Toxin-Induced Cardiovascular Failure

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KEYWORDS

• β-blocker • Cardiac arrest • Cardiac injury • Calcium channel blocker • Digoxin • Dysrhythmia • Overdose

KEY POINTS

- Adverse cardiovascular events represent an immediate life threat in the setting of acute drug overdose and poisoning.
- Drugs of abuse, amphetamine-like substances, dietary supplements, and weight-reduction agents are common causes of toxicologic tachycardia.
- Cardioactive steroids, β-adrenergic antagonists, and calcium channel blockers are important causes of toxicologic bradycardia to consider.
- High-dose insulin euglycemia should be instituted in all cases of severe β-adrenergic antagonist and calcium channel blocker poisoning.
- In cases of cardiac arrest from a suspected poisoning, consider administration of intravenous lipid emulsion during the resuscitation.

INTRODUCTION: NATURE OF THE PROBLEM

Patients involved with poisoning or drug overdose, compared with cardiac clinical trial patients, are typically younger with less cardiovascular burden. Despite this, adverse cardiovascular events (ACVE) comprise a large portion of the morbidity and mortality in drug overdose emergencies reported in the American Association of Poison Control Centers National Poisoning Data System (NPDS).[1] In 2011, among over 2.7 million poisonings reported in NPDS, cardiovascular drugs were involved in 3.7% of exposures,

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yet accounted for a disproportionate 10.8% of all reported poisoning fatalities, and were among the top three substance categories with most rapidly increasing exposures. Drug-related ACVEs include the following: myocardial injury (by biomarker or electrocardiogram [ECG] evidence); shock (hypotension or hypoperfusion requiring vasopressors); ventricular dysrhythmias (ventricular tachycardia/fibrillation, torsades des pointes); or cardiac arrest (loss of pulse requiring cardiopulmonary resuscitation).[2,3] Recently, the incidence of ACVE from hospitalized drug overdose patients was estimated to be as high as 16.9%.[4] This high morbidity implies that emergency practitioners should be particularly adept at caring for these potentially critical patients.

ADVERSE CARDIOVASCULAR EVENTS

Based on the revised clinical classification of myocardial infarction, mechanisms and pathophysiology of drug-induced myocardial injury are outlined in **Table 1**.[4,5] Drugs may cause myocardial injury through a variety of mechanisms. Myocardial injury is the most common ACVE that occurs in overdose.[4] Serum cardiac troponin I is released into the bloodstream after myocardial cell necrosis or injury.[6] Drug-induced shock is the second most common ACVE that occurs because of drug overdose.[4] A conceptual model of how drug overdose may lead to shock is illustrated in **Fig. 1**, which may manifest as cardiogenic, distributive, or hypovolemic shock.

Sudden cardiac death in a young healthy population is statistically most likely to be drug-related.[7,8] Ventricular dysrhythmia is the third most common ACVE that occurs in drug overdose.[4] Mechanisms and pathophysiology of overdose-related dysrhythmia are outlined in **Table 1**. Ventricular fibrillation is the final common pathway of most sudden cardiac deaths, but rhythm disturbances may begin with monomorphic or polymorphic ventricular tachycardia (VT) and torsades des pointes (TdP), a form of polymorphic VT that is identified characteristically on the ECG.[9] Poisoning is an infrequent cause of cardiac arrest in elderly patients, but is the leading cause of cardiac arrest in patients younger than 40 years of age.[1,10,11]

Table 1
Mechanisms and pathophysiology of ACVEs after drug overdose

ACVE	Mechanism	Pathophysiology
Myocardial injury	Decreased myocardial O_2 supply	Coronary artery vasospasm Decreased O_2 carrying capacity
	Increased myocardial O_2 demand	Hyperthermia, agitation Tachycardia, hypertension
	Myocardial cell death	Inhibition of oxidative phosphorylation
Shock	Decreased intravascular volume	Fluid losses Gastrointestinal hemorrhage
	Decreased SVR	Vasodilation
	Diminished myocardial contractility	β-Adrenergic antagonism Ca^{2+}/Na^{+} channel blockade
Ventricular dysrhythmia	Myocardial sensitization	QT prolongation/dispersion K^{+} channel blockade
	Triggered beats	Premature contractions Intracellular Ca^{2+} release

Abbreviations: ACVE, adverse cardiovascular events; SVR, systemic vascular resistance.

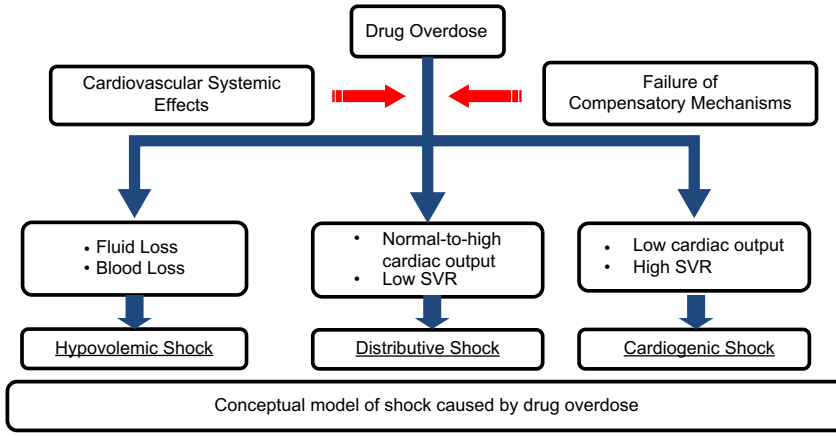

Fig. 1. Conceptual model of shock caused by drug overdose. SVR, systemic vascular resistance.

TOXICOLOGIC TACHYCARDIA

Under normal circumstances, the sinoatrial (SA) node is the most rapidly firing cardiac pacemaker. However, some drugs can speed the rate of rise during phase 4 of the action potential. Alternatively, drugs may inappropriately increase the firing rate of extrinsic pacemakers. The resultant toxicologic tachycardia may prove either disastrous or life-saving, depending on the clinical circumstances. In addition, physiologic causes of tachycardia may result from drug toxicity, such as anxiety, dehydration, pain, or hyperthermia. The most significant toxicologic causes of tachycardia include cyclic antidepressants (CA), sympathomimetics, anticholinergics, methylxanthines, and other agents that may open cardiac sodium channels.

