Calcium and Beta Receptor Antagonist Overdose: A Review and Update of Pharmacological Principles and Management

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ABSTRACT

Calcium channel and beta-adrenergic receptor antagonists are common pharmaceutical agents with multiple overlapping clinical indications. When used appropriately, these agents are safe and efficacious. In overdose, however, these agents have the potential for serious morbidity. Calcium channel blockers and beta blockers share similar physiological effects on the cardiovascular system, such as hypotension and bradycardia, in overdose and occasionally at therapeutic doses. The initial management for symptomatic overdose of both drug classes consists of supportive care measures. Other therapies including administration of glucagon, calcium, catecholamines, phosphodiesterase inhibitors and insulin have been used with varying degrees of success. In addition, intraaortic balloon pump and extracorporeal membrane oxygenation techniques have been successfully utilized in refractory cases. This article reviews beta blocker and calcium channel blocker pharmacological principles and updates current management strategies.

KEYWORDS: Beta blockers, calcium channel blockers, overdose

Objectives: Upon completion of this article, the reader should be able to: (1) discuss the mechanisms of action of clinically used calcium channel blockers and beta blockers and relate these effects to the toxicity seen with overdose; (2) describe the role for gastric decontamination following overdose; (3) understand the various therapies for the treatment of acute beta blocker and calcium channel blocker toxicity and recognize their relative advantages and disadvantages.

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Beta-adrenergic antagonists, or beta blockers (BBs), and calcium channel blockers (CCBs) are commonly used medications with similar physiological and toxic effects. These are primarily negative inotropic and chronotropic effects on the heart, which can lead to profound bradycardia and hypotension in overdose. There are now 15 BBs and 10 CCBs that are approved by the Food and Drug Administration (FDA) for clinical use in the United States.[1] Common indications for both include hypertension, supraventricular dysrhythmias, angina pectoris, and migraine headache prophylaxis. When used appropriately these agents are effica-

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cious and safe. In overdose, however, their toxic effects may result in management challenges for even the most experienced clinicians.

BBs and CCBs, whether ingested accidentally or intentionally, are the two most common cardiovascular medication classes reported to the database of the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC-TESS). In 1999 there were 9,502 BB cases and 8,844 CCB cases reported with 26 and 61 deaths, respectively.[2] Although these are the best available data, most cases of overdose go unreported. The numbers thus grossly underestimate the true incidence of ingestions and subsequent major morbidity and mortality. This article provides an overview of the physiology and pharmacology of BBs and CCBs, reviews clinical presentations and current recommended management strategies, and discusses pertinent pharmacological and clinical differences between these two important cardiovascular therapeutic classes.

PHYSIOLOGY

Calcium is one of the most important signaling mechanisms in the human body, linking extracellular or membrane-initiated events to cellular responses.[3,4] The intracellular flow of calcium is mediated by stretch-operated, receptor-operated, and voltage-gated channels. Both BBs and CCBs inhibit this intracellular current, albeit through different mechanisms.

In the heart, activation of myofibrils and subsequent myocyte contraction is intimately related to calcium regulation. The influx of calcium into the myocytes during systole initiates the further release of calcium from intracellular stores in the sarcoplasmic reticulum and, to a lesser extent, the mitochondria.[3] The strength of contraction is proportional to the amount of calcium entering the cytosol during systole. The second messenger, cyclic adenosine monophosphate (cAMP) plays a major role in this process by triggering a cascade of intracellular events that results in the intracellular flow of calcium down its electrochemical gradient.[5]

All clinically available CCBs inhibit the transmembrane flow of calcium by antagonizing the L-subtype of voltage-gated channels.[6] In the heart, this antagonism results in negative inotropy. In the peripheral vasculature, it results in smooth muscle relaxation and thus vasodilation. BBs competitively antagonize beta-adrenergic receptors, which also decreases transmembrane calcium flow by decreasing cAMP synthesis.[5] Ultimately, both BBs and CCBs inhibit myocyte contraction by altering the cytosolic calcium concentration.

