

Emergency Department Management Of Calcium-Channel Blocker, Beta Blocker, And Digoxin Toxicity

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Abstract

While it is relatively uncommon, an overdose of calcium-channel blockers, beta blockers, or digoxin has a significant morbidity and mortality rate, and its management can be complex. Digoxin toxicity can present with an acute overdose or as chronic toxicity while a patient is on therapeutic dosing, which has implications for diagnosis and management. While the patient's specific clinical presentation may depend on factors such as the time of exposure and the type of agent ingested, the differential diagnosis of the bradycardic and hypotensive patient is narrow, and toxicity from these agents must be considered. This review provides an evidence-based overview of the emergency department management of calcium-channel blocker overdose, beta blocker overdose, and digoxin toxicity.

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CME Objectives

Upon completion of this article, you should be able to:

1. Describe the pathophysiology of calcium-channel blocker, beta blocker, and digoxin toxicity.
2. Recognize symptoms and initiate appropriate diagnostic strategies for patients presenting with calcium-channel blocker, beta blocker, and digoxin toxicity.
3. Apply appropriate management for patients with calcium-channel blocker, beta blocker, and digoxin toxicity.

Prior to beginning this activity, see "Physician CME Information" on the back page.

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Case Presentations

A 44-year-old man with a history of atrial fibrillation and major depressive disorder presents to the ED via EMS after collapsing at home. His initial vital signs are: blood pressure, 92/40 mm Hg; heart rate, 41 beats/min; respiratory rate, 14 breaths/min; and fingerstick glucose, 112 mg/dL. The patient is brought to your resuscitation bay, where you begin volume resuscitation. The EMS providers said they found an empty pill bottle near where the patient was found, but they did not bring it with them. After you send the police to the patient's home to retrieve the bottle, you obtain a history from the patient. He says that he has been off any antidepressants and that he has been taking metoprolol for rate control of his atrial fibrillation. Upon completion of your primary survey, and after a liter of normal saline, you find the patient's GCS score to be 8, his heart rate to be 38 beats/min, and his blood pressure to be 84/32 mm Hg. As the nurse informs you that she can no longer feel a carotid pulse, you begin to wonder: Could this be an overdose? What drugs can cause a bradycardic arrest? . . . And how reliable was this patient in reporting his history?

Just then, an 83-year-old woman with generalized weakness and a past medical history of heart failure is brought into the ED by her daughter. Her vital signs demonstrate a sinus bradycardia at 33 beats/min and a blood pressure of 94/52 mm Hg. You find that she was recently started on an ACE inhibitor, and her baseline creatinine clearance has declined significantly. You learn that she is also on digoxin for heart failure, so you order a digoxin level. While waiting for the results, you think about whether this patient's clinical presentation is an acute indication for digoxin antibody treatment and, if so, what the indications are. You also begin to wonder what the precipitating factor to her digoxin toxicity might be.

Later that evening, a 32-year-old woman is brought to your ED via EMS after her boyfriend found her slumped over in a chair. He states that they were arguing last evening and that she was quite upset. Her boyfriend provides a medical history significant for migraine headaches, and he knows that she is taking verapamil for the same. Her fingerstick glucose is normal, and she has a heart rate of 28 beats/min and a blood pressure of 74/36 mm Hg. You consider what the best initial step in management for this patient would be. Is there a role for GI decontamination? What about hemodialysis?

Introduction

The prevalence of cardiovascular disease is increasing, due to the aging population,¹ with cardiovascular medications (especially calcium-channel blockers and beta blockers) now some of the most prescribed therapeutic agents on the market.² As a result of the growing use and availability of cardiovascular medications, there has been a rise in the number of toxic exposures. The 2011 annual report of the American Association

of Poison Control Centers found that cardiovascular medications accounted for 102,766 exposures (3.74% of all exposures reported) and nearly 11% of fatalities. This was an increase of 4795 exposures compared to rates reported from 2010. Of the cardiovascular agents, calcium-channel blockers were most often implicated in fatal exposures, with a total of 11,764 exposures reported and 26 deaths. Beta blocker exposure occurred in 23,902 cases, with 9 deaths. Digitalis exposure was reported in 2513 patients, with 27 deaths. (Of note, the numbers of cardiovascular agent exposures included 569 individuals who were exposed to cardiac glycosides of plant origin.)³

A 2007 study from the Netherlands of 1286 patients showed that, over a 4-year period, the incidence of patients with digoxin toxicity requiring hospital admission was 0.04%,⁴ which is relatively low compared to older studies. The experience is similar in North America, where it was found in the 1980s that not only were prescriptions for digoxin decreasing due to new medications being produced, but the safety monitoring had improved, leading to fewer toxic exposures.⁵ This same finding was reproduced in a 2008 study by Haynes et al, looking at data from the United Kingdom and the United States.⁶

Identifying and treating patients exhibiting toxic effects of these agents may be complex, due to the advent of newer treatment modalities and further controversies in others. Standard Advanced Cardiovascular Life Support (ACLS) protocols used for the resuscitation of patients in cardiac arrest may be insufficient, due to the complex physiologic changes that occur with poisoning from these agents, and specialized treatments are often necessary. This issue of *Emergency Medicine Practice* presents the current evidence on best-practice diagnosis and management of calcium-channel blocker, beta blocker, and digoxin toxicity.

Critical Appraisal Of The Literature

A search of literature from 1990 to 2013 was conducted in PubMed and Ovid MEDLINE[®] using the search terms *beta blocker toxicity/poisoning*, *calcium-channel blocker toxicity/poisoning*, *digitalis toxicity/poisoning*, and *digoxin toxicity/poisoning*. The Cochrane Database of Systematic Reviews was also searched. While over 1000 papers were found, only 136 were of sufficient quality to be included in this review. In an attempt to provide the most up-to-date recommendations, most studies that were conducted prior to 1990 were excluded. An attempt was made to use literature with human patients rather than animal models. Most of the evidence in the toxicology literature is in case-based or retrospective reviews. Performing high-quality randomized studies in the acutely poisoned patient is difficult,

which is important to remember when reviewing the toxicology literature.

Pathophysiology And Pharmacokinetics

Calcium-Channel Blockers

Initially developed in the 1960s, calcium-channel blockers are still used widely today in the treatment of hypertension, cardiac arrhythmias, and angina pectoris. These agents are the number one cause of fatal cardiovascular medication exposures.³ The availability of sustained-release formulations of these drugs has increased the morbidity and mortality of overdoses.

Calcium plays a critical role in intracellular messaging as well as in myocyte contraction. Blocking of calcium channels interferes with the intracellular cascade that normally results in the release of calcium from the sarcoplasmic reticulum. This interferes with the formation of the actin-myosin complex. (See Figure 1 for the role of calcium and effects of calcium-channel blockers and beta blockers.) The result is a decrease in inotropy and chronotropy, and in smooth muscle relaxation.

Commonly used calcium-channel blockers are divided into 3 main classes: (1) dihydropyridines (prototypical agent, nifedipine); (2) phenylalkylamines (prototypical agent, verapamil); and (3) benzothiazepines (prototypical agent, diltiazem).⁷ Each class exhibits particular affinity for the L-type calcium channels in cardiac myocyte and vascular smooth muscle.⁸ Agents in the dihydropyridine class bind to L-type calcium channels in vascular smooth muscle, whereas the phenylalkylamines bind to vascular and cardiac L-type calcium channels.^{7,9} In an overdose situation, receptor selectivity is essentially lost.⁷

Calcium-channel blockers are generally well-absorbed from the gastrointestinal tract and undergo a significant first-pass metabolism.¹⁰ Calcium-channel blockers are metabolized via the cytochrome system; thus, there is a risk for drug-drug interactions.¹¹ Since they are highly protein bound and have a large volume of distribution, hemodialysis is not helpful in management of calcium-channel blocker overdose.¹⁰

Beta Blockers

Developed in the 1960s, beta-adrenergic receptor antagonists have been used for several medical conditions including hypertension, congestive heart failure, thyrotoxicosis, angina, acute coronary syndromes, and essential tremor. These agents are found in various forms, including tablets, sustained-release formulations, and in combination with other agents.