In CA overdose, sodium channel blockade is also accompanied by antimuscarinic effects and α-adrenoceptor antagonism. The result is a rhythm with a wide QRS complex that may resemble VT. The duration of the QRS has also been studied as a marker of prognosis. A landmark prospective study in CA poisoned patients demonstrated that a QRS duration less than 100 milliseconds was an indicator of good prognosis, whereas a QRS greater than 100 milliseconds was associated with increased risk of seizures, and greater than 160 milliseconds was associated with increased risk of ventricular dysrhythmia.[12] CAs seem to preferentially antagonize the right-sided intraventricular conductive system. Delayed depolarization of the right ventricle results in several ECG findings that are specific to the CA poisoning, which include a right axis deviation between 130 and 270 degrees, and a terminal 40 milliseconds R-wave in aVR.[13] While later studies found varying degrees of sensitivity and specificity for these markers in CA poisoning, they remain valuable indicators to actively seek out and address. Additional ECG manifestations of right ventricular depolarization delay include the Brugada pattern and right bundle branch block.[14]

Sympathomimetics encompass drugs of abuse (eg, cocaine, amphetamines, "bath salts"), and amphetamine-like substances, which include decongestants (eg, pseudoephedrine), dietary supplements (eg, ephedra, ma huang), and weight-reduction agents (eg, phentermine and fenfluramine ["phen-fen"], phenylpropanolamine). Increased central nervous system (CNS) synaptic terminal output of norepinephrine leads to α- and β-adrenoceptor agonism at the postsynaptic receptor, which clinically results in tachycardia and hypertension. Additionally, ST segment changes may result from coronary

artery vasoconstriction leading to myocardial injury. Sympathomimetics may generate early after depolarizations, which can lead to malignant cardiac dysrhythmias.

Anticholinergic toxicity results in tachycardia by reducing the baseline suppressive vagal tone on the SA node. Common anticholinergic toxins include such drugs as diphenhydramine and CAs, and such plants as *Datura stramonium* (Jimson weed). Clinical hallmarks of anticholinergic toxicity include skin flushing, drying of sweat glands and mucous membranes, mild hyperthermia, decreased bowel sounds, urinary retention, and altered mental status. Management includes supportive care and antidotal administration of physostigmine (contraindications include cardiac conduction abnormalities, such as a prolonged QRS or PR interval in severe cases of central and peripheral toxicity).

Methylxanthines are plant-derived alkaloids from tea leaves, coffee beans, and cacao beans. Commonly encountered methylxanthines include caffeine, theophylline, and theobromine. Structurally, they are all variants of the compound xanthine and similar to adenosine, an inhibitory CNS neurotransmitter. The mechanism of toxicity includes adenosine receptor antagonism, release of endogenous epinephrine from the adrenals, histamine release in the respiratory smooth muscle, and phosphodiesterase inhibition. Antagonism of adenosine receptors in the CNS results in agitation and seizures. Endogenous epinephrine release causes cardiac and CNS excitation along with gastrointestinal (eg, vomiting) and metabolic (eg, hypokalemia, hyperthermia) effects. Histaminergic effects in respiratory smooth muscle results in bronchodilation. Phosphodiesterase inhibition results in elevated intracellular cAMP, which enhances adrenergic effects (ie, cardiac stimulation, CNS excitation). Cardiovascular manifestations of methylxanthine toxicity include tachycardia, palpitations, premature ventricular contractions, and rarely dysrhythmias. Additionally, severe hypokalemia may complicate the clinical presentation with associated ECG changes. Sinus tachycardia is the most common ECG finding, followed by multifocal atrial tachycardia, and rarely myocardial injury. Cardiac complications are the main cause of death in methylxanthine poisoning; thus, management of cardiovascular toxicity should be aggressive. Gastrointestinal decontamination often includes multidose activated charcoal (MDAC). Supraventricular tachycardia is managed with calcium channel blockers (CCBs) or β-adrenergic antagonists (BAAs, β-blockers). Ventricular dysrhythmias should be treated with lidocaine or β-blockers. Supportive care should include blood pressure support and correction of electrolyte anomalies. Severe toxicity warrants extracorporeal removal with hemodialysis or hemoperfusion (if available).

Sodium channel activators or openers, such as aconitine or monkshood, are popular in Asian herbal medicine. These agents have severe cardiovascular manifestations in overdose. Aconite, the active alkaloid in *Aconitum* spp., may cause cardiac arrest at doses as low as 2 mg.[15] The mechanism of toxicity is sodium channel opening, resulting in prolonged myocardial sodium current influx and slowed repolarization. Initial bradycardia caused by central parasympathetic stimulation causes vulnerability to subsequent early after depolarizations leading to VT, ventricular fibrillation, or torsades des pointes. Supportive management should include aggressive measures, such as orogastric lavage, atropine for bradycardia, and cardiac pacing. Cardiac arrest may require prolonged cardiopulmonary resuscitation with consideration of cardiac bypass or placement of a balloon pump until toxicity resolves.

TOXICOLOGIC BRADYCARDIA

Bradycardia is defined as a ventricular rate of less than 60 beats per minute. Although this can be a normal variant in well-conditioned subjects, bradycardia usually arises

from two basic disturbances. The first disturbance is from depression of the dominant pacemaker, typically the sinus node, causing sinus bradycardia. The other disturbance is a block in the conduction system where impulses are incompletely carried to the atrioventricular (AV) node and the ventricular tissues. The causes of bradycardia are diverse and can include hypothermia, myocardial infarction, and pharmacologic agents.

Medications that can cause significant bradycardia include the agents in **Box 1**. Most of the drugs causing bradycardia are from the cardiovascular drug class. Although many of the medications are safe when dosed appropriately, there are a few types within the cardiovascular drug class associated with significant morbidity and mortality in the overdose setting that is important for the clinician to be aware of. The two major classes of importance are the BAAs or β-blockers and the calcium channel antagonist or CCBs. Although other agents such as cardioactive steroids (ie, digoxin) and α_2-adrenergic agents (ie, clonidine, tizanidine) are associated with toxicity, BAAs and CCBs are responsible for most of the reported deaths related to cardioactive medication poisoning.

A brief discussion of the cardiac cycle is critical to understand the mechanism of β-blockers and CCBs along with the various treatment modalities discussed in this article. The normal cardiac cycle consists of a complex series of ion movements that result in myocyte depolarization and repolarization. In normal conditions the heart rate is determined by the SA node. Pacemaker cell depolarization is caused by either rhythmic release of calcium from the sarcoplasmic reticulum or inward cation current. During systole, voltage sensitive L-type calcium channels located on the membrane myocyte open. This allows calcium to flow down its concentration gradient into the myocyte. The local increase in calcium concentration triggers the ryanodine receptors to release more calcium that results in binding with troponin C and allows actin-myosin interaction with subsequent myocyte contraction. During diastole, several pumps actively remove calcium from the cytosol that results in dissociation of calcium from troponin with relaxation.