PHARMACOLOGY

Calcium Channel Blockers

CCBs are rapidly absorbed via the oral route and undergo extensive first-pass hepatic metabolism, predominantly by the CYP3A subgroup of cytochrome P450 enzymes.[6] Toxicity is usually evident within 20 to 60 minutes of ingesting regular-release preparations but may be delayed several hours in sustained-release preparations. Most CCBs are > 90% protein bound and have volumes of distribution in excess of 2 L/kg.[7] These properties make them particularly unsuitable for elimination via extracorporeal methods. The half-lives of CCBs are highly variable but for most agents are less than 12 hours, amlodipine and bepridil being notable exceptions. In the setting of an overdose the hepatic enzymes responsible for the metabolism of CCBs can become saturated, thus greatly prolonging their elimination half-lives.[8,9]

Verapamil, diltiazem, and nifedipine were the first three CCBs introduced to the U.S. market and remain the prototypical agents for the three main classes of CCBs: the phenylalkylamines, the benzothiazepines, and the dihydropyridines (Table 1). Each group can be further characterized by its relative affinity for myocardial channels and smooth muscle channels. For example, the

Table 1 Selected Pharmacologic Properties of Calcium Channel Blockers

Drug Class		Protein Binding (%)	$T_{1/2}$ (Hours)	Bioavailability (%)	Volume of Distribution (L/kg)
Phenylalkylamine	Verapamil	90	3–7	20–35	5
Benzothiazepine	Diltiazem	80	4–6	40–60	3
Dihydropyridines	Amlodipine	> 90	30–50	60–90	21
	Felodipine	> 99	11–16	20	10
	Isradipine	95	2	20	3
	Nicardipine	> 95	2–4	35	0.7
	Nifedipine	99	2–5	45–70	1
	Nimodipine	> 95	1–2	10	1
	Nisoldipine	99	7–12	5	4–5
Other	Bepridil	99	24	60	

effects of verapamil are predominantly confined to the heart in therapeutic doses, whereas those of nifedipine (and the other dihydropyridines) are almost exclusively confined to the peripheral blood vessels. Diltiazem is generally considered to have greater affinity for the cardiac channels than the peripheral blood vessel channels, though its cardiodepressant effects are only about one third as potent as those of verapamil.[7] In severe overdoses, channel selectivity is lost and these pharmacodynamic nuances may disappear. The clinical experience with CCB toxicity highlights the differences among the different classes of CCBs. In a multicenter series review of CCB overdose, verapamil was noted to have depressed atrioventricular nodal conduction more frequently and more severely than either diltiazem or nifedipine.[10] Dysrhythmias, hypotension, and depression of the sinoatrial node occurred with equal frequency.

Beta Blockers

BBs comprise a pharmacologically diverse group (Table 2). Channel selectivity is an important consideration for any physician prescribing these medications. For example, $beta_1$-selective agents are considered safer than nonselective agents for diabetic or asthmatic patients. As with CCBs, distinctions among the various BBs tend to disappear in overdose situations.

For most BB overdoses symptoms will be evident within 6 hours of ingestion.[11] Important exceptions include nadolol, sotalol, or any sustained-release preparations. Most BBs have half-lives in the 3- to 6-hour range and apparent volumes of distribution of 2 to 4 L/kg.[12] The more lipid soluble compounds require hepatic biotransformation prior to secretion and can therefore accumulate with hepatic insufficiency. In contrast, the water-soluble compounds are excreted by the kidney and can accumulate with renal insufficiency. Esmolol is water soluble but does not accumulate in renal failure to any significant extent because it is metabolized by erythrocyte esterases.[13]

Some BBs pose additional risks in overdose due to their ability to block fast sodium channels, a property that is also termed membrane stabilizing activity. This effect has little therapeutic value but agents with this ability, such as propanolol, acebutolol, and oxprenolol, have been reported to be more dangerous in overdose.[14–16] Clinically, patients who overdose with one of these medications are more likely to present with seizures, coma, and hypotension associated with a widened QRS and ventricular dysrhythmias.[15,17,18] Sotalol is unique in that it prolongs the action potential duration by blocking the delayed rectifier potassium channels responsible for repolarization. This results in a prolongation of the QT interval and predisposes to torsades de pointes and ventricular fibrillation even with therapeutic doses.[19,20]

PATHOPHYSIOLOGY

The main physiological derangements caused by CCBs and BBs, myocardial depression and hypotension, are exaggerations of their therapeutic effects. The final common pathway for CCB and BB toxicity is a hypodynamic state with ensuing tissue hypoperfusion. Early symptoms include weakness and lightheadedness, which

