] Watson WA, Litovitz TL, Klein-Schwartz W, et al. 2003 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2004;22:335–404.
[5] Watson WA, Litovitz TL, Rodgers GC, et al. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2005;23:589–666.
[6] Lai MW, Klein-Schwartz W, Rodgers GC, et al. 2005 Annual report of the American Association of Poison Control Centers' National Poisoning and Exposure Database. Clin Toxicol 2006;44:803–932.
[7] Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
[8] Jones AE, Tayal VS, Sullivan DM, et al. Randomized, controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of nontraumatic hypotension in emergency department patients. Crit Care Med 2004;32:1703–8.
[9] Katz AM. Calcium channel diversity in the cardiovascular system. J Am Coll Cardiol 1996; 28:522–9.
[10] Sperelakis N, Wahler GM. Regulation of Ca2+ influx in myocardial cells by beta adrenergic receptors, cyclic nucleotides, and phosphorylation. Mol Cell Biochem 1988;82:19–28.
[11] Katz AM. Selectivity and toxicity of antiarrhythmic drugs: molecular interactions with ion channels. Am J Med 1998;104:179–95.
[12] DeWitt CR, Waksman JC. Pharmacology, pathophysiology, and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev 2004;23:223–38.
[13] Masters TN, Glaviano VV. Effects of d,l-propranolol on myocardial free fatty acid and carbohydrate metabolism. J Pharmacol Exp Ther 1969;167:187–93.
[14] Kline J, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. Crit Care Med 1995;23:1251–63.
[15] Devis G, Somers G, Obberghen E, et al. Calcium antagonists and islet function. I. Inhibition of insulin release by verapamil. Diabetes 1975;24:247–51.
[16] Kline JA, Raymond RM, Schroeder JD, et al. The diabetogenic effects of acute verapamil poisoning. Toxicol Appl Pharmacol 1997;145:357–62.
[17] Weinstein RS. Recognition and management of poisoning with beta-adrenergic blocking agents. Ann Emerg Med 1984;13:1123–31.
[18] Ramoska EA, Spiller HA, Winter M, et al. A one-year evaluation of calcium channel blocker overdoses: toxicity and treatment. Ann Emerg Med 1993;22:196–200.
[19] Smith HJ, Briscoe MG. The relative sensitization by acidosis of five calcium blockers in cat papillary muscles. J Mol Cell Cardiol 1985;17:1709–16.
[20] Tanen DA, Ruha AM, Curry SC, et al. Hypertonic sodium bicarbonate is effective in the acute management of verapamil toxicity in a swine model. Ann Emerg Med 2000;36: 547–53.
[21] Holstege CP, Kirk MA, Furbee RB, et al. Wide complex dysrhythmia in calcium channel blocker overdose responsive to sodium bicarbonate therapy [abstract]. J Toxicol Clin Toxicol 1998;36:509.
[22] Watling SM, Crain JL, Edwards TD, et al. Verapamil overdose: case report and review of the literature. Ann Pharmacother 1992;26:1373–8.
[23] Enyeart JJ, Price WA, Hoffman DA, et al. Profound hyperglycemia and metabolic acidosis after verapamil overdose. J Am Coll Cardiol 1983;2:1228–31.
[24] Roth A, Miller HI, Belhassen B, et al. Slow-release verapamil and hyperglycemic metabolic acidosis. Ann Intern Med 1989;110:171–2.
[25] Yuan TH, Kerns WP, Tomaszewski CA, et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol Clin Toxicol 1999;37:463–7.
[26] Rooney M, Massey KL, Jamali F, et al. Acebutolol overdose treated with hemodialysis and extracorporeal membrane oxygenation. J Clin Pharmacol 1996;36:760–3.
[27] Shore ET, Cepin D, Davidson MJ. Metoprolol overdose. Ann Emerg Med 1981;10:524–7.

[28] Buiumsohn A, Eisenberg ES, Jacob H, et al. Seizures and intraventricular conduction defect in propranolol poisoning. A report of two cases. Ann Intern Med 1979;91:860–2.
[29] Herrington DM, Insley BM, Weinmann GG. Nifedipine overdose. Am J Med 1986;81: 344–6.
[30] Humbert VH, Munn NJ, Hawkins RF. Noncardiogenic pulmonary edema complicating massive diltiazem overdose. Chest 1991;99:258–60.