β-adrenergic receptors are divided into β_1, β_2, and β_3 subtypes. In normal individuals, about 80% of all cardiac β-receptors are β_1 and 20% are β_2, with a very small number of β_3 receptors.[16] β_1 adrenergic receptors mediate increased inotropy involving cAMP and various protein kinases. Stimulation of this receptor subtype also increases chronotrophy. Acute β-adrenergic stimulation improves cardiac function but chronic stimulation results in several detrimental effects, such as dysrhythmias and impaired contraction. BAAs competitively antagonize the effects of catecholamines at the β-receptors to blunt the chronotropic and inotropic response to catecholamines. β_2-adrenergic receptors mediate smooth muscle relaxation in various

Box 1
Agents causing bradycardia

- α_2-Adrenergic agonists (eg, clonidine, tizanidine)
- β-Adrenergic antagonists
- Calcium channel blockers
- Cardioactive steroids (eg, digoxin, foxglove, yellow oleander)
- Cholinergic agents (eg, organophosphates, carbamates, sarin)
- Ergot alkaloids
- Opioids

tissues, such as the lung and peripheral vascular tissue, so stimulation of this receptor subtype leads to bronchodilation and peripheral vasodilation. β_3-adrenergic receptor mediates lipolysis in adipose tissue and thermogenesis in skeletal muscles.

BAAs are commonly used to treat hypertension, tachydysrhythmias, and coronary artery disease. Other indications include congestive heart failure, migraine headaches, anxiety, and hyperthyroidism. Within this diverse class of medications are certain BAAs that contain additional properties that are important for clinician to be aware (**Table 2**). Propranolol is the very lipid-soluble and considered the most toxic of the BAAs. Propranolol has membrane-stabilizing effects that result in inhibition of fast sodium channels similar to what is seen with tricyclic antidepressants, resulting in seizures and dysrhythmias.[17,18] Sotalol is another BAA with additional potassium channel blocking, resulting in QT prolongation and an additional TdP liability.

CCBs are a commonly used cardiovascular drug class. The primary action of all CCBs available in the United States is antagonism of the L-type voltage-gated calcium channels.[19] Although CCBs are often structurally classified into three groups (**Box 2**), it is often more logical to classify them into two groups based on their mechanism of action: nondihydropyridine and dihydropyridine CCBs. The former includes verapamil and diltiazem, whereas the latter includes such drugs as nifedipine and amlodipine. Each group binds a slightly different region of the α_{1c} subunit of the calcium channel and thus has different affinities for the various L-type calcium channels, both in the myocardium and the vascular smooth muscle. Verapamil and diltiazem have inhibitory effects at the SA and AV nodal tissue and are commonly used to achieve rate control in atrial flutter and atrial fibrillation and abolishing supraventricular reentrant tachycardias. The dihydropyridines have little effect on the myocardium at therapeutic doses and act primarily at the peripheral vascular tissue to produce resulting in dilatation. They are often used for various conditions with increased vascular tone, such as hypertension, migraine headaches, and postintracranial bleed vasospasm.

The clinical hallmarks of BAA and CCB poisoning are primarily an extension of their therapeutic effects and include hypotension and bradycardia from the combination of myocardial depression and peripheral vasodilation. A variety of myocardial conduction abnormalities may also occur with significant poisonings (idioventricular rhythms, complete heart block, and junctional escape rhythms).[20,21] Certain BAAs, such as sotalol,

Table 2
Selected β-adrenergic antagonists

Selective β_1-Antagonists	Nonselective β_1- and β_2-Antagonists	β_1- and β_2-Antagonists with α_1-Antagonism
Acebutolol[a,b]	Carteolol[b,c]	Carvedilol[a]
Atenolol	Levobunolol[c]	Labetalol[a,b]
Betaxolol[a,c]	Metipranol[c]	
Bisoprolol	Naldolol	
Esmolol	Oxprenolol[a,b]	
Metoprolol[a]	Penbutolol[b]	
	Pindolol[a,b]	
	Propanolol[a]	
	Sotalol[d]	
	Timolol[c]	

[a] Membrane stabilizing (sodium channel blocking) activity.
[b] Intrinsic sympathomimetic (agonist) activity.
[c] Available as an antiglaucoma formulation.
[d] Potassium channel blocking activity.

Box 2
Calcium channel blockers

- Benzothiazepine
  - Diltiazem[a]
- Dihydropyridines
  - First generation
    - Nicardipine
    - Nifedipine
  - Second generation
    - Felodipine
    - Isradipine
    - Nimodipine
    - Nisoldipine
  - Third generation
    - Amlodipine
    - Clevidipine
- Phenylalkylamine
  - Verapamil[a]

[a] Sodium channel inhibition.

block the potassium rectifier channel, which can lead to QT prolongation, resulting in torsades de pointes.[22] The negative inotropic effects may be so profound, particularly with verapamil, that ventricular contraction may be completely ablated. Dihydropyridines, particularly amlodipine, may increase nitric oxide (NO) release, contributing to toxicity. Early symptoms may include dizziness and lightheadedness. Patients with severe poisoning may manifest syncope, altered mental status, coma, and sudden death.[23,24] Patients may also present asymptomatic with early ingestions but deteriorate rapidly into severe cardiogenic shock, especially with large ingestions of sustained-release preparations.

Although BAA and CCB poisoning are indistinguishable in many cases, there are some features that may aid in separating the two drug classes. CCB poisoning may cause hyperglycemia, caused by the blockage of pancreatic L-type calcium channels in the pancreas resulting in decreased insulin secretion.[25] This is in contrast to BAAs, which can cause hypoglycemia, although this is a less reliable presentation in toxicity. Another feature that may be seen in isolated CCB poisoning is preservation of mental status. BAA poisoning is commonly associated with lethargy and depressed mental status. The mechanism for this difference is not entirely clear, but research points to calcium channel–mediated apoptosis, and CCBs may preserve CNS function. Distinguishing between the two classes is not essential and management should be initiated based on the premise that either or both drug classes may be involved.

TOXICOLOGIC VASOCONSTRICTION

Toxicologic vasoconstriction can result from exposure to numerous substances, including drugs of abuse, such cocaine and amphetamines, and dieting drugs and

antimigraine medications. Toxicologic vasoconstriction often occurs through direct stimulation of α-adrenergic receptors, although it can also occur indirectly by actions on other receptors causing release of endogenous catecholamines or inhibition of vasodilatory neuropeptides. It is often seen as part of a sympathomimetic toxidrome consisting of hypertension; tachycardia (or sometimes reflex bradycardia); hyperthermia; agitation; diaphoresis; and seizures. Toxicologic vasoconstriction may directly cause end-organ damage by local ischemia or infarction of nearly any part of the body, or it may cause damage by the effects of severe hypertension.