Table 2 Selected Pharmacologic Properties of Beta Blockers

Beta Blocker	Receptor Selectivity	Protein Binding (%)	$T_{1/2}$ (Hours)	Bioavailability (%)	V_D (L/kg)	Lipid Solubility	Primary Metabolism	Membrane Stabilization
Acebutolol	$Beta_1$	25	3–4	70	1.2	Low	Hepatic	+
Atenolol	$Beta_1$	5–10	6–9	50–60	1	Low	Renal	−
Betaxolol	$Beta_1$	50	14–22	90	5–13	Low	Hepatic	+
Bisoprolol	$Beta_1$	30	9–12	80	3	Low	Renal	−
Carteolol	$Beta_1$,$Beta_2$	30	6	85		Low	Renal	+
Carvedilol	$Alpha_1$, $Beta_1$,$Beta_2$	25–35	6–8	20	1–2	High	Hepatic	+
Esmolol	$Beta_1$	55	9 minutes	N/A	2	Low	Erythrocyte Esterases	−
Labetalol	$Alpha_1$, $Beta_1$,$Beta_2$	50	6–8	90	9	Moderate	Renal	−
Metoprolol	$Beta_1$	10	3–4	90	4	Moderate	Hepatic	−
Nadolol	$Beta_1$,$Beta_2$	25–30	20–24	30	2	Low	Renal	−
Penbutalol	$Beta_1$,$Beta_2$	80–98	5	100	0.5	High	Hepatic	−
Pindolol	$Beta_1$,$Beta_2$	50	3–4	95	2	Moderate	Hepatic	+
Propranolol	$Beta_1$,$Beta_2$	90	3–5	90	4	High	Hepatic	+
Sotalol	$Beta_1$,$Beta_2$	0	7–15	80	2	Low	Renal	−
Timolol	$Beta_1$,$Beta_2$	10	4	90	2	Moderate	Hepatic	−

may progress to depressed mental status and death. Mental status changes are more frequently seen with BB ingestion, in particular with the more lipophyllic agents.[16,18] For example, large ingestions of propranolol, a highly lipophyllic BB, frequently result in seizures and mental status depression.[16] A finding of altered mental status without hypotension is not characteristic of CCB toxicity and should prompt a search for other ingestants or possible causes.

Bradycardia, junctional escape beats, idioventricular rhythms, and complete heart block are the rhythm disturbances seen most often with significant ingestions of CCBs.[21,22] BB toxicity also causes bradycardia but ventricular conduction defects tend to be more common with BBs than with CCBs. Mild hyperkalemia may be observed with therapeutic and toxic levels of BBs.[23] In severe overdoses these electrolyte disturbances may further lower the threshold for serious rhythm abnormalities.

Bowel infarction, stroke, hyperglycemia, and noncardiogenic pulmonary edema have also been reported as complications of CCB toxicity.[24–27] Similarly, there are case reports of many complications with BB ingestion including mesenteric ischemia, acute renal failure, rhabdomyolysis, and a variety of dermatological conditions.[28–31] Hypoglycemia may be observed with BB toxicity in children but is usually not seen in adults unless they are diabetic.[16] Hyperglycemia is frequently noted with CCB toxicity even in nondiabetic subjects.[7]

DIFFERENTIAL DIAGNOSES

There are a variety of toxicological causes of hypotension and bradycardia in addition to BBs and CCBs. These include digoxin, clonidine, antidysrhythmics, opioids, sedative hypnotics, and organophosphates. Nontoxicological causes of bradycardia and hypotension include hyperkalemia, hypothermia, cardiac ischemia, myxedema coma, intracranial hemorrhage, and sick sinus syndrome.

TREATMENT

Evaluation and Stabilization

The initial management of BB and CCB overdose is similar. If the patient is hypotensive on presentation, supportive care measures including resuscitation with isotonic crystalloid fluid are indicated. Bradycardia may be treated with atropine according to the usual ACLS (advanced cardiac life support) guidelines.[32] In overdose patients who require endotracheal intubation, atropine prior to laryngoscopy will blunt reflex vagal stimulation that may exacerbate preexisting bradycardia. If bradycardia is refractory to atropine then other pharmacotherapeutic measures and transcutaneous (or transvenous) pacing may be considered. Review of the clinical literature indicates that capture rarely results in improved cardiac output and perfusion pressure in the setting of massive ingestions.[7,33,34] Serum electrolytes (including ionized calcium), as well as renal and hepatic functions, should be monitored. In any patient suspected of intentional overdose, obtaining serum acetaminophen and aspirin concentrations is recommended because of their widespread availability.