While several subtypes of the beta receptor exist, 2 are of clinical importance: (1) beta-1 and (2) beta-2. Beta-1 receptors are found primarily on cardiac myocytes and are G-coupled, cyclic-AMP receptors. (See Figure 1.) Their function is to enhance calcium release

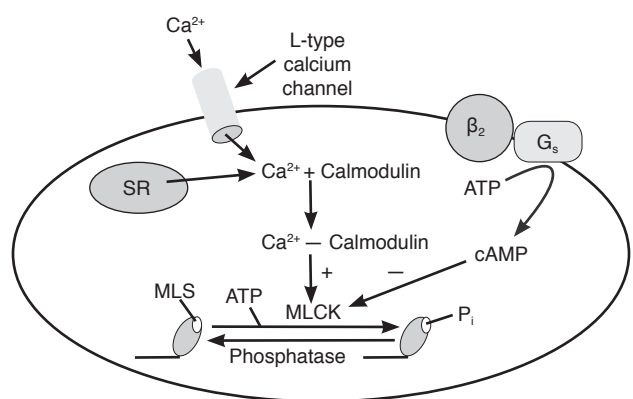
from the sarcoplasmic reticulum, thus increasing inotropy and chronotropy.⁸ Beta-2 receptors are found in the lungs and the vascular smooth muscle. Their mechanism of action is less well understood, but activation results in smooth muscle relaxation. Some agents act on both types of beta receptors (eg, propranolol), while others are more selective and bind with greater affinity to the beta-1 receptors (eg, metoprolol).

There are a number of other properties that affect the clinical effects of the various beta blockers. (Of note, not all these properties are present in all agents.) The first property is lipophilicity. The more lipophilic the agent is, the greater central nervous system permeability there is. Propranolol is a classic example of an agent exhibiting this characteristic. Lipophilicity also increases drug entry into the central nervous system, which can increase neurologic side effects, including seizures (in therapeutic dosing) or decreased level of consciousness (in overdose).

The second important property seen in some beta blockers (eg, propranolol and acebutolol) is membrane stabilizing activity (MSA) or sodium channel blockade. With therapeutic doses, there is little to no MSA activity; however, in overdose, QRS widening (such as that seen with tricyclic antidepressant overdose) may be seen.¹² The inhibition of myocardial fast sodium channels causes QRS widening and increases the potential for other dysrhythmias. MSA is also postulated to contribute to the seizure activity and central nervous system depression seen with some beta blockers in overdose.⁸

Co-ingestants are an important factor in the development of cardiovascular instability;¹³ however, exposure to beta blockers with MSA, even in the absence of co-ingestants, was associated with

Figure 1. The Role Of Calcium In Myocardial Contraction



Abbreviations: ATP, adenosine triphosphate; Ca²⁺, calcium; Calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; G_s, stimulatory G protein; P_i, myosin phosphorylation; MLC, myosin light chain; MLCK, myosin light chain kinase; SR, sarcoplasmic reticulum. Used with permission of Richard E. Klabunde, PhD, www.CVpharmacology.com, 2009.

an increased risk of cardiovascular instability in a 2000 prospective study.¹³ Several older papers have also reported significant mortality in patients who overdosed with beta blockers that had MSA properties.^{14,15} Though the study populations in these papers were small, they demonstrated the importance of identifying these agents correctly and appreciating their potential for significant complications.

Digoxin

Digoxin has a long tradition in medicine. William Withering first wrote about the systemic effects of the foxglove plant in 1785, observing its "power over the motion of the heart, to a degree yet unobserved in any other medicine."¹⁶ Digitalis subsequently became a first-line treatment of atrial dysrhythmias and congestive heart failure.

Digoxin is 65% to 80% absorbed from the gastrointestinal tract, has a high volume of distribution, and is excreted primarily through the kidneys.¹⁷ With a half-life of 36 hours and a narrow therapeutic level (0.64-1.2 nmol/mL or 0.5-0.9 ng/mL¹⁸), digoxin therapy has the potential for serious adverse effects.¹⁹

Digoxin functions by blocking the sodium-potassium ATPase pump, resulting in an increase in intracellular sodium. Higher levels of intracellular sodium increase the resting membrane potential, causing a decrease of the sodium/calcium channel transport. As a result, a higher intracellular level of calcium exists. As a result of the increase of intracellular calcium, more calcium is released from the sarcoplasmic reticulum, resulting in increased contractility.²⁰ Digoxin also increases vagal tone and can manifest parasympathomimetic effects (such as bradycardia).¹⁹ At toxic concentrations, there is an increase in automaticity in all cardiac cells other than the sinoatrial node due to increased influx of sodium into the cell, increasing phase 4 depolarization. Coupled with a lowered resting membrane potential, this increases the risk of dysrhythmias.²¹

Electrolyte abnormalities such as hypomagnesemia, hypercalcemia, hypernatremia, and hypokalemia all affect digoxin levels.^{19,20,22} Several drug-drug interactions have also been well described. The postulated mechanisms of these interactions include: (1) reduction of protein binding of digoxin, resulting in an increase in bioavailability; (2) alteration in renal function or electrolyte levels; and (3) inactivation of P-glycoproteins in the gastrointestinal and genitourinary tract, resulting in more digoxin absorption and less excretion, respectively.^{20,22-24} Changes in volume status and electrolyte abnormalities are also associated with the potential to induce digoxin toxicity.²⁰ Bacteria present within the bowels also metabolize digoxin to an inactive form. The use of antibiotics decreases gut flora, resulting in an increase in digoxin absorp-

tion systemically, potentially inducing toxicity.²⁵⁻²⁸

Digoxin-like substances can also be found in various plants and in toads.^{22,29,30} See **Table 1** for a brief listing of common plants containing digoxin-like substances.²⁰

Differential Diagnosis

The differential diagnosis of the bradycardic hypotensive patient is short. Included in the list are acute coronary syndromes (usually inferior myocardial infarctions with various blocks), hyperkalemia, endocrine disorders (specifically hypothyroid), hypothermia, and poisoning. Within the realm of toxicology, clonidine and cholinergic toxicity should also be considered. For more information on bradydysrhythmias, see the September 2013 issue of *Emergency Medicine Practice*.

Prehospital Care

The approach in the prehospital setting is the same as with any other acute poisoning. The airway, breathing, and circulation must be evaluated, attended to, and frequently reassessed. Even though patients may have normal vital signs initially, rapid decompensation may occur during transport, and emergency medical services (EMS) crews should

Table 1. Common Plants Containing Digoxin-Like Substances

Common Name	Botanic Name
Foxglove	<i>Digitalis purpurea</i> , <i>Digitalis lanterna</i>
Common oleander	<i>Nerium oleander</i>
Yellow oleander	<i>Thevetia peruviana</i>
Lily of the valley	<i>Convallaria majalis</i>
Red squill	<i>Urginea maritima</i>
Ouabain	<i>Strophanthus gratus</i>
Dogbane	<i>Apocynum cannabinum</i>
Wallflower	<i>Cheiranthus cheiri</i>
Milkweed	<i>Asclepias spp</i>
Mock azalea	<i>Menziesia ferruginea</i>
Pheasant's eye	<i>Adonis spp</i>
Star of Bethlehem	<i>Ornithogalum umbellatum</i>
Wintersweet, bushman's poison	<i>Carissa acokanthera</i>
Sea mango	<i>Cerbera manghas</i>
Frangipani	<i>Plumeria rubra</i>
King's crown	<i>Calotropis procera</i>
Rubber vine	<i>Cryptostegia grandiflora</i>

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anticipate this. Establishing early intravenous access is crucial, and all patients should be placed on a cardiac monitor. A fingerstick glucose check should be performed on patients with any alteration in their level of consciousness, and abnormal values should be treated. If the patient is in cardiac arrest, standard ACLS algorithms should be followed. Patients should be rapidly transported to the nearest treating facility.

EMS personnel should attempt to find out what types of medications are present in the patient's home. The scene should be surveyed for any evidence of pills or empty pill bottles, which should be brought to the emergency department (ED) for further identification. The EMS crew should perform a 12-lead electrocardiogram (ECG) for transmission to the receiving facility. This is vital, as ST-elevation acute coronary syndromes can present with bradycardia, heart blocks, and hypotension.