Cocaine is a tropane alkaloid derived from the leaves of the coca plant with anesthetic and sympathomimetic activity. Cocaine is a schedule II substance sometimes used as a local anesthetic and vasoconstrictive agent, particularly in otolaryngologic procedures. It is more commonly encountered as a drug of abuse that can be nasally insufflated, smoked, ingested, or injected. In 2011, a national survey found that 14.3% of Americans over the age of 12 had used cocaine in their lifetime.[26] Cocaine was related to 488,101 emergency department visits in 2010.[27] Cocaine blocks the reuptake of dopamine, epinephrine, norepinephrine, and serotonin, and produces a sympathomimetic toxidrome with profound vasospasm. The vasoconstrictive effects of cocaine have been shown to produce deleterious effects in nearly every organ system. The danger of cocaine's vasoactive effects is heightened by associated hypercoagulability, impaired thrombolysis, and accelerated atherosclerosis. In particular, the hypertension, tachycardia, and increased oxygen demand, combined with vasoconstriction, atherosclerosis, and a hypercoagulable state create a particular significant cardiovascular threat. Cocaine can cause myocardial ischemia and infarction even in young adults, and may be responsible for 25% of myocardial infarctions in adults younger than 45 years.[28] Cocaine has been associated with ischemia and infarction of the brain, eyes, nasal septum, heart, lungs, intestines, colon, spleen, kidney, limbs, and skin. In pregnant women cocaine use is associated with intrauterine growth restriction by vasoconstriction of fetal blood supply.[29] The hypertension resulting from vasoconstriction can also cause nontraumatic hemorrhage. This is particularly dangerous in the CNS, where cocaine has been noted to precipitate subarachnoid, intraventricular, and intraparenchymal bleeding.[30]

Amphetamines refer to the class of substances structurally related to phenylethylamine. This class includes the well-known drugs of abuse methamphetamine and methylenedioxymethamphetamine, hundreds of structurally similar designer amphetamines, and synthetic cathinones, or "bath salts." Synthetic cathinones in particular have experienced an explosion in popularity in recent years.[31] Illicit use of amphetamines was estimated to be related to 159,783 emergency department visits in 2010.[27] This class also includes the prescription medications methylphenidate, pemoline, phentermine, phendimetrazine, amphetamine, dextroamphetamine, and methamphetamine, which have historically been prescribed for a variety of indications but currently are limited to treatment of attention-deficit/hyperactivity disorder, narcolepsy, and short-term weight reduction. Prescriptions for amphetamines are increasing; in the 5 years between 1996 and 2000, total US amphetamine prescriptions increased from 1.3 million to nearly 8 million.[32] Misuse of prescription amphetamines was related to 15,416 emergency department visits in 2010.[27] The primary mechanism of action of amphetamines is the release of catecholamines, particularly dopamine and norepinephrine, from the presynaptic terminals. Some amphetamines, such as methylenedioxymethamphetamine, have increased serotonergic effects. The catecholamine release results in the stimulation of peripheral α- and β-adrenergic receptors causing a sympathomimetic toxidrome. Similar to cocaine, vasospasm combined with hypertension and tachycardia can cause cerebral ischemia, infarction,

or hemorrhage; myocardial ischemia or infarction; ischemic colitis; aortic dissection; and obstetric complications. In addition, case reports are emerging of compartment syndrome associated with synthetic cathinone use, possibly caused by a combination of agitation, vasospasm, and muscle reperfusion.[33]

There are several dieting agents that have demonstrated vasoconstrictive toxic effects, including phenylpropanolamine, ephedrine, phentermine, fenfluramine, and dexfenfluramine. Phenylpropanolamine is a sympathomimetic amine that directly stimulates α-adrenergic receptors, and also causes norepinephrine release. It can cause severe hypertension, and was withdrawn after it was noted to cause hemorrhagic stroke in women.[34] Ephedrine is another sympathomimetic amine used in dieting agents. Ephedrine is the primary alkaloid in the ephedra plant (ma huang), which also contains several other ephedra alkaloids. Ephedra was formerly used as a dieting agent, but was banned because of the risk of adverse events including hypertension, myocardial infarction, cardiac arrest, and stroke.[35] It can still be found in traditional Chinese medicine preparations for asthma and colds. Phentermine is an amphetamine-like substance that was previously sold in combination with fenfluramine ("phen-fen"), and is still available by prescription as an anorectic; it has been associated with stroke.[36] Fenfluramine and dexfenfluramine are serotonergic agents available as dieting aids. Both drugs were associated with primary pulmonary hypertension, and have since been withdrawn.[37]

Ergot alkaloids are substances largely derived from the fungus *Claviceps purpurea*, including ergotamine, dihydroergotamine, ergonvine, methylergonovine, methsergide, and bromocriptine. They are most commonly used to treat vascular headaches, but may also be used in obstetrics and Parkinson disease, among other clinical uses. Ergot alkaloids act centrally and peripherally on serotonergic, dopaminergic, and α-adrenergic receptors.[38] The bioavailability of ergot alkaloids is highly variable, as is the dose at which toxicity occurs. The classic toxicologic syndrome of ergotism from epidemic outbreaks of fungal grain infections includes gangrene; nausea and vomiting; abnormal sensations, such as burning, formications, and pruritis; and CNS manifestations, such as hallucinations, seizure, and coma. However, in modern times ergot toxicity tends to be related to use of pharmacologic products and to be more exclusively vascular in nature.[39] Vascular complications most frequently involve the peripheral vasculature of the lower extremities, but may also be seen in coronary, cerebral, mesenteric, and renal vascular beds.[39–43]

Triptans are antimigraine medications that produce vasoconstrictive effects through interaction with 5-HT_{1B} and 5-HT_{1D} receptors. They include sumatriptan, naratriptan, zolmitriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and may be administered orally, sublingually, or subcutaneously. They have been observed to have toxic vasoconstrictive effects at therapeutic and supratherapeutic doses. The desired effects of triptans occur through vasoconstriction in the CNS; however, they have also been known to cause adverse neurologic events including transient ischemic attack, stroke, and spinal cord infarction.[44–46] Additionally, sumatriptan can cause chest pressure or pain in up to 15% of users, which may or may not reflect ischemia of coronary vessels.[47] Sumatriptan has been associated with myocardial ischemia and infarction in several cases.[48–50] Triptans have also been associated with splenic infarct, renal infarct, and ischemic colitis.[38,51,52]

DIGOXIN AND CARDIOACTIVE STEROID TOXICITY

Digoxin is a prototypical cardioactive steroids used in medicine for many years. Today, digoxin is used to treat patients with congestive heart failure and/or rate control

of rapid ventricular response caused by atrial fibrillation or flutter. Digoxin was originally procured from foxglove plant (*Digitalis lanata*), and there are several other naturally occurring sources that may cause severe toxicity in humans.[53] **Table 3** lists various sources. It is important for the emergency providers to recognize that these cardioactive steroids may be incorporated into several readily available legal and illegally prepared products. Severe toxicity from cardioactive steroids has been documented in products sold for increased sexual performance and male enhancement, herbal colon cleansing, and as rodenticides.[53]

Clinically there is a combination of increased ventricular automaticity and increased vagal effects resulting AV nodal blocking. This lethal combination can produce almost any type of dysrthymias, except for a rapidly conducted supraventricular tachycardia. **Box 3** provides common ECG findings associated with cardioactive steroid poisoning.[54]