[31] American Academy of Clinical Toxicology. European Association of Poison Centres and Clinical Toxicologists. Position paper: gastric lavage. J Toxicol Clin Toxicol 2004;42: 933–43.
[32] American Academy of Clinical Toxicology. European Association of Poison Centres and Clinical Toxicologists. Position statement: single-dose activated charcoal. J Toxicol Clin Toxicol 1997;35:721–41.
[33] Spiller HA, Meyers A, Ziemba T, et al. Delayed onset of cardiac arrhythmias from sustained-release verapamil. Ann Emerg Med 1991;20:201–3.
[34] Laine K, Kivisto KT, Neuvonen PJ. Effect of delayed administration of activated charcoal on the absorption of conventional and slow-release verapamil. J Toxicol Clin Toxicol 1997; 35:263–8.
[35] American Academy of Clinical Toxicology. European Association of Poison Centres and Clinical Toxicologists. Position paper: whole bowel irrigation. J Toxicol Clin Toxicol 2004;42:843–54.
[36] Buckley N, Dawson AH, Howarth D, et al. Slow-release verapamil poisoning: use of polyethylene glycol whole bowel irrigation and high-dose calcium. Med J Aust 1993;158:202–4.
[37] Haddad LM. Resuscitation after nifedipine overdose exclusively with intravenous calcium. Am J Emerg Med 1996;14:602–3.
[38] Hariman RJ, Mangiardi LM, McAllister RG, et al. Reversal of the cardiovascular effects of verapamil by calcium and sodium: differences between electrophysiologic and hemodynamic responses. Circulation 1979;59:797–804.
[39] Gay R, Algeo S, Lee R, et al. Treatment of verapamil toxicity in intact dogs. J Clin Invest 1986;77:1805–11.
[40] Strubelt O, Diederich K-W. Experimental investigations of the antidotal treatment of nifedipine overdosage. Clin Toxicol 1986;24:135–49.
[41] Perkins CM. Serious verapamil poisoning: treatment with intravenous calcium gluconate. Br Med J 1978;2:1127.
[42] Chimienti M, Previtali M, Medici A, et al. Acute verapamil poisoning: successful treatment with epinephrine. Clin Cardiol 1982;5:219–22.
[43] Crump BJ, Holt DW, Vale JA. Lack of response to intravenous calcium in severe verapamil poisoning. Lancet 1982;2:939–40.
[44] Horowitz BZ, Rhee KJ. Massive verapamil ingestion: a report of two cases and a review of the literature. Am J Emerg Med 1989;7:624–31.
[45] Li Saw Hee FL, Lip GYH. Case report: fatal verapamil overdosage despite intensive therapy and use of high dose intravenous calcium. J Hum Hypertens 1996;10:495–6.
[46] Strubelt O. Evaluation of antidotes against the acute cardiovascular toxicity of propranolol. Toxicology 2006;31:261–70.
[47] Langemeijer J, de Wildt D, de Groot G, et al. Calcium interferes with the cardiodepressive effects of beta-blocker overdose in isolated rat hearts. J Toxicol Clin Toxicol 1986;24: 111–33.
[48] Love JN, Hanfling D, Howell JM. Hemodynamic effects of calcium chloride in a canine model of acute propranolol intoxication. Ann Emerg Med 1996;28:1–6.
[49] Jones JL. Metoprolol overdose. Ann Emerg Med 1982;11:114–5.
[50] Sangster B, de Wildt D, van Dijk A, et al. A case of acebutolol intoxication. J Toxicol Clin Toxicol 1983;20:69–77.
[51] Tai YT, Lo CW, Chow WH, et al. Successful resuscitation and survival following massive overdose of metoprolol. Br J Clin Pract 1990;44:746–7.

[52] Pertoldi F, D'Olando L, Mercante WP. Electromechanical dissociation 48 hours after atenolol overdose: usefulness of calcium chloride. Ann Emerg Med 1998;31:777–81.
[53] Brimacombe JR, Scully M, Swainston R. Propranolol overdose–a dramatic response to calcium chloride. Med J Aust 1991;155:267–8.
[54] Cote CJ, Drop LJ, Daniels AL, et al. Calcium chloride versus calcium gluconate: comparison of ionization and cardiovascular effects in children and dogs. Anesthesiology 1987;66: 465–70.
[55] Martin TJ, Kang Y, Robertson KM, et al. Ionization and hemodynamic effects of calcium chloride and calcium gluconate in the absence of hepatic function. Anesthesiology 1990;73: 62–5.