Emergency Department Evaluation

General Approach To Diagnosis

All patients should have their airway, breathing, and circulation assessed and, if necessary, attended to. All patients should have at least 2 large-bore intravenous lines established and be placed on cardiorespiratory monitoring. If peripheral intravenous access cannot be established, an intraosseous line is a reasonable temporary measure while awaiting central line placement. All patients should have an ECG performed immediately upon arrival. If possible, a history with a focus on the time of ingestion and amount ingested is key. Look for potential precipitating factors (eg, gastroenteritis leading to volume and electrolyte imbalances). Also, pay attention to other medications the patient may be taking. Patients should be monitored closely and frequently reassessed, as rapid changes to their clinical status may occur.

Calcium-Channel Blockers And Beta Blockers

If the patient is initially stable, a history should be obtained, concentrating on the following questions: (1) what was ingested?, (2) how much was ingested?, (3) what was the time of ingestion?, (4) is there a presence of co-ingestants?, and (5) what is the formulation of ingested product (regular vs sustained release)? In unstable patients, part of the initial assessment is to exclude other causes of shock, such as trauma, hemorrhage, or sepsis. The history may need to be obtained from the paramedic crew and/or family members.

The majority of patients with a toxic ingestion of either a calcium-channel blocker or beta blocker present with bradycardia and hypotension. Differentiating between a calcium-channel blocker or beta blocker may prove difficult on clinical grounds.

While it has been reported that beta blockers may produce hypoglycemia and that hyperglycemia is a marker of calcium-channel blocker overdose,^{8,31,32} these findings are rare and should not routinely be relied upon. While hyperglycemia should not be used to differentiate the toxins, it may have prognostic value in the setting of calcium-channel blocker toxicity. A retrospective review of 40 patients performed by Levine et al found that patients presenting with elevated serum glucose levels correlated with severity of toxicity.³³ End-point markers that were examined were the need for vasopressors, cardiac pacing, and death. This review found that, in patients with at least 1 end point, there was statistically significant elevation in serum glucose compared to patients with no end-point markers. While this study was well conducted, it did not include any calcium-channel blockers from the dihydropyridine group, nor has it been prospectively validated.

Digoxin

Digoxin toxicity may be due to an acute ingestion or it may be chronic (occurring while on therapy). Acute toxicity may present initially as a bradycardia with or without hypotension. Chronic toxicity may be difficult to diagnose, as the initial presentation may be vague and extracardiac manifestations may predominate. Patients with an acute overdose may remain asymptomatic for hours, due to the time required for digoxin to distribute to tissues. In chronic toxicity, this does not occur because digoxin is already in a steady state.³⁴ It is critical to maintain a high degree of suspicion, especially in the elderly.³⁴

Chronic toxicity may occur as a result of alterations in electrolytes (such as hypokalemia), alterations in excretion or absorption, or even volume status. The patient may present with vague symptoms that may include loss of appetite (seen in 28% of patients), abdominal pain (seen in 26%), nausea (seen in 45%), and neuropsychiatric manifestations (eg, delirium, confusion, seizures) (seen in 4.8%).^{20,34-36}

Classic visual changes that include photophobia, photopsia, decreased visual acuity, scotomas, and the classic xanthopsia (yellow halos) have also been described, but they are rare.³⁷ A review paper published in 1972 found that 95% of patients on digitalis exhibited some visual disturbances.³⁸ In a more recent retrospective review of 42 patients with digoxin toxicity, only 1 patient was found to have exhibited visual disturbances.³⁴ It is likely that the high incidence of visual disturbances in older studies were due to the variability in digitalis preparations and the lack of serum monitoring available during that era. **Table 2 (see page 6)** outlines the cardiac and noncardiac presentations of digoxin toxicity. **Table 3 (see page 6)** provides a comparison of acute versus chronic digoxin toxicity. **Table 4 (see page 6)** identifies potential precipitating causes of chronic digoxin toxicity.

Diagnostic Studies

Laboratory Studies

Patients with a suspected cardiotoxic overdose require a complete blood count, chemistry with extended electrolytes (calcium, magnesium, phosphate), glucose, coagulation studies, lactate, and a digoxin level. Lactate levels are not routinely elevated with ingestion of these agents, and they are not useful as an initial screen of severity (as over half of patients will have an initial lactate level $< 3 \text{ mmol/L}$ ³⁹), but they may serve a role in differentiating other mechanisms of shock. Obtain serum salicylate, acetaminophen, osmolality, and ethanol levels, especially in patients with any alteration in mental status,⁴⁰ as well as beta-hCG in female patients. Either an arterial or venous blood gas will provide useful information as to the acid-base status. With the growing ability to also receive basic electrolytes or even hemoglobin levels with blood gases, they are very useful initial screening tools. A computed tomographic (CT) study of the brain should be obtained in patients who are intubated or who have a decreased level of consciousness in order to exclude a structural etiology of the central nervous system depression.

Urine drug or "tox screens" are of limited utility in the acute management of the overdose patient and should not be routinely obtained. Serum levels of calcium-channel blockers or beta blockers are not available routinely, and there is no correlation between serum concentration and toxicity.⁴¹

Table 2. Clinical Presentations Of Digoxin Toxicity^{20,34,50}

- Visual disturbances (halos, color disturbances)
- Hallucinations
- Anhedonia
- Confusion
- Seizures
- Delirium
- Weakness
- Weight loss
- Fatigue
- Anorexia
- Nausea and/or vomiting
- Abdominal pain

Table 3. Features Of Acute Versus Chronic Digoxin Toxicity

Features	Acute Digoxin Toxicity	Chronic Digoxin Toxicity
Age	Younger	Older
Cardiovascular status	Normal myocardium	Underlying cardiovascular disease
Digoxin level	High	Normal to high
Potassium level	Normal to high	Normal to low
Symptoms	Cardiac symptoms predominate	Noncardiac symptoms predominate
Types of cardiac symptoms	Atrioventricular conduction blocks common	Various dysrhythmias

Laboratory Studies For Digoxin Toxicity

Serum digoxin level testing is available in most institutions, with a therapeutic range of 0.8 to 2 ng/mL. In an acute overdose, it is most beneficial to draw serum digoxin levels 6 hours after the time of ingestion to allow tissue equilibration. If the sample is drawn too soon, it may be falsely elevated, as it takes 4 to 6 hours for digoxin to equilibrate to the tissue, due to its kinetics. The serum concentration of digoxin at steady state can be used to calculate the antidote dose (see the Treatment section, page 12). Other sources of cardiac glycosides may cause elevation of serum digoxin concentrations, but these levels do not correlate with the degree of toxicity from these agents. As with any laboratory result, a digoxin level must be interpreted in the clinical context of the patient. It is critical to note that patients with elevated levels may not necessarily exhibit signs of digoxin toxicity and that patients with subtherapeutic levels may be toxic.^{19,51-53}

A review of serum digoxin levels in the Digitalis Investigation Group (DIG) trial demonstrated that rising serum digoxin levels are associated with an increase in mortality.⁵⁴ Treatment with digoxin-specific antibody fragments, however, will cause a false elevation in the serum digoxin levels after treatment.^{55,56} Patient management should be based solely on clinical status after treatment with the antidote.

Patients with potential digoxin toxicity must have their potassium and magnesium levels monitored and corrected. Hypokalemia has the potential to exacerbate digoxin toxicity, even when digoxin is at therapeutic levels.^{5,19,57} Hypokalemia enhances the cardiac effects of digoxin, and induces dysrhythmias at lower digoxin concentrations.^{5,21} Potassium should be administered until normal ranges are reached in hypokalemic patients with chronic digoxin toxicity.⁵

Hyperkalemia, on the other hand, can be a marker of acute digoxin toxicity. Hyperkalemia occurs as a result of the blockade of the Na^+/K^+ -ATPase pump, but it can also occur from the use of potassium-sparing diuretics, renal failure, angiotensin-converting enzyme (ACE) inhibitors, or potassium supplementation.⁵⁸ High levels of potassium slow the conduction of electrical impulses within the conduction system of the heart, leading to a progressive widening of the PR, QRS, and QT intervals. In acute digitalis overdose, hyperkalemia

Table 4. Factors Associated With Chronic Toxicity

- Age
- Hypothyroidism
- Hepatic disease
- Renal disease
- Low potassium or magnesium
- High calcium or sodium
- Alkalosis
- Hypoxemia
- Drug interactions: quinidine, verapamil, amiodarone, macrolides, spironolactone

has been well described in the literature as a marker of both morbidity and mortality.^{20,59,60} Bismuth et al reported that, in patients with digitoxin overdose, a serum potassium level > 5.5 mEq/L was associated with a 100% mortality.⁶¹ A recent retrospective study of patients presenting with chronic digoxin toxicity found that patients treated with digoxin-specific antibody fragments had a significant mortality risk if their potassium was > 5.0 mEq/L (odds ratio of death, 36.7).⁶²

Electrocardiogram

Calcium-Channel Blocker And Beta Blocker Overdose

The ECG is essential in the evaluation of a patient with suspected cardiovascular toxicity. While bradycardia may be commonly seen, a wide variety of dysrhythmias and blocks are possible. See Table 5 for a summary of the most common ECG findings for calcium-channel blockers and beta blockers.