BBs and CCBs may be detected by gas and liquid chromatography methodologies. Determination of serum concentrations may be useful for diagnostic confirmation and medical–legal purposes, but are rarely available in a timely and useful manner for the acute management of the poisoned patient. Urine toxicological screening is likewise rarely helpful in the acute setting. An electrocardiogram may provide clues to the severity of the ingestion as well as to the presence of cardiotoxic co-ingestants. Invasive hemodynamic monitoring is recommended when the patient does not respond to conservative measures such as fluids and atropine. Arterial line and pulmonary catheter data will optimize the selection and infusion rate of vasopressor agents.

Decontamination

Gastrointestinal decontamination with activated charcoal (1 gm/kg up to 50 gm) should be considered for all significant overdoses. Orogastric lavage with a large-bore tube (36–42F in the adult) may be useful, especially in patients who present within 1 hour of ingestion and are symptomatic, or who have ingested massive amounts of either drug. Atropine should be administered (or be available) prior to insertion of the gastric tube in case of symptomatic vagal stimulation.[33] Whole-bowel irrigation (WBI) with polyethylene glycol should also be instituted for ingestions of sustained-release preparations and continued until the effluent is clear or an ileus develops. The use of extracoporeal decontamination methods, such as charcoal hemoperfusion or hemodialysis, is generally not helpful; although some beta-adrenergic antagonists (e.g., atenolol, acebutolol, sotalol) have a relatively small volume of distribution and may thus be amenable to extracoporeal elimination.

Pharmacotherapy

There are a variety of pharmacological options available for the patient who remains unresponsive to fluids and atropine (Table 3). However, much of the reported human data consist of case reports and case series, with multiple interventions taking place simultaneously in an attempt to restore hemodynamic stability. Direct comparison of the efficacy of the various treatment options is therefore difficult.

CALCIUM

Both BB and CCB toxicity result in intracellular hypocalcemia. Therefore, calcium salts (gluconate or chloride) are logical first-line agents. It is well documented that the

Table 3 Pharmacotherapeutic Options for Severe Beta-adrenergic Receptor and Calcium Channel Antagonist Poisoning

	Pediatric Bolus Dose	Adult Bolus Dose	Infusion Rate
Calcium	0.15–0.35 mEq/kg	13–25 mEq	0.5 mEq/kg/hr[a]
10% calcium chloride	10–25 mg/kg	1–2 gm	0.4 mL/kg/hr
10% calcium gluconate	30–75 mg/kg	3–6 gm	1.2 mL/kg/hr
Glucagon	50–150 mcg/kg	5–10 mg	2–10 mg/hr[b]
Insulin[c]	0.1 units/kg	5–10 units	1–10 units/kg/hr
Catecholamines	[d]	[d]	[d]

[a]Alternatively, repeat boluses every 15 to 20 minutes.
[b]Dilute the lyophylized glucagon powder in sterile water; the diluent provided by manufacturer contains phenol.
[c]Dextrose infusion co-administered to maintain euglycemia.
[d]Per usual dosing guidelines.

administration of calcium prior to the infusion of verapamil or diltiazem can blunt the hypotensive response that often accompanies the intravenous use of these medications.[35,36] In overdose, the results are often much less dramatic. Calcium may modestly improve conduction, inotropy, and blood pressure but significant ingestions rarely respond to calcium as the sole agent.[37–39] The initial recommended dose is 13 to 25 mEq for the average-sized adult and may be followed by repeat boluses or by an infusion. If concomitant cardiac glycoside toxicity is suspected, parenteral administration of calcium should be approached cautiously. There is a theoretical risk of potentiating toxic intracellular calcium concentrations associated with digitalis toxicity.[40]

GLUCAGON

Glucagon has become an accepted antidote to beta-blocker poisoning because it stimulates cAMP synthesis independent of the beta-adrenergic receptor.[41] Glucagon has shown positive inotropic and chronotropic effects despite beta-receptor blockade in numerous animal models and in humans.[42,43] Several animal studies and case reports have also demonstrated a benefit in CCB toxicity, though many treatment failures have been noted as well.[44–46] Side effects include dose-dependent nausea and vomiting, hyperglycemia, hypokalemia, and allergic reactions.[47]

CATECHOLAMINES

No one catecholamine has been shown to be consistently effective in CCB or BB overdoses. These medications are started in the usual doses and titrated rapidly until the desired clinical response is achieved. It should be noted that extraordinarily high doses may be required before a response is seen, especially with BB toxicity.[14,33] Pulmonary artery catheter data may be invaluable in assisting with the choice of vasopressor as well its optimal titration.