[56] Buckley N, Whyte IM, Dawson AH. Overdose with calcium channel blockers. Br Med J 1994;308:1639.
[57] Carlon GC, Howland WS, Goldiner PL, et al. Adverse effects of calcium administration. Report of two cases. Arch Surg 1978;113:882–5.
[58] Parmley WW. The role of glucagon in cardiac therapy. N Engl J Med 1971;285:801–2.
[59] Holger JS, Engebretsen KM, Obetz CL, et al. A comparison of vasopressin and glucagon in beta-blocker induced toxicity. Clin Toxicol 2006;44:45–51.
[60] Chernish SM, Maglinte DDT, Brunelle RL. The laboratory response to glucagon: dosages used in gastrointestinal examinations. Invest Radiol 1988;23:847–52.
[61] Murad F, Vaughn M. Effect of glucagon on rat heart adenyl cyclase. Biochem Pharmacol 1969;18:1053–9.
[62] Levey GS, Fletcher MA, Klein I, et al. The characterization of I125-glucagon binding in a solubilized preparation of cat myocardial adenylate cyclase. J Biol Chem 1974;249:2665–73.
[63] Glick G, Parmley WW, Wechsler AS, et al. Glucagon: its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta-receptor blockade with propranolol. Circ Res 1968;22:789–99.
[64] Lucchesi BR. Cardiac actions of glucagon. Circ Res 1968;22:777–87.
[65] Kosinski EJ, Malindzak GS. Glucagon and isoproterenol in reversing propranolol toxicity. Arch Intern Med 1973;132:840–3.
[66] Love JN, Leasure JA, Mundt DJ, et al. A comparison of amrinone and glucagon therapy for cardiovascular depression associated with propranolol toxicity in a canine model. J Toxicol Clin Toxicol 1992;30:399–412.
[67] Kerns W, Schroeder JD, Williams C, et al. Insulin improves survival in a canine model of acute beta-blocker toxicity. Ann Emerg Med 1997;29:748–57.
[68] Toet AE, Wemer J, Vleeming W, et al. Experimental study of the detrimental effect of dopamine/glucagon combination in d,l-propranolol intoxication. Hum Exp Toxicol 1996;15:411–21.
[69] Adlerfliegel F, Leeman M, Demaeyer P, et al. Sotalol poisoning associated with asystole. Intensive Care Med 1993;19:57–8.
[70] Ehgartner GR, Zelinka MA. Hemodynamic instability following intentional nadolol overdose. Arch Intern Med 1988;148:801–2.
[71] Lewis M, Kallenbach J, Germond C, et al. Survival following massive overdose of adrenergic blocking agents (acebutolol and labetalol). Eur Heart J 1983;4:328–32.
[72] Illingworth RN. Glucagon for beta-blocker poisoning. Practitioner 1978;223:683–5.
[73] McVey FK, Corke CF. Extracorporeal circulation in the management of massive propranolol overdose. Anaesthesia 1991;46:744–6.
[74] O'Mahony D, O'Leary P, Molloy MG. Severe oxprenolol poisoning: the importance of glucagon infusion. Hum Exp Toxicol 1990;9:101–3.
[75] Peterson CD, Leeder JS, Sterner S. Glucagon therapy for beta-blocker overdose. Drug Intell Clin Pharm 1984;18:394–8.
[76] Smith RC, Wilkinson J, Hull RL. Glucagon for propranolol overdose. J Am Med Assoc 1985;254:2412.

[77] Love JN, Sachdeva DK, Bessman ES, et al. A potential role for glucagon in the treatment of drug-induced symptomatic bradycardia. Chest 1998;114:323–6.
[78] Wilkinson J. Beta blocker overdoses. Ann Emerg Med 1986;15:982.
[79] Freestone S, Thomas HM, Bhamra HK, et al. Severe atenolol poisoning: treatment with prenalterol. Hum Toxicol 1986;5:343–5.
[80] Gerkin R, Curry SC. Significant bradycardia following acute self-poisoning with atenolol [abstract]. Vet Hum Toxicol 1987;29:479.
[81] Hurwitz MD, Kallenbach J, Pincus JS. Massive propranolol overdose. Am J Med 1986;81: 1118.
[82] Perrot D, Bui-Xuan B, Bouffard Y, et al. A case of sotalol poisoning with fatal outcome. J Toxicol Clin Toxicol 1988;26:389–96.