The clinical presentation of calcium-channel blocker overdose varies depending on the agent ingested. Verapamil and diltiazem cause severe bradycardias and variable heart blocks.^{8,42-46} Drugs in the dihydropyridine class (including nifedipine) tend to produce more hypotension rather than conduction abnormalities, and they can cause a reflex tachycardia soon after overdose.^{8,10,47}

Beta blockers decrease cardiac automaticity and impede the conduction velocity through the atrioventricular node, producing PR prolongation. Love et al performed a prospective cohort study examining the ECG findings in patients with beta-blocker toxicity. In this study of 12 patients exhibiting toxicity, first-degree heart block was the most common finding. QRS interval prolongation was also seen, but only 7 of 12 patients had both first-degree block and prolongation of the QRS interval.⁴⁸ The study also included 2 patients with acebutolol exposure who demonstrated a disproportionate prolongation of the QTc interval as well as an R wave in aVR > 3 mm. Both of these patients developed ventricular tachydysrhythmias.⁴⁸ A case report published by Rennyson and Littmann also found a Brugada-type pattern in the setting of propranolol poisoning.⁴⁹ The patient's ECG returned to baseline once the propranolol was metabolized.

Digoxin Toxicity

Digoxin toxicity can produce a wide variety of

Table 5. Electrocardiogram Manifestations Of Calcium-Channel Blocker And Beta Blocker Toxicity⁴⁸

- | | |
|-----------------------|------------------------------------|
| • Normal sinus rhythm | • Variable atrioventricular blocks |
| • Sinus tachycardia | • Junctional rhythms |
| • Sinus bradycardia | • Bundle branch blocks |
| • PR prolongation | • QT prolongation |

dysrhythmias as a result of conduction delays and increased automaticity. At therapeutic serum levels, digoxin may produce a characteristic ECG change: the scooped appearance of the ST-segment.⁵⁰ (See Figure 2.) A landmark paper from 1966 summarized the key ECG manifestations found in patients with digoxin toxicity;⁶³ a summary can be found in Table 6 (page 9). ECG manifestations may be a junctional rhythm (see Figure 3, page 8) to ventricular tachycardia (see Figure 4, page 8). A commonly seen dysrhythmia in digoxin toxicity is paroxysmal atrial tachycardia with atrioventricular nodal block. A rarer dysrhythmia, bidirectional ventricular tachycardia,^{50,64-66} is sometimes considered pathognomonic for digitoxin toxicity, but it is also encountered in aconitine toxicity. Examples of both are seen in Figures 5 and 6 (page 8).

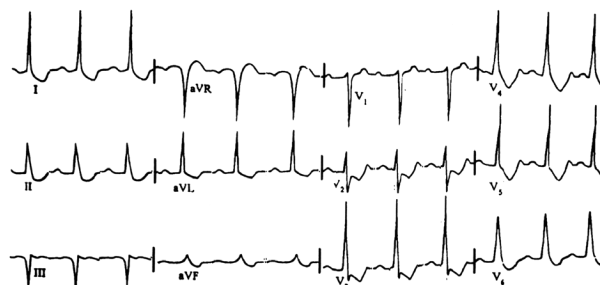
Treatment

Treatment For Calcium-Channel Blocker And Beta Blocker Overdose

Although overdoses of calcium-channel blockers and beta blockers are uncommon, they have a high mortality rate, and management may be complicated, so consultation with a toxicologist or Poison Center is recommended. A 2012 retrospective study from Canada found that in 103 patients with calcium-channel blocker toxicity, patients who had similar presenting signs but whose care followed recommendations of the Quebec Poison Control Center (QPCC) had a mortality rate of 0% compared to a mortality rate of 10% in those who did not receive QPCC-recommended management. The group whose care did not follow the recommendations of the QPCC had significantly delayed time to initial consult. This may mean that patients deteriorated, rendering them unsalvageable.⁶⁷

Calcium-channel blockers and beta blockers will be covered together in this section, as there is considerable overlap in how these 2 agents are managed. Key differences will be highlighted.

Figure 2. Electrocardiogram Of Scooping Dig Effect



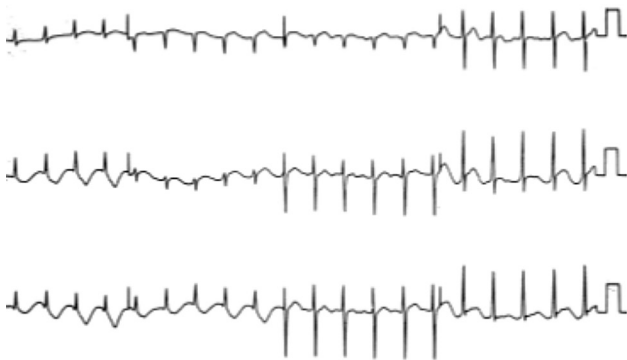
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Gastrointestinal Decontamination

Prevention of the absorption of calcium-channel blockers and beta blockers from the gastrointestinal tract seems to be a logical method to slow or prevent systemic toxicity from occurring. However, this must be done with caution, with particular attention paid to airway protection. Emesis should not be induced by any means. Activated charcoal can be considered if patients present to the ED within 1 to 2 hours of ingestion of a nonsustained-release product.⁶⁸ In a volunteer study of 32 healthy patients, charcoal administration was found to decrease absorption by nearly 50% at 2 hours from ingestion. The effect was lost if charcoal was given at 6 hours postingestion.⁶⁹ The dose for activated charcoal is 25 to 100 grams. There is currently insufficient evidence to recommend the use of cathartic agents in any overdose. A 2004 position statement by the American Academy of Clinical Toxicologists stated that routine cathartic use has no role in management of patients who have overdosed.⁷⁰

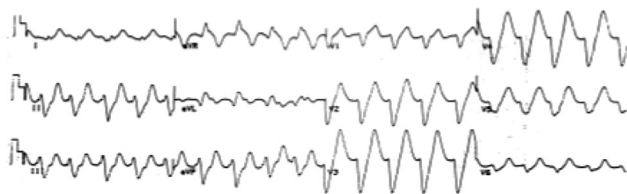
Whole-bowel irrigation should be strongly considered in patients who have ingested a sustained-release formulation and are hemodynamically stable.⁷¹ Polyethylene glycol, dosed orally at 1500 to 2000 mL/h, should be administered until rectal effluent is

Figure 3. Electrocardiogram Tracing Demonstrating Junctional Rhythm



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Figure 4. Electrocardiogram Of Ventricular Tachycardia



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clear. However, in patients who are unstable, whole-bowel irrigation may be deleterious. A case series of 2 hemodynamically unstable patients who received whole-bowel irrigation reported poor outcomes.⁷² While the first patient had a delayed presentation (3 hours after ingestion), the other patient presented within 15 minutes of ingestion. Both patients were not intubated prior to their hemodynamic collapse, and they both aspirated their gastrointestinal contents. This illustrates that administering whole-bowel irrigation to an unstable patient with an unsecured airway may lead to undesirable outcomes.