Dopamine has been used successfully in both CCB and BB overdoses. However, because some of its effects are mediated by catecholamine release, catecholamine depletion in severe overdoses may limit its usefulness in this setting. Isoproterenol, a beta-adrenergic agonist, is theoretically a logical agent for BB toxicity. However, the high dose infusions of isoproterenol often required in these cases may result in dysrhythmias and significant peripheral vasodilation from $beta_2$-adrenergic stimulation.[14] Dobutamine is likewise a logical agent for BB toxicity but it is not always effective.[48] Pure alpha agonists should be utilized with caution in BB poisoned patients because the unopposed alpha stimulation may result in heart failure. Because of its dual alpha and beta effects, epinephrine is a reasonable first choice, particularly for CCB overdoses.[49] Alternatively, an equally appropriate strategy in CCB toxicity is to use agents with different spectra of activity, such as dobutamine (beta) and norepinephrine (alpha).

OTHER INOTROPIC AGENTS

Phosphodiesterase inhibitors (amrinone and milrinone) are theoretically beneficial in beta-blocker toxicity because they increase intracellular concentrations of cAMP independent of beta-adrenergic receptor stimulation. In animal and human trials of BB toxicity they have been shown to have a positive inotropic effect.[50,51] Phosphodiesterase inhibitors may also be useful in CCB overdose because increasing intracellular cAMP may recruit nonantagonized channels.[52] These agents should be used in conjunction with a vasopressor because alone they are likely to result in peripheral vasodilatation and may actually worsen preexisting hypotension. Their utility is also limited by their long half-lives, which make titration difficult.

HYPERINSULINEMIC EUGLYCEMIA

Hyperinsulinemic euglycemia (HIE) refers to the use of high doses of insulin (1–10 units/kg) with concurrent glucose infusion to maintain euglycemia. The rationale for this approach is twofold. First, insulin by itself has inotropic properties. Second, it promotes the more efficient utilization of glucose by myocytes during stressed states. HIE was recently shown to improve cardiac performance and increase survival in canine models of propranolol and verapamil toxicity.[53–55]

This approach is showing promise at the bedside as well. In a recent series, patients who remained hypotensive despite calcium, glucagon, and vasopressors were treated with HIE.[56] All patients demonstrated improved hemodynamic parameters and all survived to hospital discharge.

Nonpharmacological Adjuncts

There have been isolated case reports of success with intra-aortic balloon pump (IABP) counterpulsation, extracorporeal membrane oxygenation, and even cardiopulmonary bypass.[57–59] These modalities are usually reserved for severely intoxicated patients who have hypotension and bradycardia refractory to conventional therapies. They work by providing hemodynamic support until the toxin can be metabolized or excreted.

CONCLUSION

BBs and CCBs are ubiquitous pharmacological agents with the potential for serious cardiovascular consequences. Their widespread use makes it likely that critical care and emergency medicine physicians will manage symptomatic cases of BB and CCB toxicity multiple times during their careers. An understanding of their basic mechanism of action and the resulting pathophysiology of their misuse is essential for the development of a rational approach to treating BB and CCB toxicity. Because severe intoxications may not respond to a single therapeutic approach, knowledge of the various treatment modalities will enable an optimal response for problematic clinical presentations.