[83] Zaritsky AL, Horowitz M, Chernow B. Glucagon antagonism of calcium channel blocker-induced myocardial dysfunction. Crit Care Med 1988;16:246–51.
[84] Stone CK, May WA, Carroll R. Glucagon and phenylephrine combination vs glucagon alone in experimental verapamil overdose. Ann Emerg Med 1995;25:369–74.
[85] Stone CK, Thomas SH, Koury SI, et al. Glucagon and phenylephrine combination vs glucagon alone in experimental verapamil overdose. Acad Emerg Med 1996;3:120–5.
[86] Tuncok Y, Apaydin S, Kalkan S, et al. The effects of amrinone and glucagon on verapamil-induced cardiovascular toxicity in anaesthetized rats. International Journal of Investigative Pathology 1996;77:207–12.
[87] Kline JA, Tomaszewski CA, Schroeder JD, et al. Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine. J Pharmacol Exp Ther 1993;267:744–50.
[88] Jolly SR, Kipnis JN, Lucchesi BR. Cardiovascular depression by verapamil: reversal by glucagon and interactions with propranolol. Pharmacology 1987;35:249–55.
[89] Sabatier J, Pouyet T, Shelvey G, et al. Antagonistic effects of epinephrine, glucagon and methylatropine but not calcium chloride against atrio-ventricular conduction disturbances produced by high doses of diltiazem, in conscious dogs. Fundam Clin Pharmacol 1991;5: 93–106.
[90] Doyon S, Roberts JR. The use of glucagon in a case of calcium channel blocker overdose. Ann Emerg Med 1993;22:1229–33.
[91] Pollack CV. Utility of glucagon in the emergency department. J Emerg Med 1993;11: 195–205.
[92] Quezado Z, Lippmann M, Wertheimer J. Severe cardiac, respiratory, and metabolic complications of massive verapamil overdose. Crit Care Med 1991;19:436–8.
[93] Walter FG, Frye G, Mullen JT, et al. Amelioration of nifedipine poisoning associated with glucagon therapy. Ann Emerg Med 1993;22:1234–7.
[94] Wolf LR, Spadafora MP, Otten EJ. Use of amrinone and glucagon in a case of calcium channel blocker overdose. Ann Emerg Med 1993;22:1225–8.
[95] Erickson FC, Ling LJ, Grande GA, et al. Diltiazem overdose: case report and review. J Emerg Med 1991;9:357–66.
[96] Williams JF, Childress RH, Chip JN, et al. Hemodynamic effects of glucagon in patients with heart disease. Circulation 1969;39:38–47.
[97] vander Ark CR, Reynolds EW. Clinical evaluation of glucagon by continuous infusion in the treatment of low cardiac output states. Am Heart J 1970;79:481–7.
[98] Hall-Boyer K, Zaloga GP, Chernow B. Glucagon: hormone or therapeutic agent? Crit Care Med 1984;12:584–9.
[99] Love JN, Tandy TK. Beta-adrenoceptor antagonist toxicity: a survey of glucagon availability. Ann Emerg Med 1993;22:267–8.
[100] Donovan KD, Gerace RV, Dreyer JF. Acebutolol-induced ventricular tachycardia reversed with sodium bicarbonate. J Toxicol Clin Toxicol 1999;37:481–4.
[101] Lindvall K, Sojgren A. High-dose prenalterol in beta-blockade intoxication. Acta Med Scand 1985;218:525–8.

[102] Goenen M, Col J, Compere A, et al. Treatment of severe verapamil poisoning with combined amrinone-isoproterenol therapy. Am J Cardiol 1986;58:1142–3.
[103] Avery GJ, Spotnitz HM, Rose EA, et al. Pharmacologic antagonism of beta-adrenergic blockade in dogs. I. Hemodynamic effects of isoproterenol, dopamine, and epinephrine in acute propranolol administration. J Thorac Cardiovasc Surg 1979;77:267–76.
[104] Richards DA, Prichard BN, Boakes AJ, et al. Pharmacological basis for antihypertensive effects of intravenous labetalol. Br Heart J 1977;39:99–106.
[105] Anthony T, Jastremski M, Elliott W, et al. Charcoal hemoperfusion for the treatment of a combined diltiazem and metoprolol overdose. Ann Emerg Med 1986;15:1344–8.