Insulin/Glucose

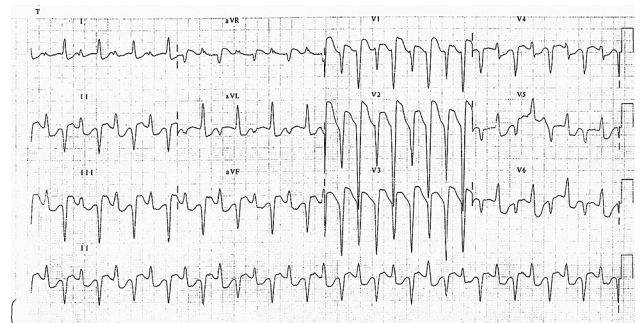
Patients who present with stable hemodynamics are treated according to the ACLS algorithm for the bradycardic patient. For the patient severely poisoned with a calcium-channel blocker or a beta blocker, high-dose insulin euglycemic therapy has become a mainstay of treatment. Several case series and reports showing good success with its use have made insulin/glucose a first-line intervention in the treatment of the unstable calcium-channel blocker-

Figure 5. Electrocardiogram Of Paroxysmal Atrial Tachycardia With Variable Block



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Figure 6. Electrocardiogram Of Bidirectional Ventricular Tachycardia



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toxic or beta blocker-toxic patient. Other agents (covered in following sections) should be tried in the stable patient.

The most commonly accepted theory regarding the mechanism of action of high-dose insulin therapy is that insulin supports the heart metabolically during shock states.³¹ When cardiac myocytes are under physiologic stress, their metabolism converts from free fatty acids to glucose. Insulin further promotes carbohydrate metabolism by increasing glucose uptake into the myocyte as well as increasing lactate uptake and providing further substrate for energy.^{31,32,73} Several studies have reported a positive effect of high-dose insulin therapy on calcium-channel blocker and beta blocker toxicity.^{8,31,74-83}

An initial bolus of 0.5 to 1 U/kg of regular insulin is given, followed by an infusion of 0.5 to 1 U/kg/h, titrated to a mean arterial pressure that ensures adequate end-organ perfusion.³¹ It is important that concurrent glucose administration occurs. With the bolus dose, give 25 g of dextrose, followed by an infusion of 0.5 g/kg/h. For the average adult weighing 80 kg, this equates to 800 mL/h of 5% dextrose solution. It may be necessary to use more-concentrated formulations (such as 10% or higher) to decrease the amount of volume administered. If the use of a more-concentrated glucose concentration is required, the placement of a central line is recommended.³¹ The 10% concentration of dextrose would equate to 400 mL/h in the average adult. It is suggested to supplement with dextrose at 0.5 g/kg/h and to monitor glucose frequently.¹⁴

Potential complications of high-dose insulin therapy are hypoglycemia and hypokalemia. However, a 2013 retrospective review of 46 patients receiving high-dose insulin therapy found that no hypoglycemic events occurred (13 patients in the review were underdosed with the insulin).⁷⁷ It is also important to monitor potassium and magnesium levels, as they may fluctuate. While no evidence-based consensus exists regarding the ideal time frame for checking serum potassium and glucose

levels, it is reasonable to check the serum glucose every 30 minutes until the glucose level stabilizes and then every hour thereafter, and to check serum potassium levels every hour until the patient is stable and then every 2 hours thereafter.

Calcium

Although it seems like a natural reversal agent (particularly for calcium-channel blocker toxicity), the evidence for calcium is weak. There are case reports describing both efficacy and lack of efficacy in giving calcium for calcium-channel blocker overdose.^{8,31} Dosing of calcium is also not well defined, and no dose-effect relationship was found in a study where doses ranged from 4.5 to 95.3 mEq.⁴⁷ Dosing recommendations commonly found in the literature are to give 10 to 20 mL of 10% calcium chloride or 30 to 60 mL of 10% calcium gluconate.^{8,31} (Note that calcium chloride contains 3 times the amount of ionized calcium, so less is required.) It is also recommended that calcium chloride be given through a central line to avoid injury in case of extravasation into the tissue. Calcium gluconate can be given safely via a peripheral intravenous line. We do not recommend more than a single dose of calcium, as its efficacy is uncertain and too much calcium can be deleterious.

Atropine

While atropine is used in the management of a bradycardic, hypotensive patient, it is rarely effective with either calcium-channel blocker or beta blocker overdose.^{15,31,47} Two studies examined the utility of atropine in calcium-channel blocker and beta blocker toxicity. Between the 2 studies, a total of 17 patients had atropine administered. It was found to have had a positive effect in only 5 patients.^{15,47} Of those 5 patients, 2 patients were receiving isoproterenol and/or epinephrine concurrently,¹⁵ raising the question of which of those agents actually improved the patients' hemodynamics. A trial of atropine dosed at 0.5 to 1 mg every 2 minutes, up to a total of 3 mg, may be used.

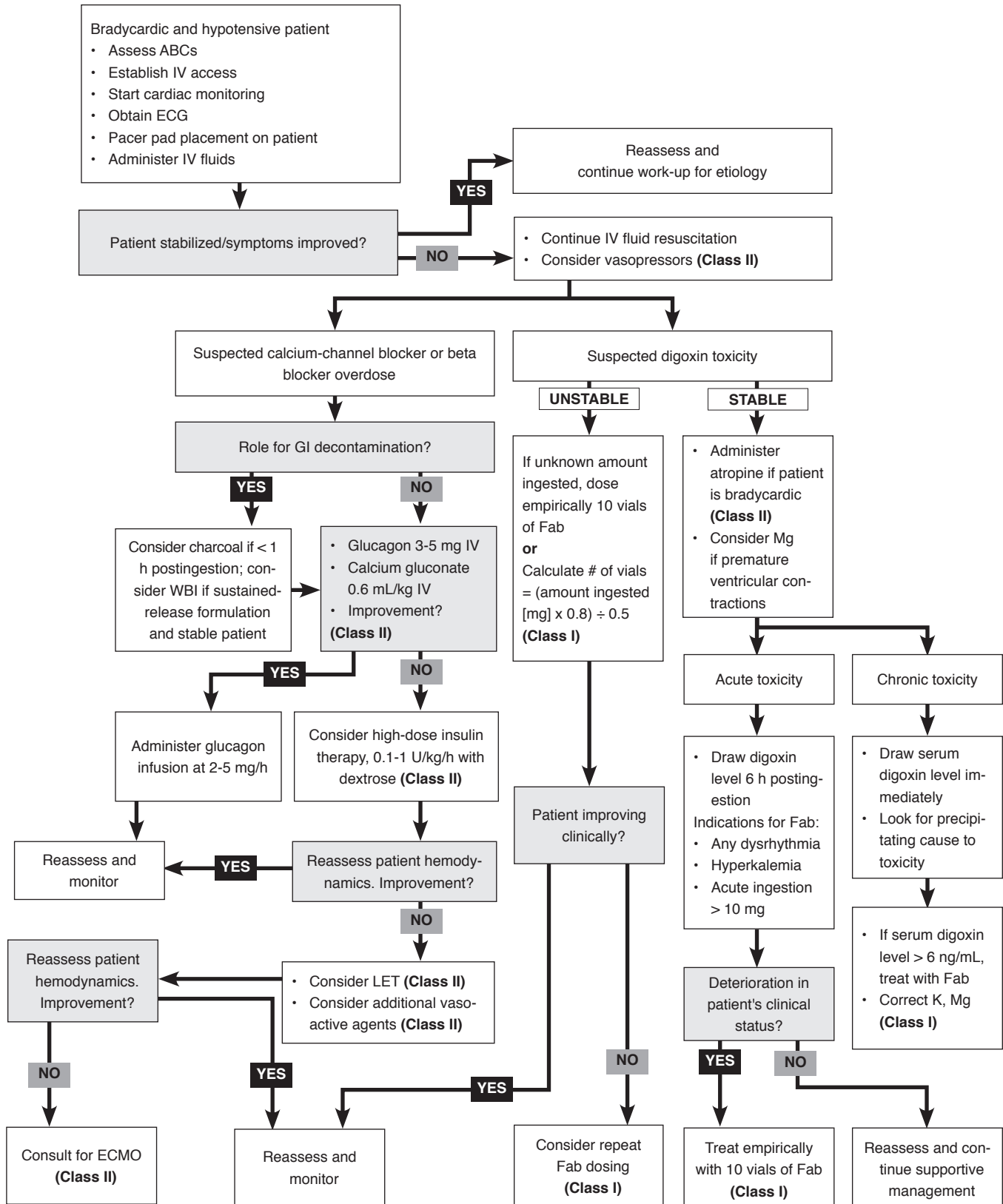
Vasopressors

Vasopressor agents are commonly used in the management of the hypotension found in calcium-channel blocker or beta blocker overdose. A wide variety of agents, including epinephrine, norepinephrine, vasopressin, dopamine, and dobutamine have been used, with variable success.^{8,31,45,47,84,85} While this may not be due to a direct failure of the vasopressor, it demonstrates that, even when multiple agents are used to treat the poisoning, the toxicity may be too great. While no head-to-head comparisons in humans have been performed, a recent animal study comparing insulin therapy to vasopressin and epinephrine found that insulin therapy was superior, producing a better blood pressure and heart rate response.⁸⁶ Standard dosing of these agents may