The noncardiac clinical manifestations may vary with acute or chronic exposure. Acute toxicity presents with nausea and vomiting, and may be accompanied by lethargy, confusion, and weakness. Before the introduction of specific antidotal therapy, a potassium level greater than 5.5 mEq/L in the setting of acute digitoxin overdose was associated with 100% mortality.[55] Although hyperkalemia is a key prognostic feature and manifestation of acute toxicity, it is rarely high enough to cause clinical toxicity. Lethal dysrhythmias lead to demise. Chronic digoxin toxicity may produce vague clinical presentations. A more insidious symptom spectrum may include gastrointestinal upset, drowsiness, headache, visual disturbances, and delirium.[56] **Box 4** indicates several risk factors that may lead to chronic digoxin toxicity. In addition to acute toxicity, chronic toxicity is also associated with hyperkalemia, which seems to increase mortality and antidote requirements.[57]

Table 3
Selected cardioactive steroids

Origin	Source
Pharmaceutical preparations	Deslanoside C (desacetyl lanatoside C)[a]
	Digoxin
	Digitoxin[a]
	Gitalin[a]
	Lanatoside C[a]
	Ouabain[a]
Animals	Bufo toads (*Bufo* spp.)
	Fireflies (*Photius* spp.)
	Milkweed butterflies (*Danainae* spp.)
Plants	Bushman's poison (*Carissa acokanthera*)
	Crown flower (*Calotropis gigantea*)
	Dogbane (*Apocynum cannabinum*)
	Foxglove (*Digitalis* spp)
	Lily of the valley (*Convallaria mejalis*)
	Milkweed (*Asclepias* spp)
	Oleander (*Nerium oleander*)
	Ordeal tree (*Tanghinia venenifera*)
	Red squill (sea onion, *Urginea maritime*)
	Rubber vine (*Cryptostegia grandifolia*)
	Sea mango (*Cerbera manghas*)
	Wintersweet (*Carissa spectabilis*)
	Woody liana (*Strophanthus gratus*)
	Yellow oleander (*Thevetia peruviana*)

[a] Not commercially available in the United States.

Box 3
ECG findings in cardioactive steroids

- Atrial fibrillation or flutter with slow ventricular response
- Atrial tachycardia with high-grade atrioventricular block
- Bidirectional ventricular tachycardia (rare, but pathognomonic)
- Premature ventricular contractions (most common)
- "Scooped" T waves (marker of therapeutic use, not necessarily overdose)
- Sinus bradycardia
- Ventricular fibrillation
- Ventricular tachycardia

Cardioactive steroid toxicity should be considered when patients present with unexplained bradycardia, nausea and vomiting, history of congestive heart failure or atrial fibrillation and flutter, ECG findings in **Box 3**, and in patients who are prescribed digoxin with risk factors in **Box 4**.

GENERAL MANAGEMENT APPROACH

Aggressive attention to airway, breathing, and circulation is mandatory. Intravenous access should be obtained, with appropriate laboratory evaluations as described below. All patients with suspected cardiovascular poisoning should undergo prompt evaluation and be placed on a monitor even when the initial vital signs are normal. Early gastrointestinal decontamination and pharmacologic therapies should be considered before patients become unstable. This is particularly important in the setting of ingestions of sustained-release formulations. All patients who become hypotensive should receive a fluid bolus of 10 to 20 mL/kg of crystalloid, repeated as needed. Caution for aggressive fluid resuscitation should be given to patients with congestive heart failure, acute lung injury, or renal failure.

Diagnostic Testing

Any patients with suspected cardiovascular poisoning should be evaluated for potential hemodynamic compromise. All patients should be placed on continuous cardiopulmonary monitoring, and a 12-lead ECG performed to evaluate for potential QRS or QT interval widening. Bedside glucometry may suggest BAA or CCB toxicity, as previously described. A chest radiograph, pulse oximetry, and serum chemistry should also be obtained in the setting of hypotension. The most specific biomarker

Box 4
Risk factors leading to chronic digoxin toxicity

- Change in kidney function (often unrecognized)
- Dehydration
- Dose unadjusted for renal insufficiency
- Drug interactions (amiodarone, quinidine, verapamil, others)
- Macrolide use (decreased gut flora that normally metabolizes digoxin)

for end-organ injury in drug-induced shock is serum lactate.[58] Cardioactive steroids should be a consideration in the setting of bradycardia with hyperkalemia and normal renal function, in which case a serum digoxin concentration may be useful. Most hospitals are able to process emergent digoxin assays, but in patients with significant toxicity, empiric therapy may be required.

In patients with exposure to an agent that may cause toxic vasoconstriction, focal neurologic deficits should prompt investigation with imaging, usually noncontrast brain computed tomography. Chest pain should be taken seriously even in young patients, and should involve routine evaluations, such as an ECG, cardiac enzymes, and chest radiography. The potential for acute coronary syndromes, aortic/arterial dissections, pulmonary infarction, and pulmonary hypertension should be contemplated and evaluated where appropriate. Abdominal pain and bloody stools should prompt consideration of mesenteric ischemia and ischemic colitis. Renal and splenic infarct may also occur. Limb ischemia, rhabdomyolysis, and compartment syndrome should be included in the differential of muscular pain. Creatinine kinase testing should be considered in any patient with a sympathomimetic toxidrome.

Gastrointestinal Decontamination

Gastrointestinal decontamination should strongly be considered in all patients who present with a significant ingestion of a cardiotoxic agent, such as BAA or CCB, given their morbidity in severe poisoning. Patients who present early with minimal or no symptoms may have delayed cardiovascular toxicity that can be profound and refractory to conventional treatment, making early gastrointestinal decontamination a cornerstone in management. Ipecac was once commonly used in all cases of suspected ingestions to induce emesis to help prevent gastrointestinal absorption, thus potentially limiting significant toxicity. Significant complications including aspiration, perforation, and the potential for rapid deterioration in patients with BAA or CCB poisoning do not warrant its use. The efficacy of orogastric lavage has not been evaluated with BAA or CCB poisoning, but because of significant morbidity, this technique should be considered by capable practitioners for all patients who present early after large ingestions and for patients who are critically ill. When performing this technique it is important to use a large-caliber tube, because the pills may be large and/or poorly soluble. Because lavage may increase vagal tone, exacerbating any bradydysrhythmias, atropine may be required as a pretreatment.[59]

The use of activated charcoal should be considered in all patients with ingestions of BAAs of CCBs. Awake patients should receive 1 g/kg of activated charcoal orally. Activated charcoal should be withheld in patients who have altered mental status or where a sudden decline in mental status is expected (ie, tricyclic antidepressant ingestion) because of concern for aspiration, unless the airway is definitively protected. MDAC (0.5 g/kg) without a cathartic should be administered to nearly all patients with either sustained-release pill ingestions or signs of continuing absorption.[60] The effect of MDAC may be a result of the continuous presence of activated charcoal throughout the gastrointestinal tract, which may continue to absorb drugs that are extended-release. MDAC should not be administered to a patient with inadequate gastrointestinal function. Whole-bowel irrigation (WBI) with polyethylene glycol-electrolyte lavage solution (PEG-ELS, 1–2 L/h orally or by nasogastric tube in adults, up to 500 mL/h in children) should be considered for patients who ingest sustained-release products. WBI should be withheld in patients who have immediate-release ingestion because of concern for enhancing absorption by the dissolution of pill fragments. Administration is continued until the rectal effluent is clear.[61]