REFERENCES

1. The United States Pharmacopeial Convention. USPDI: Approved Drug Products and Legal Requirements. 20th ed. Taunton, Mass.: World Color Book Services; 2000
2. Litovitz TL, Klein-Schwartz W, White S, et al. 1999 Annual Report of the American Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2000;18: 517–574
3. Adams RJ, Schwartz A. Comparative mechanisms for contraction of cardiac and skeletal muscle. Chest 1980;78: 123–137
4. Hartshorne DJ. Biochemical basis for contraction of vascular smooth muscle. Chest 1980:78:140–149
5. Abernethy DR, Schwartz JB. Calcium-antagonist drugs. N Engl J Med 1999;341:1447–1457
6. Levitski A, Marbach I, Bar-Sinai A. The signal transduction between beta receptors and adenyl cyclase. Life Sci 1993;52: 2093–2100
7. DeRoos F. Calcium channel blockers. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, Howland MA, Hoffman RS, eds. Goldfrank's Toxicologic Emergencies. 6th ed. Stamford, Conn.: Appleton & Lange; 1998: 829–843
8. Buckley CD, Aronson JK. Prolonged half-life of verapamil in a case of overdose: implications for therapy. Br J Clin Pharmacol 1995;39:680–683
9. Adams BD, Browne WT. Amlodipine overdose causes prolonged calcium channel blocker toxicity. Am J Emerg Med 1998;16:527–528
10. 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
11. Love JN. Beta-blocker toxicity after overdose: when do symptoms develop in adults? J Emerg Med 1994;12:799–802
12. Brubracher JR. Beta-adrenergic antagonists. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, Howland MA, Hoffman RS, eds. Goldfrank's Toxicologic Emergencies. 6th ed. Stamford, Conn.: Appleton & Lange; 1998:809–825
13. Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. Clin Pharm 1995;28:190–202
14. Henry JA, Cassidy SL. Membrane stabilizing activity: a major cause of fatal poisoning. Lancet 1986;8495:1414–1417
15. Pritchard BN, Battersby LA, Cruikshank JM. Overdosage with beta adrenergic blocking agents. Adv Drug React Poison Rev 1984;3:91–111
16. Reith DM, Dawson AH, Epid D, et al. Relative toxicity of beta blockers in overdose. Clin Toxicol 1996;34:273–278
17. Buiumsohn A, Eisenberg ES, Jacob H, et al. Seizures and intraventricular conduction defect in propanolol poisoning: a report of two cases. Ann Int Med 1979;91:860–862
18. Frishman W, Jacob H, Eisenberg E, Ribner H. Clinical pharmacology of the new beta-adrenergic blocking drugs, VIII: Self-poisoning with beta-adrenergic blocking agents: recognition and Management. Am Heart J 1979;98:798–811
19. Hohnloser SH, Woolsey RL. Sotalol. N Engl J Med 1994; 331:31–38
20. Krapf R, Gertsch M. Torsade de pointes induced by sotalol despite therapeutic plasma sotalol concentrations. Br Med J 1985;290:1784–1785
21. Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. Am J Emerg Med 1995;13:444–450
22. Ramoska EA, Spiller HA, Myers A. Calcium channel blocker toxicity. Ann Emerg Med 1990;19:649–653
23. Lundborg P. The effect of adrenergic blockade on potassium concentrations in different conditions. Acta Med Scand 1983; 672:121–126
24. Wax P. Intestinal infarction due to nifedipine overdose. J Toxicol Clin Toxicol 1995;33:725–728
25. Samniah N, Schlaeffer F. Cerebral infarction associated with oral verapamil overdose. J Toxicol Clin Toxicol 1988;26: 365–369
26. Devis G, Somers G, Van Obberghen E, et al. Calcium antagonists and islet function: inhibition of insulin release by verapamil. Diabetes 1975;24:547–551
27. Brass BJ, Winchester-Penny S, Lipper BL. Massive verapamil overdose complicated by noncardiogenic pulmonary edema. Am J Emerg Med 1996;14:459–461
28. Pettei MJ, Levy J, Abramson S. Nonocclusive mesenteric ischemia associated with propanolol overdose: implications regarding splanchnic circulation. J Pediatr Gastroenterol and Nutr 1990;10:544–547
29. Rooney M, Massey KL, Jamali F, et al. Acebutolol overdose treated with hemodialysis and extracorporeal membrane oxygenation. J Clin Pharmacol 1996;36:760–763
30. Schofield PM, Beath SV, Mant TK, et al. Recovery after severe oxprenolol overdose complicated by rhabdomyolysis. Human Toxicol 1985;4:57–60