Table 6. Dysrhythmias Seen In Digoxin Toxicity

- Premature atrial and ventricular contractions
- Junctional rhythm
- Variable degrees of heart block
- Paroxysmal atrial tachycardia with block
- Atrial flutter and fibrillation with slow ventricular response
- Sinus bradycardia
- Ventricular tachycardia
- Ventricular fibrillation
- Bidirectional ventricular tachycardia
- Bradydysrhythmias
- Tachydysrhythmias
- Increased PR interval
- Increased automaticity

Clinical Pathway For Emergency Department Management Of Cardiotoxicity



Abbreviations: ABCs, airway, breathing, circulation; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; IV, intravenous; K, potassium; LET, lipid emulsion therapy; Mg, magnesium; WBI, whole bowel irrigation.
For class of evidence definitions, see page 11.

not be adequate, and higher doses (as well as the use of multiple agents) may be required in the severely poisoned patient.^{31,87}

In a 2013 retrospective review of 48 patients, ischemic complications during treatment of calcium-channel blocker overdose with vasopressors was assessed. Despite using higher than suggested dosing regimens of vasopressors, it was noted that only 2 of 33 patients exhibited ischemic complications as a result of vasopressor use.⁴⁵ Patients receiving vasopressor agents should have invasive blood pressure monitoring. Selecting which vasopressor to use depends on the provider's comfort level, as no single agent has been shown to be superior to another when treating calcium-channel blocker or beta blocker toxicity.³¹

Glucagon

Glucagon is produced in the pancreas and plays a key role in glucose homeostasis. Its role as a chronotropic and inotropic agent has been studied since the 1960s.⁸⁸ Glucagon exerts its effect by increasing cyclic adenosine monophosphate (cAMP). During calcium-channel blocker or beta blocker toxicity, the amount of cAMP is reduced, leading to negative inotropic and chronotropic effects. It is postulated that glucagon bypasses normal catecholamine-driven production of cAMP. Several case reports indicate its use early in the management of the toxic patient, with good success.^{43,88-92} In a well-done systematic review of 30 studies in animal models, glucagon was found to increase heart rate with minimal effects on blood pressure.⁹¹ Initial dosing is 3 to 5 mg intravenously over 1 to 2 minutes. If no improvement in the hemodynamic status is noted within 5 minutes, a repeat dose of 4 to 10 mg can be used.^{91,93} As a result of its short half-life, a maintenance infusion is recommended if hemodynamic effect is noted from the initial bolus dose. The maintenance rate is 2 to 5 mg/h. The most common adverse effects are nausea and vomiting, and it is suggested that patients be pretreated with an antiemetic prior to administra-

tion of glucagon. Glucagon therapy has largely been replaced by insulin/glucose administration.

Phosphodiesterase Inhibitors

The phosphodiesterase inhibitors (eg, amrinone, milrinone, and enoximone) function by preventing the degradation of cAMP within the cell. There are a few case reports describing efficacy in both calcium-channel blocker and beta blocker toxicity.⁹⁴⁻⁹⁶ In 2 of these papers, a phosphodiesterase inhibitor was added to glucagon.^{94,95} Potential side effects of phosphodiesterase inhibitors are hypotension secondary to vasodilation, which may be detrimental to the already-hypotensive patient. Also, several of the phosphodiesterase inhibitors have prolonged half-lives, which make them difficult to titrate.⁸ Routine use of these agents is not recommended.

Sodium Bicarbonate

Sodium bicarbonate may be indicated if there is a widened QRS, indicating the presence of sodium channel blockade.⁹⁷⁻⁹⁹ In the setting of a wide QRS complex and calcium-channel blocker or beta blocker toxicity, it may be reasonable to trial a sodium bicarbonate bolus. If the QRS shortens, consideration can be given to an infusion of sodium bicarbonate; however, it is not used routinely in management of either calcium-channel blocker or beta blocker overdose.

Pacing

Either transthoracic or transvenous pacing may be considered if the patient remains refractory to other therapies; however, its efficacy is uncertain.^{15,47,100,101} The goal heart rate should be 50 to 60 beats/min.³¹ While the heart rate does rise, inotropy does not necessarily rise, making pacing efficacy doubtful.

Extracorporeal Membrane Oxygenation And Intra-Aortic Balloon Pump

Extracorporeal membrane oxygenation (ECMO) has been used in the management of refractory shock

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I

- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:

- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II

- Safe, acceptable
- Probably useful

Level of Evidence:

- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III

- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:

- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate

- Continuing area of research
- No recommendations until further research

Level of Evidence:

- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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in calcium-channel blocker or beta blocker overdose.¹⁰²⁻¹⁰⁴ As there are no clear guidelines for the management of poisoned patients, most inclusion criteria have been extrapolated from ECMO use in the patient population with acute respiratory distress syndrome.¹⁰³ There are a few case reports of good outcomes using an intra-aortic balloon pump in severely poisoned calcium-channel blocker or beta blocker patients.^{105,106} Both modalities usually require a tertiary care hospital setting to provide the necessary services, thus limiting their routine use. These treatments should be reserved for patients with refractory shock despite optimal medical treatment.

Dialysis

Because calcium-channel blockers are highly protein bound and have a large volume of distribution, hemodialysis is not indicated or useful. A 2012 report described 3 patients treated successfully with extracorporeal albumin dialysis, utilizing a molecular adsorbent recirculating system that allows for selective removal of protein-bound toxins;⁸⁵ however, this modality is not widely available. Most beta blockers also are not dialyzable, as they are highly protein bound. The exceptions to this are atenolol, acebutolol, nadolol, and sotalol, which demonstrate unique hydrophilic properties and have minimal protein binding.^{31,104,107} Hemodialysis is not routinely indicated in the management of either calcium-channel blocker or beta blocker overdose.

Treatment For Digoxin Toxicity

Bowel Decontamination

In an acute ingestion of digoxin that presents within 1 to 2 hours of the exposure, it is reasonable to administer activated charcoal to prevent absorption^{108,109} at a dose of 25 to 100 g. It is critical to ensure that the patient is protecting his airway if charcoal administration is being considered.

Atropine

Bradycardia may be due to the vagal effects of digoxin and a trial of atropine administration (0.5-1 mg in an adult) is reasonable and may be the only treatment required. An intensive care unit-based study of 46 patients with digoxin toxicity found that patients who received atropine had a nearly 50% success rate in the resolution of their bradycardia.¹¹⁰ A confounding factor was that all patients received digoxin antibody at some point, and it is not clear how much time elapsed between atropine administration and digoxin antibody administration. Thus, the true efficacy of atropine in this study is in question.

Digoxin-Specific Antibody Fragments

The definitive treatment of digoxin toxicity is digoxin-specific antibody fragments (digoxin immune Fab) treatment. While they were developed

in the 1960s, it was not until 1976 that the first case report utilizing digoxin immune Fab was published.¹¹¹ Fab antibody fragments work by binding to digoxin found in the vascular space, creating a gradient between tissue and serum. This results in digoxin being released from the tissue into the vascular space.

A landmark study of 150 patients in 1990 demonstrated the clear efficacy of digoxin immune Fab in patients with severe digoxin toxicity.¹¹² Over 90% of the patients had a positive response, and 75% of these patients exhibited a response within 60 minutes of digoxin immune Fab administration. What is most astounding is that 54% of the 56 patients who sustained cardiac arrest survived.¹¹² In a 2010 study, 3 out of 7 patients had improvement of symptoms within 4 hours of administration of DigiFAB®.¹¹³ A 2000 in vivo study randomized 16 patients to equal doses of Digibind® or DigiFAB® and found no major clinical differences between the 2 agents.¹¹⁴ The indications for administration of digoxin immune Fab can be found in **Table 7**.