Management of Toxicologic Vasoconstriction

The principles for management of toxicologic vasoconstriction are generally similar regardless of substance. Testing to identify the offending substance is rarely of use in medical decision-making. Diagnosis and reversal of toxic vasoconstrictive effects and treatment of the accompanying symptoms of a sympathomimetic toxidrome are critical actions. Management of associated hyperthermia is of utmost importance and should be treated aggressively with cooling. Agitation and seizures should be treated with benzodiazepines, which may in some cases obviate the need for antihypertensive agents. Local vasoconstriction and systemic hypertension can be controlled with direct-acting vasodilators, such as nitroglycerin or nitroprusside; α-adrenergic antagonists, such as phentolamine; or titratable CCBs.[38,62] β-blockade is contraindicated in toxic ingestions with α-adrenergic effects, particularly cocaine, because of the risk of unopposed α activity.[62] Aspirin and heparin or low-molecular-weight heparin are recommended for myocardial ischemia, but the indication for revascularization with thrombolysis or cardiac catheterization is less clear, and should be decided based on the clinical situation.[38,62,63] The management of toxicologic vasoconstriction should prioritize treatment of a sympathomimetic toxidrome with benzodiazepines, cooling, and intravenous fluids, and should focus on identifying end-organ damage of vasoconstriction and treating this damage with vasodilators, α-adrenergic antagonists, CCBs, aspirin, and heparin as clinically indicated.

Management of Toxicologic Bradycardia

Patients often require pharmacologic intervention in significant ingestions. The use of agents should focus on maintaining the cardiac output and peripheral tone. Various agents, such as atropine, dopamine, and phosphodiesterase inhibitors, have been used with success; no single intervention as been shown to consistently treat severe poisoning. Although patients with unintentional or small ingestions often respond well to crystalloids and atropine, significant ingestions often require more aggressive management and multiple pharmacologic agents.

Although it would be ideal to initiate each therapy individually and monitor the patient's hemodynamic response to each treatment, in the most critically ill patients, multiple therapies may be administered simultaneously. The following is a description of recommended treatment modalities and agents.

Atropine

Atropine competitively antagonizes the muscarinic acetylcholine receptor. It is commonly used as a first-line agent in the treatment of symptomatic bradycardia from toxicologic causes that include organophosphorus compounds, cardioactive steroids, BAAs, and CCBs. Although atropine has been shown experimentally to improve heart rate and cardiac output, it is often ineffective in the setting of severe poisoning.[64] Atropine dosing for drug-induced bradycardia is similar to that dose used in advanced cardiac life support. Dosing should begin with 0.5 to 1 mg (0.02 mg/kg in children, with a minimum of 0.1 mg) intravenously every 2 or 3 minutes up to a maximum dose of 3 mg in all patients with symptomatic bradycardia.

Atropine is relatively safe when dosed appropriately. However, treatment failures should be anticipated in severely poisoned patients. In patients with suspected ingestions of extended-release formulations where in WBI or MDAC will be used, the use of atropine must be carefully considered, weighing the potential benefits of improved hemodynamics against the potential decreased gastrointestinal motility from atropine's antimuscarinic effects.

Calcium

Calcium is often used for CCB poisoning or other causes of toxicologic hypotension. The exact mechanism is not clear, but is most likely from an increase in extracellular calcium concentration with an increase in transmembrane concentration gradient. Pretreatment with intravenous Ca^{2+} prevents hypotension without diminishing the antidysrhythmic efficacy before verapamil use in the therapeutic setting.[65] This also is observed with CCB poisoning where Ca^{2+} tends to improve blood pressure more than heart rate. Experimental models have also demonstrated the utility of calcium salts with CCC poisoning. In verapamil-poisoned dogs, improvement in inotropy and blood pressure was demonstrated after increasing the serum Ca^{2+} concentration by 2 mEq/L with an intravenous infusion of 10% calcium chloride ($CaCl_2$) at 3 mg/kg/min.[66]

Clinical experiences demonstrate that calcium ions reverse the negative inotropy, impaired conduction, and hypotension in humans poisoned by CCBs.[60,67] Unfortunately, this effect is often short lived and more severely poisoned patients may not improve significantly with Ca^{2+} administration. Although some authors believe that these failures might represent inadequate dosing, optimal effective dosing of Ca^{2+} is unclear and they recommend repeat doses of calcium salts to increase the serum ionized calcium to very high concentrations.[68] Caution in the administration of Ca^{2+} should be exercised in patients who may have suspected acute cardioactive steroid poisoning as a cause of their bradycardia. The use of Ca^{2+} in the setting of cardioactive steroid poisoning may result in cardiac complications, such as asystole.[69]

Reasonable recommendations for poisoned adults include an initial intravenous infusion of approximately 10 to 20 mL of 10% calcium chloride or 30 to 60 mL of 10% calcium gluconate, followed by either repeat boluses every 15 to 20 minutes for up to three to four doses or a continuous infusion. Careful selection and attention to the type of calcium salt used is critical for dosing. Although there is no difference in efficacy of calcium chloride or calcium gluconate, 1 g of calcium chloride contains 13.4 mEq of Ca^{2+}, which is more than three times the 4.3 mEq found in 1 g of calcium gluconate. Consequently, to administer equimolar doses of Ca^{2+}, three times the volume of calcium gluconate compared with that of calcium chloride is required.

The main limitation of using calcium chloride, however, is the significant potential for tissue injury if extravasated. Administration should ideally be by central venous access. If repeat dosing or continuous infusions are necessary serum Ca^{2+} and PO_4^{-3} concentrations should be closely monitored to detect developing hypercalcemia or hypophosphatemia. Caution should be exercised with aggressive calcium salt use because there are reports of fatality with the use of infusions. Other adverse effects of intravenous Ca^{2+} include nausea, vomiting, flushing, constipation, confusion, and angina.