[106] Koch AR, Vogelaers GP, Decruyenaere JM, et al. Fatal intoxication with amlodipine. J Toxicol Clin Toxicol 1995;33:253–6.
[107] Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, Molinoff PB, et al, editors. Goodman and Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; 1996. p. 199–248.
[108] Weissler AM, Altschuld RA, Gibb LE, et al. Effect of insulin on the performance and metabolism of the anoxic isolated perfused rat heart. Circ Res 1973;32:108–16.
[109] Farah AE, Alousi AA. The actions of insulin on cardiac contractility. Life Sci 1981;29: 975–1000.
[110] Reikeras O, Gunnes P, Sorlie D, et al. Metabolic effects of high doses of insulin during acute left ventricular failure in dogs. Eur Heart J 1985;6:451–7.
[111] Law WR, McLane MP, Raymond RM. Effect of insulin on myocardial contractility during canine endotoxin shock. Cardiovasc Res 1988;22:777–85.
[112] Raymond RM, McLane MP, Law WR, et al. Myocardial insulin resistance during acute endotoxin shock in dogs. Diabetes 1988;37:1684–8.
[113] Kline JA, Raymond RM, Leonova E, et al. Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. Cardiovasc Res 1997;34: 289–98.
[114] Spurlock BW, Virani NA, Henry CA. Verapamil overdose. West J Med 1991;154:208–11.
[115] Howard DC. Glucagon for reaction to combined calcium channel blocker and beta-blocker use. J Emerg Nurs 1996;22:173–5.
[116] Kline JA, Leonova E, Williams TC, et al. Myocardial metabolism during graded intraportal verapamil infusion in awake dogs. J Cardiovasc Pharmacol 1996;27:719–26.
[117] Place R, Carlson A, Leiken J, et al. Hyperinsulin therapy in the treatment of verapamil overdose [abstract]. J Toxicol Clin Toxicol 2000;38:576–7.
[118] Boyer EW, Duic PA, Evans A. Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. Pediatr Emerg Care 2002;18:36–7.
[119] Boyer EW, Shannon M. Treatment of calcium-channel-blocker intoxication with insulin infusion. N Engl J Med 2001;344:1721–2.
[120] Herbert JX, O'Malley C, Tracey JA, et al. Verapamil overdosage unresponsive to dextrose/insulin therapy [abstract]. J Toxicol Clin Toxicol 2001;39:293–4.
[121] Cumpston K, Mycyk M, Pallasch E, et al. Failure of hyperinsulinemia/euglycemia therapy in severe diltiazem overdose [abstract]. J Toxicol Clin Toxicol 2002;40:618.
[122] Marques M, Gomes E, de Oliviera J. Treatment of calcium channel blocker intoxication with insulin infusion: case report and literature review. Resuscitation 2003;57:211–3.
[123] Rasmussen L, Husted SE, Johnsen SP. Severe intoxication after an intentional overdose of amlodipine. Acta Anaesthesiol Scand 2003;47:1038–40.
[124] Meyer M, Stremski E, Scanlon M. Verapamil-induced hypotension reversed with dextrose-insulin [abstract]. J Toxicol Clin Toxicol 2001;39:500.
[125] Marraffa JM, Stork CM, Medicis JJ, et al. Massive amlodipine overdose successfully treated using high-dose vasopressin [abstract]. J Toxicol Clin Toxicol 2004;42:732–3.
[126] Greene SL, Gawarammana IB, Dargan PI, et al. Safety of high dose insulin therapy in calcium channel antagonist overdose [abstract]. J Toxicol Clin Toxicol 2006;44:758.

[127] Miller AD, Maloney GE, Kanter MZ, et al. Hypoglycemia in patients treated with high-dose insulin for calcium channel blocker poisoning [abstract]. J Toxicol Clin Toxicol 2006;44:782–3.
[128] Harris NS. Case records of the Massachusetts General Hospital. Case 24-2006. A 40-year-old woman with hypotension after an overdose of amlodipine. N Engl J Med 2006;355: 602–11.
[129] Kebler R, McDonald FD, Cadnapaphornchai P. Dynamic changes in serum phosphorus levels in diabetic ketoacidosis. Am J Med 1985;79:571–6.
[130] Ionescu-Tirgoviste C, Bruckner I, Mihalache N, et al. Plasma phosphorus and magnesium values during treatment of severe diabetic ketoacidosis. Med Interne 1981;19:66–8.