A single vial of digoxin immune Fab binds 0.5 mg of digoxin. Calculations based on serum digoxin levels (or estimates of amount ingested) are used to calculate the dosages required for digoxin immune Fab. (**See Table 8 for calculations.**) Empirically, 10 vials can be administered to adults presenting with acute digoxin toxicity, with a repeat 10-vial dose if necessary.^{115,116} In a patient with chronic toxicity, an empiric dose of 1 to 2 vials may be administered and can be repeated, if necessary.^{115,116}

Laboratory tests measure total digoxin, which will include what is bound to it after treatment with

Table 7. Indications For Administration Of Digoxin-Specific Antibodies^{22,115,116}

- Ingestion of ≥ 10 mg of digoxin (4 mg in children)
- Acute ingestion with a serum steady-state level > 10 ng/mL
- Chronic toxicity with a serum steady-state level > 6 ng/mL
- Any cardiac dysrhythmia, irrespective of serum digoxin level, not managed by more conservative treatments
- Serum potassium levels of > 5.5 mEq/L with an acute digoxin overdose
- Toxicity with nondigoxin cardioactive steroids (ie, plant or animal)

Table 8. Digoxin Fab Antibodies Dosing Calculations^{18,21,22}

$$\text{Number of vials} = \frac{\text{serum digoxin concentration (ng/mL)} \times \text{patient weight (kg)}}{100}$$

$$\text{Number of vials} = \frac{\text{serum digoxin concentration (nmol/L)} \times 0.781 \times \text{patient weight (kg)}}{100}$$

$$\text{Number of vials} = \frac{\text{amount ingested (mg)} \times 80\% \text{ bioavailability}}{0.5 \text{ (mg/vial)}}$$

digoxin immune Fab. Therefore, after the administration of digoxin immune Fab, the serum levels of digoxin may be elevated. Further management of the poisoned patient should rely solely on clinical status, and serum levels should no longer be used to guide therapy.^{20,115,116} Another important management issue is that Fab fragments are renally excreted. In patients with underlying renal dysfunction, prolonged observation is necessary after treatment to ensure complete resolution of toxicity.

Digoxin immune Fab has also been reported to be efficacious in managing digitalis toxicity from digitoxin or from plant or animal sources.^{117,118}

Pacing/Cardioversion

Cardiac pacing is not recommended in patients with digoxin toxicity. There are numerous case reports of patients receiving cardiac pacing who then deteriorate with unstable rhythms.^{20,119,120} In a 1993 retrospective study of 92 digoxin-toxic patients, complications of pacing occurred in 36%, with a fatal outcome in 13%.¹²⁰ Bradycardic patients may be initially treated with atropine. If there is an inadequate response, then digoxin immune Fab is indicated.

Similarly, cardioversion should not be done in a digoxin-toxic patient, as the myocardium becomes sensitized and there is a significant risk of the rhythm deteriorating to ventricular fibrillation. Unstable patients should receive digoxin immune Fab.⁷¹

Extracorporeal Management

Digoxin has a large volume of distribution and is highly protein bound, so hemodialysis is not indicated. A 2007 case report described a patient with acute renal failure and digoxin toxicity who was successfully treated with digoxin immune Fab and plasmapheresis.¹²¹

Electrolyte Maintenance

In a patient with an acute digoxin overdose, hyperkalemia is an indication for the administration of digoxin immune Fab.⁶¹ If there is an anticipated delay for the administration of digoxin immune Fab, then decreasing potassium levels using dextrose, insulin, or sodium bicarbonate may be considered as a temporizing measure; however, care must be taken since these patients are at risk for becoming hypokalemic once digoxin immune Fab treatment is initiated.²²

Hypokalemic patients are often hypomagnesemic as well.⁵ A 2013 case report described a patient who presented with abdominal pain and palpitations and had normal digoxin and potassium levels but was severely hypomagnesemic. The symptoms resolved with magnesium replacement, suggesting that magnesium deficiency may play a role in digoxin toxicity.⁵² Intravenous magnesium may be considered for the management of ventricular dysrhythmias associated with digoxin toxicity if digoxin immune

Fab is not readily available.¹²² Patients presenting with hypokalemia or hypomagnesemia should have their deficiency corrected, particularly if they are to undergo treatment with digoxin immune Fab.^{20,52}

Special Circumstances

Sotalol

Sotalol, a beta blocker with inward-K channel-blocking activity, has the potential to prolong the QT interval and induce ventricular dysrhythmias, including torsades de pointes.¹²³ Sotalol toxicity that presents with bradycardia and hypotension should be treated as any other beta blocker; however, if the patient is demonstrating torsades de pointes, standard treatments such as magnesium or overdrive pacing should be considered.⁹³ Given the high benefit-to-risk ratio, it is reasonable to administer magnesium sulfate prophylactically in patients who present with a sotalol ingestion and prolonged QTc.

Use Of Calcium In Digoxin Toxicity

Calcium administration is a standard practice in the management of hyperkalemia; however, in the setting of acute digoxin toxicity, the use of calcium is controversial. There are case reports of digoxin-toxic and hyperkalemic patients who were given calcium and then subsequently went into cardiac arrest.²⁰ The concept of the digoxin-poisoned patient being given calcium that precipitated “stone heart” arose from a paper published in the 1930s, where 2 patients received intravenous calcium and subsequently died of cardiac arrest. What is unknown is the serum potassium or calcium levels of these patients. Animal studies that corroborated the “stone heart” idea were found to have administered rapid levels of calcium with high serum levels (> 5 mmol/L or 20 mg/dL).²⁰ More-recent literature suggests that administration of calcium is safe in these patients.^{58,124} A 2011 study by Levine et al of 159 patients exhibiting cardiac glycoside toxicity found that 23 patients received intravenous calcium. Five of those 23 patients died, and none of the deaths occurred within an hour of calcium administration. The mortality rate in the group that did not receive calcium was 20%, with no statistical significance between the 2 groups.¹²⁴ Furthermore, a multivariate analysis of the patient data was conducted to ensure no errors occurred in the association of calcium and death. Again, calcium was found to have played no role in the death of these patients.⁶⁵ Based on these more-recent data, it is appropriate to administer intravenous calcium in bradycardic, wide-complex-rhythm patients who are likely to have hyperkalemia and in whom it is not known whether they are on digoxin. Hyperkalemia in the digoxin-toxic patient is an indication for the administration of digoxin immune Fab—which is a known safe treatment—rather than calcium.

Controversies And Cutting Edge

Lipid Emulsion Therapy

The use of lipid emulsion therapy has increased dramatically in the management of cardiovascular instability in overdose of cardiotoxic medications. While initially described in the management of cardiovascular collapse secondary to local anesthetic toxicity, it has been used in the management of hemodynamic instability unresponsive to supportive care in a number of overdose situations, including the ingestion of calcium-channel blockers and beta blockers.^{81,125-129} While the exact mechanism is unclear, 3 proposed theories as to how lipid emulsion therapy works have been described. The first is the enhancement of fatty acid transport across the mitochondrial membrane, thus enhancing the ability of the cell to produce the necessary energy to function. The second is increasing cardiac myocyte calcium levels, allowing for increased inotropy. The third is the establishment of a new medium for which the lipid-soluble drug will equilibrate to (a so-called lipid sink), pulling the toxin from tissue into the lipid solution.¹³⁰

The suggested dosing regimen is 20% lipid emulsion given as a 1.5 mL/kg bolus over 2 to 3 minutes, followed by a 0.25-mL/kg/min infusion.¹³¹ A repeat bolus dose can be administered in an asystole or pulseless electrical activity arrest situation or if the patient improves after the initial dose but then manifests hemodynamic instability.¹³¹ Once lipid emulsion therapy has been administered, it may interfere with many biochemical laboratory tests such as glucose, magnesium, and creatinine, but not potassium.

Methylene Blue

Two recent case reports describe the use of methylene blue in the management of severe calcium-channel blocker and beta blocker toxicity.^{132,133} The accumulation of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle results in vasodilatation as well as a decreased response to vasopressors. Methylene blue decreases the production of cGMP by inhibiting nitric oxide synthase and guanylate cyclase. Methylene blue has been described in other refractory shock states (such as sepsis and anaphylaxis).¹³⁴ The suggested dose from these papers is 2 mg/kg over 20 minutes, followed by a 1-mg/kg/h infusion. Despite these reports, methylene blue is not routinely indicated in either calcium-channel blocker or beta blocker toxicity.