Cardioactive steroid poisoning and digoxin-specific antibody fragments

Cardioactive steroid poisoning should be considered in patients presenting with increased ventricular automaticity and a high-degree AV block. Patients who are unstable with acute life-threatening dysrthymias warrant emergent empiric treatment with digoxin-specific antibody fragments (Digibind, Digifab).[70] **Box 5** provides indications to treat with digoxin immune antibody fragments. These antibodies bind free serum digoxin, and also reach interstitial sites to bind digoxin at such sites as the myocardial cell. The digoxin-antibody complex is renally eliminated.[70] Some patients may demonstrate reversal of ventricular dysrthymias within 2 minutes and most have resolution of all dysrthymias within 30 minutes.[71]

The ECG should guide diagnosis and management because serum concentrations do not correlate well with toxicity. **Table 4** describes the dosing regimens for

Box 5
Indications for digoxin-specific antibody fragments

Any potential cardioactive steroid dysrhythmia

Bradydysrhythmia refractory to atropine

Chronic poisoning with end-organ manifestations (eg, altered mental status, gastrointestinal distress, renal impairment)

Digoxin ingestion of 10 mg or more in an adult (4 mg in a child)

Digoxin concentration[a] equal to or exceeding 15 ng/mL at anytime or $\geq$10 ng/mL beyond 6 hours postingestion

Nondigoxin cardioactive steroid poisoning

Potassium exceeding 5 mEq/L in acute digoxin toxicity

Shock or hemodynamic instability

[a] Some laboratories report digoxin concentrations in mmol/L. To convert mmol/L to ng/mL, multiply by 0.78.

digoxin-specific antibody fragments. Because it makes several assumptions about the volume of distribution and bioavailability, the clinical picture should guide the potential need for administration of additional vials. It should also be noted that once digoxin immune antibody fragments are provided, routine hospital assays for digoxin are useless, and will likely be falsely elevated, because they measure free digoxin and digoxin bound to antibodies.

Acute cardioactive steroid poisoning may present with elevated serum potassium, which is a poor prognostic marker but rarely the cause of toxicity. If therapy for hyperkalemia is required, sodium bicarbonate and insulin and glucose can be used safely. Concurrent calcium therapy for the treatment of hyperkalemia is to be avoided when cardioactive steroid poisoning is suspected or confirmed. Intracellular calcium is already elevated, and administration of calcium salts is believed to cause tetanic myocardial contractions or "stone heart" that was reported to be fatal in the 1930s.[69] The administration of digoxin-specific antibody fragments lowers serum potassium.[70] This and other potential complications of therapy are provided in **Box 6**.

It is critical to understand in patients poisoned with nondigoxin cardioactive steroids that the cross-reactivity in the serum assays and the digoxin-specific antibody

Table 4
Dosing of digoxin-specific antibody fragments[a]

Clinical Scenario	Dose
Empiric dosing, acute toxicity	10–20 vials (adult or pediatric)
Empiric dosing, chronic toxicity	3–6 vials (adult) 1–2 vials (child)
Known ingested digoxin dose	$\text{Vials} = \frac{\text{Amount ingested (mg)} \times 0.8}{0.5\ \text{mg}}$
Known serum digoxin concentration[b]	$\text{Vials} = \frac{[\text{digoxin concentration (ng/mL)}] \times [\text{weight (kg)}]}{100}$

[a] Each vial binds ~0.5 mg digoxin.
[b] Some laboratories report digoxin concentrations in mmol/L. To use this equation, to convert mmol/L to ng/mL, multiply by 0.78.

Box 6
Complications of digoxin-specific antibody fragment

Acute decomposition of underlying congestive heart failure or rapid atrial fibrillation after digoxin removal (very rare)

Acute lowering of potassium

Severe hypokalemia should be treated in chronic toxicity cases before administration

Allergic reaction (sheep-derived product)

Allergies to papain or papaya extracts may also increase the risk (very rare)

fragments is incomplete. Patients may have negative or "therapeutic" serum digoxin concentrations even with severe acute life-threatening poisoning. They may also require very large amounts of digoxin-specific antibody fragments; 35 vials of digoxin-specific antibody fragment were insufficient to save one patient who ingested a cardioactive steroid–containing compound derived from a bufo toad.[72,73]

Glucagon

Glucagon is an endogenous polypeptide hormone secreted by the pancreatic α cells used for its inotropic and chronotropic effects for BAA poisoning (off label). Thus, glucagon is unique in that it is functionally a "pure" β_1 agonist, with no peripheral vasodilatory effects.[74] However, in CCB poisoning, because the cellular lesion is downstream from adenylate cyclase, glucagon may have limited effect is this setting. There are reports of successes and failures of glucagon in CCB-poisoned patients who failed to respond to fluids, calcium salts, or dopamine and dobutamine.[75,76] There is also experimental evidence that illustrates the failure of glucagon with severe CCB poisoning compared with other preferred treatments, such as high-insulin therapy.[77] Dosing for glucagon is not well established. An initial dose of 3 to 5 mg intravenously, slowly over 1 to 2 minutes, is reasonable in adults, and if no hemodynamic improvement occurs within 5 minutes, retreatment with a dose of 4 to 10 mg may be effective. The initial pediatric dose is 50 μg/kg. Because of glucagon's short half-life, repeat doses may be useful. A maintenance infusion should be initiated once a desired effect is achieved. Common adverse effects include vomiting and hyperglycemia, particularly in diabetics or during continuous infusion. Patients who receive repeat administration of glucagon may exhibit tachyphylaxis, which is an acute decrease in response to a drug after repeated administration.

High-dose insulin euglycemia therapy

CCB poisoning often results in metabolic derangements resembling diabetes including acidemia, hyperglycemia, and insulin deficiency. Supportive care and traditional treatment detailed previously are not always sufficient in severe poisonings. Insulin, however, has been used historically to augment cardiac function and when administered in high doses can ameliorate many of the previously mentioned abnormalities. In recent years high-dose insulin euglycemia (HIE) therapy for CCB and BAA poisoning has been shown to have a greater effect on hemodynamics than conventional measures, such as vasopressors. HIE which is an off label therapy, has now emerged as the treatment of choice for severe cases of CCB and BAA poisonings.

In addition to impairment in myocardial function and vascular tone induced by calcium channel inhibition, CCB and BAA poisoning cause metabolic derangements, which further compromise cardiac function. Under conditions of stress like those induced by cardiotoxic drug poisoning, the heart's energy source shifts away from

preferred free fatty acids toward carbohydrates, which require insulin for uptake into myocardial cells.[78] Simultaneously, CCBs and BAAs inhibit calcium-dependent insulin release from the β-islet cells of the pancreas and induce insulin resistance. Glucose uptake into myocardium then relies on concentration gradients rather than insulin-mediated active transport, and use of the heart's primary energy source is impaired. HIE exerts its therapeutic effect through two pathways: increased inotropy and vascular dilation. Insulin improves inotropy through the PI3K pathways and through augmented glucose uptake into myocardial cells, improving energy supply and use. Insulin-mediated induction of endothelial nitric oxide synthase vasodilates coronary, pulmonary, and systemic vasculature thus improving perfusion and increasing cardiac output independent of increased inotropy.[76]