[131] Frishman WH. Beta-adrenergic blockers. Med Clin North Am 1988;72:37–81.
[132] Nicolas F, Villers D, Rozo L, et al. Severe self-poisoning with acebutolol in association with alcohol. Crit Care Med 1987;15:173–4.
[133] Offenstadt G, Hericord P, Amstutz P. Intoxication volontaire par le pindolol [Intentional overdose of pindolol]. Nouv Presse Med 1976;5:1539.
[134] Rosen MR, Ilvento JP, Gelband H, et al. Effects of verapamil on electrophysiologic properties of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 1974;189:414–22.
[135] Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil, and diltiazem. Am J Cardiol 1980;46:1047–58.
[136] Yatani A, Brown AM. The calcium channel blocker nitrendipine blocks sodium channels in neonatal rat cardiac myocytes. Circ Res 1985;57:868–75.
[137] Prakash P, Tripathi O. Verapamil and TTX inhibit +Vmax but differentially alter the duration of action potential of adult chicken ventricular myocardium. Indian J Biochem Biophys 1998;35:123–30.
[138] Love JN, Howell JM, Newsome JT, et al. The effect of sodium bicarbonate on propranolol-induced cardiovascular toxicity in a canine model. J Toxicol Clin Toxicol 2000;38: 421–8.
[139] Brubacher JR. Beta-adrenergic antagonists. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al, editors. Goldfrank's toxicologic emergencies. New York: McGraw-Hill; 2002. p. 741–61.
[140] Saitz R, Williams BW, Farber HW. Atenolol-induced cardiovascular collapse treated with hemodialysis. Crit Care Med 1991;19:116–8.
[141] Salhanick SD, Wax PM. Treatment of atenolol overdose in a patient with renal failure using serial hemodialysis and hemoperfusion and associated echocardiographic findings. Vet Hum Toxicol 2000;42:224–5.
[142] Kenyon CJ, Aldinger GE, Joshipura P, et al. Successful resuscitation using external cardiac pacing in beta adrenergic antagonist-induced bradyasystolic arrest. Ann Emerg Med 1988; 17:711–3.
[143] Ehara T, Daufmann R. The voltage- and time-dependent effects of (-)-verapamil on the slow inward current in isolated cat ventricular myocardium. J Pharmacol Exp Ther 1978; 207:49–55.
[144] Holzer M, Sterz F, Schoerkhuber W, et al. Successful resuscitation of a verapamil-intoxicated patient with percutaneous cardiopulmonary bypass. Crit Care Med 1999;27:2818–23.
[145] Hendren WG, Schieber RS, Garrettson LK. Extracorporeal bypass for the treatment of verapamil poisoning. Ann Emerg Med 1989;18:984–7.
[146] Lane AS, Woodward AC, Goldman MR. Massive propranolol overdose poorly responsive to pharmacologic therapy: use of the intra-aortic balloon pump. Ann Emerg Med 1987;16: 1381–3.
[147] Frierson J, Bailly D, Shultz T, et al. Refractory cardiogenic shock and complete heart block after unsuspected verapamil-SR and atenolol overdose. Clin Cardiol 1991;14:933–5.
[148] Hill RE, Heard K, Bogdan GM, et al. Attenuation of verapamil-induced myocardial toxicity in an ex-vivo rat model using a verapamil-specific ovine immunoglobin. Acad Emerg Med 2001;8:950–5.

[149] Tebbutt S, Harvey M, Nicholson T, et al. Intralipid prolongs survival in a rat model of verapamil toxicity. Acad Emerg Med 2006;13:134–9.
[150] Noguera I, Medina P, Segarra G, et al. Potentiation by vasopressin of adrenergic vasoconstriction in the rat isolated mesenteric artery. Br J Pharmacol 1997;122:1315–20.
[151] Holstege CP, Hunter Y, Baer AB, et al. Massive caffeine overdose requiring vasopressin infusion and hemodialysis. J Toxicol Clin Toxicol 2003;41:1003–8.
[152] Sztajnkrycer MD, Bond GR, Johnson SB, et al. Use of vasopressin in a canine model of severe verapamil poisoning: a preliminary descriptive study. Acad Emerg Med 2004;11: 1253–61.
[153] Barry JD, Durkovich DW, Richardson W, et al. Vasopressin treatment of verapamil toxicity in the porcine model. J Med Toxicol 2005;1:3–10.