31. Thomson DF, Skaehill PA. Drug induced lichen planus. Pharmacother 1994;14:561–571
32. Anonymous. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care, VI: Advanced cardiovascular life support, VIIA: Principles and practice of ACLS. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 2000;102:I136–139
33. Taboulet P, Cariou A, Berdeaux A, et al. Pathophysiology and management of self-poisoning with beta-blockers. Clin Toxicol 1993;31:531–551
34. Lane AS, Woodward AC, Goldman MR. Massive propanolol overdose poorly responsive to pharmacologic therapy: use of the intra-aortic balloon pump. Ann Emerg Med 1987;16: 1381–1383
35. Haltori VT, Mandel WJ, Pete T. Calcium for myocardial depression from verapamil. N Engl J Med 1982;306:238
36. Lipman J, Jardine I, Roos C, et al. Intravenous calcium chloride as an antidote to verapamil-induced hypotension. Intensive Care Med 1982;8:55–57
37. Love JN, Hanfling D, Howell JM. Hemodynamic effects of calcium chloride in a canine model of acute propanolol intoxication. Ann Emerg Med 1996;28:1–6
38. Crump BJ, Holt DW, Vale JA. Lack of response to intravenous calcium in severe verapamil poisoning. Lancet 1982;2:939–940
39. Luscher TF, Noll G, Sturmer T, et al. Calcium gluconate in severe verapamil intoxication. N Engl J Med 1994;330:718–719
40. Nola GT, Pope S, Harrison DC. Assessment of the synergistic relationship between serum calcium and digitalis. Am Heart J 1970;79:499–507
41. Yagami T. Differential coupling of glucagon and beta-adrenergic receptors with the small and large forms of the stimulatory G protein. Mol Pharmacol 1995;48:849–854
42. Glick G, Parmley W, Weschler A, et al. Glucagon: its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta receptor blockade with propanolol. Circ Res 1968;22:789–799
43. Parmley WW, Glick G, Sonnenblick E. Cardiovascular effects of glucagons in man. N Engl J Med 1968;279:12–17
44. Doyon S, Roberts JR. The use of glucagon in a case of calcium channel blocker overdose. Ann Emerg Med 1993;22: 1229–1233
45. Stone CK, Thomas SH, Koury SI, et al. Glucagon and phenylephrine combination vs glucagon alone in experimental verapamil overdose. Acad Emerg Med 1996;3:120–125
46. Walter FG, Frye G, Mullen JT, et al. Amelioration of nifedipine poisoning associated with glucagon therapy. Ann Emerg Med 1993;22:1234–1237
47. Lvoff R, Wilken D. Glucagon in heart failure and in cardiogenic shock: experience of 50 patients. Circulation 1972;45: 534–542
48. Shore ET, Cepin D, Davidson MJ. Metoprolol overdose. Ann Emerg Med 1981;10:524–527
49. Chimienti M, Previtali M, Medici A, et al. Acute verapamil poisoning: successful treatment with epinephrine. Clin Cardiol 1982;5:219–222
50. Lee KC, Cannif PC, Hamel DW, et al. Cardiovascular and renal effects of milrinone in beta adrenoreceptor blocked and non-blocked anesthetized dogs. Drugs Exp Clin Res 1991; 18:145–158
51. Travill CM, Pugh S, Noble MIM. The inotropic and hemodynamic effects of intravenous milrinone when reflex adrenergic stimulation is suppressed by beta-adrenergic blockade. Clin Ther 1994;16:783–792
52. Wolf LR, Spadafora MP, Otten EJ. Use of amrinone and glucagon in a case of calcium channel blocker overdose. Ann Emerg Med 1993;22:1225–1228
53. Kerns W, Schroeder D, Williams C, et al. Insulin improves survival in a canine model of acute beta-blocker toxicity. Ann Emerg Med 1997;29:748–757
54. Kline JA, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. Crit Care Med 1995;23:1251–1263
55. Kline JA, Tomaszewski CA, Schroeder JD, Raymond RM. Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine. J Pharm Exp Ther 1993;267:744–750
56. Yuan TH, Kerns WP, Tomaszewski, et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol Clin Toxicol 1999;37:463–474
57. Melanson P, Shih RD, DeRoos F, et al. Intra-aortic balloon counterpulsation in calcium channel blocker overdose. Vet Hum Toxicol 1993;35:345
58. Mcvey FK, Corke CF. Extracorporeal circulation in the management of massive beta blocker overdose. Anesthesia 1991; 46:744–746
59. Hendren WG, Schieber RS, Garrettson LK, et al. Extracorporeal bypass for the treatment of verapamil poisoning. Ann Emerg Med 1989;18:984–987