L-Carnitine

A recent case report of a severe amlodipine and metformin overdose described the use of L-carnitine.¹³⁵ The patient ingested 3 grams of amlodipine and presented in refractory shock despite maximal therapy. The patient received 6 g L-carnitine intrave-

nously, followed by 1 g every 4 hours, and survived to discharge. The postulated mechanism of action of L-carnitine is reversal of free fatty acid metabolism from glucose in the myocytes, decreasing insulin resistance and increasing uptake and oxidation of free fatty acids.¹³⁵ Despite this report, L-carnitine is not routinely indicated in either calcium-channel blocker or beta blocker toxicity.

Disposition

Asymptomatic patients who have ingested a non-sustained-release calcium-channel blocker or beta blocker formulation should be observed for a period of at least 6 hours.^{13,136} If they remain asymptomatic, they may be discharged. Patients who become symptomatic must be treated and admitted for monitoring. Patients who have ingested sustained-release formulations should be observed for effects for up to 24 hours. Patients who ingested sotalol should be observed for at least 12 hours.

Patients with digoxin toxicity should be admitted if they are symptomatic. Patients who remain asymptomatic after 6 hours after an acute ingestion and have 2 documented digoxin levels that are stable or declining (in the setting of normal electrolytes and renal function) may be discharged with close follow-up.

Patients who have deliberately overdosed should be evaluated by psychiatry. Likewise, elderly patients who have taken their medications incorrectly should be evaluated for cognitive compromise and ability to care for themselves.

Summary

With an aging population and growing comorbidities, the use of calcium-channel blockers and beta blockers continues to increase. Patients with calcium-channel blocker or beta blocker overdose can be treated in a fairly similar manner by initiating basic interventions first, including resuscitation, intravenous fluids, and continuous cardiac monitoring. These patients may decompensate rapidly, and anticipating this may prevent an unfavorable outcome. If basic interventions do not resolve hemodynamic instability, initiate high-dose insulin therapy, vasopressors, and, if still unstable, lipid emulsion therapy.

Acute digoxin overdose is uncommon, but it may present with life-threatening dysrhythmias and blocks. Prompt administration of digoxin immune Fab may be life saving. Chronic digoxin toxicity is more common, but it may be insidious and often presents with extracardiac symptoms. One must have a high level of suspicion and always order a digoxin level in the elderly patient with vague symptoms who is on digoxin. Again, treatment with digoxin immune Fab may be indicated.

Case Conclusions

For your 44-year-old patient with atrial fibrillation and no carotid pulse, you initiated CPR and successfully intubated him. You then repeated another fluid bolus. After 2 rounds of CPR, you began to wonder what else could be done. You asked the nurses to start insulin at a dose of 1 U/kg/h with dextrose, and then you initiated lipid emulsion therapy. Approximately 10 minutes passed by, and the patient remained pulseless. You began considering ECMO, but on the next pulse check, you felt a pulse. The lipid emulsion infusion continued, and the ICU team was notified.

The blood work on your 83-year-old female patient who was taking digoxin for heart failure was returned, and her digoxin level was markedly elevated at 6.43 ng/

mL. With a weight of 95 kg, you calculated the correct dosing of digoxin immune Fab and then administered 7 vials, with resolution of her bradycardia and hypotension. She was admitted to the ICU for monitoring of her cardiac status.

For the young woman who had been taking verapamil for migraine and collapsed, you tracheally intubated her, gave her atropine and calcium, and started her on a norepinephrine infusion. However, despite these therapies, she remained hypotensive and bradycardic. You then administered high-dose insulin therapy (1 U/kg/h), with a 10% dextrose infusion. Her hemodynamic status began to stabilize, with resolution of her hypotension and bradycardia. She was admitted to the ICU for further management.

Risk Management Pitfalls For Cardiotoxicity

- "I'll just wait on the digoxin level to guide my treatment."**
Patients with acute digoxin overdose may be asymptomatic despite an elevated digoxin level if the blood is drawn before it has equilibrated in the tissues. They may manifest toxicity despite a drop in the level when the drug has entered the cell. Clinical evaluation is the most important parameter.
- "The bradycardia and hypotension did not resolve after administering digoxin immune Fab. I'll just give more."**
Do not forget to rule out other cardiotoxic medications as potential causes for the clinical scenario you are encountering. Particularly in patients with suicidal ingestion, multiple agents may be contributing to the clinical scenario.
- "I thought for sure this was a poisoning!"**
Do not forget to rule out other etiologies of the patient's clinical picture.
- "Is there really any harm in administering calcium to the patient with digoxin toxicity?"**
Despite new evidence showing (potentially) no harm, treat these patients with digoxin-specific antibodies, and avoid the risk of calcium.
- "I treated my patient with digoxin immune Fab, and now the serum level is higher than before! Now what do I do?"**
After administration of digoxin immune Fab, serum concentration measurements of digoxin are no longer useful. Use the patient's clinical picture to guide whether the patient requires further digoxin immune Fab treatment.
- "I was worried about giving so much insulin."**
Patients with either calcium-channel blocker or beta blocker toxicity may require very high doses of insulin (up to 1 U/kg/h, which is 70 U/h in a 70-kg patient).
- "The patient was acting bizarre and having vision changes, but he had a normal ECG. It couldn't have been digoxin toxicity."**
Do not forget the extracardiac manifestations with chronic digoxin toxicity, which may be the actual presenting complaint of the patient.
- "Shouldn't we have lipid emulsion as a rescue drug?"**
Be sure your ED has lipid emulsion in stock. If it is needed, it is needed quickly.
- "The patient's magnesium was low, but that shouldn't have mattered, should it?"**
Remember the potential role of hypomagnesemia in chronic digoxin toxicity. Hypomagnesemia and hypokalemia can sensitize the myocardium, even at therapeutic levels of digoxin. Hypomagnesemia can also increase myocardial digoxin uptake, so it is critical to ensure normal serum magnesium levels. Magnesium should also be administered in patients presenting with sotalol toxicity and prolonged QTc before they go into torsades de pointes.
- "I wasn't sure who to call for help."**
Cardiovascular medication poisonings are complicated to manage, and some treatment options are unfamiliar to the treating staff and physician. Call your local poison center or toxicologist for guidance.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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CME Questions



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- Which electrolyte is responsible for the increase in inotropy in normal digoxin physiology?
 - K⁺
 - Na⁺
 - Ca²⁺
 - Mg²⁺
- Regarding chronic digoxin toxicity, which of the following is TRUE?
 - Patients are generally young.
 - Patients present primarily with cardiac manifestations.
 - It can be precipitated by changes in electrolytes.
 - The threshold for giving digoxin immune Fab is the same as for acute digoxin toxicity.
- Which electrolyte disorder can exacerbate digoxin toxicity?
 - Hyponatremia
 - Hyperkalemia
 - Hypokalemia
 - Hypernatremia
- Which ECG finding is sometimes thought of as pathognomonic for digoxin toxicity?
 - Bidirectional ventricular tachycardia
 - Atrial fibrillation
 - Sinus bradycardia
 - Third-degree heart block

5. A 20-year-old woman presents with bradycardia and hypotension in a suspected calcium-channel blocker overdose. After intravenous fluids and atropine, the patient's clinical condition is unchanged. What is the next agent of choice?
 - a. Glucagon
 - b. Milrinone
 - c. Calcium
 - d. High-dose insulin and euglycemic therapy

6. Hemodialysis can be used in an overdose of which of the following agents?
 - a. Verapamil
 - b. Digoxin
 - c. Diltiazem
 - d. Acebutolol

7. A patient presents with bradycardia and hypotension from a presumed digoxin overdose. The laboratory results show a potassium level of 6.8 mmol/L. Which of the following is the most appropriate management?
 - a. Calcium
 - b. Hemodialysis
 - c. Digoxin immune Fab
 - d. Insulin and dextrose

8. Which of the following is an indication for administration of digoxin immune Fab?
 - a. Acute ingestion with a normal ECG
 - b. Acute ingestion with potassium of 5.6 mEq/L
 - c. Acute ingestion with serum level of 1.2
 - d. None of the above

9. Which of the following is not a proposed mechanism of action for lipid emulsion therapy?
 - a. It acts as a "lipid sink."
 - b. It improves fatty acid transport across the myocardium.
 - c. It increases inotropy by increasing intracellular calcium.
 - d. It promotes glucose uptake by the myocardium.

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