Animal studies have established HIE as superior to conventional treatment across multiple hemodynamic parameters including improved coronary artery blood flow, contractility, cardiac output, and overall survival. On the contrary, vasopressors increase systemic vascular resistance, increasing afterload and decreasing cardiac output, and have been repeatedly shown to be less effective than HIE in cardiotoxic drug poisoning. Clinical studies of HIE are limited to case reports and case series but consistently show beneficial effects of HIE in cardiotoxic drug poisonings.[79] In a review of 78 cases of CCB and BAA poisonings that received HIE after conventional therapy, survival was 88%. In the few cases of HIE treatment failure, insufficient dosing, concomitant vasopressor use, and delayed treatment have been cited.[76]

Although the dose of insulin is not definitively established, most clinicians recommend a bolus of 1 U/kg of regular human insulin along with 0.5 g/kg of dextrose. If blood glucose is greater than 300–400 mg/dL (16.6–22.2 mmol/L), the dextrose bolus is withheld. An infusion of regular insulin should follow the bolus, starting at 1 U/kg/h and titrated up to 2 U/kg/h or higher if no improvement is evident after 15 to 30 minutes. A continuous dextrose infusion beginning at 0.5 g/kg/h should also be started. D25W or D50W administered by a central venous catheter may be used to avoid large fluid volumes required with more dilute dextrose solutions. Some authors advocate the use of even higher doses (10 U/kg) of insulin, and case reports of doses more than 10 U/kg have not been associated with clinically significant adverse events.[80] Glucose should be monitored every half hour for the first 4 hours and titrated to maintain euglycemia. Potassium concentrations should also be monitored closely because insulin shifts potassium intracellularly. The response to insulin is typically delayed for 15 to 60 minutes. This necessitates early consideration for HIE if severe poisoning is suspected or with evidence of myocardial dysfunction. There are no studies evaluating the best way to discontinue HIE after cardiac function improves. A taper and abrupt cessation have been used but glucose and potassium should be monitored after HIE discontinuation for prolonged hypoglycemia and hypokalemia as insulin clears. The primary complications of HIE include hypoglycemia and electrolyte imbalances, particularly hypokalemia from intracellular potassium shifts. It is important to impress on the clinical team caring for these patients that HIE is safe and effective. Clinical human experiences support the lack of clinically relevant episodes of hypoglycemia or hypokalemia.[81]

Intravenous lipid emulsion

Intravenous lipid emulsion (ILE), also referred to in the literature as intravenous fat emulsion (IFE), is a 20% free fatty acid mixture used to deliver parenteral calories to patients unable to take oral nutrition.[82] After its unintentional discovery in the early 1990s as an antidote to bupivacaine toxicity,[83,84] ILE has since been widely studied in bupivacaine and other local anesthetics and is now firmly established in the anesthesia literature as an antidote to local-anesthetic systemic toxicity. The first nonlocal

anesthetic use of ILE was published in 2008 describing an adolescent with a buproprion and lamotrigine overdose who survived cardiovascular collapse after an anesthesiologist suggested giving ILE when maximal therapy had failed.[49] ILE is now emerging as a potential off label rescue therapy for other cardiotoxic lipophilic drugs including CCBs and BAAs.[85]

There are three proposed mechanisms of action for ILE in the treatment of cardiovascular toxicity. First, ILE provides a myocardial energy substrate in the form of free fatty acids, the preferred energy source of the heart. Provision of free fatty acids is particularly important in CCB toxicity because induced insulin deficiency limits the heart's ability to use carbohydrates. Second, ILE increases myocardial calcium as a result of triglyceride activity on calcium channels. This may have specific benefit in CCB and BAA toxicity by improving function of antagonized ion channels. Third and perhaps the prevailing theory is the lipid sink model where lipid-soluble drugs can be extracted and contained, thus limiting the drug's ability to exert toxic effects on tissues.

An important property of medications that may determine the effectiveness of IFE is the lipophilicity of a drug. Lipophilicity is the tendency of a drug to partition between lipophilic phase and the aqueous phase, and value of lipophilicity most commonly refers to logarithm of partition coefficient P (log P) between these two phases. For ionizable compounds, the partition is changed as a function of pH; this relationship follows a distribution constant (log D). Drugs that are highly lipophillic may benefit more from the use of IFE in severe poisoning. Based on a favorable (positive) Log D/Log P, CCBs and BAAs that might be particularly amenable to ILE include amlodipine, bepridil, diltiazem, felodipine, isradipine nicardipine, nimodipine, verapamil, acebutolol, betaxolol, carvedilol, labetalol, levobunolol, penbutolol, and propranolol.

Animal data demonstrate improved hemodynamics and survival after ILE administration, and case reports show survival in patients with severe cardiotoxicity receiving ILE after failure of standard therapy.[86] A retrospective chart review showed a 55% survival to discharge in patients with cardiovascular collapse and extremely poor predicted outcome after receiving ILE for cardiotoxic drug ingestions.[85]

Dosing strategies are based on animal data and case reports. Expert opinion recommends an initial bolus of 1.5 mg/kg ideal body weight of 20% ILE to be infused over 1 minute followed by an infusion of 0.25 mL/kg/min. The bolus dose can be repeated up to two times for refractory cardiovascular collapse and the infusion dose can be doubled to 0.5 mL/kg/min for persistent hypotension. The infusion should be continued for 10 minutes after stabilization of hemodynamics. The maximum dose should not exceed 10 mL/kg over the first 30 minutes.[87] The data supporting dosing regimens are extremely limited and the necessity of an infusion is debated among experts. One small review found no improvement in survival for patients receiving infusions or multiple boluses compared with those receiving a single bolus.[88]

Concern exists over possible adverse effects of ILE, primarily lipid embolic complications seen when administering lipid in high doses or rapid infusions. No such pulmonary complications have been reported for ILE when used as an antidote. Hyperamylasemia without subsequent pancreatitis has been reported. Lipemia subsequent to ILE infusion can potentially alter interpretation of laboratory values. There exists one case report of this complication, occurring after a massive ILE overdose.[89] Currently, ILE as rescue therapy is considered reasonable for refractory cardiovascular collapse after ingestion of cardiotoxic drugs.

Adjunctive Hemodynamic Support

The most severely cardiovascular-poisoned patients may not respond to any pharmacologic intervention. Transthoracic or intravenous cardiac pacing may be required to

improve heart rate, as several case reports demonstrate. However, in a prospective cohort of CCB poisonings, two of four patients with significant bradycardia requiring electrical pacing failed electrical capture. In addition, even if electrical pacing is effective in increasing the heart rate, blood pressure often remains unchanged due to persistent impaired inotropy.[21] More invasive measures may be considered as bridge therapies while awaiting toxin elimination. Intra-aortic balloon counterpulsation is one such supportive option to be considered in cardiovascular poisoning refractory to pharmacologic therapy. Intra-aortic balloon counterpulsation was used successfully to improve cardiac output and blood pressure in a patient with a mixed verapamil and atenolol overdose. Severely cardiovascular-poisoned patients have also been supported for days and subsequently recovered fully with the more invasive and technologically demanding extracorporeal membrane oxygenation and emergent open and percutaneous cardiopulmonary bypass. The major limitation of all these technologies, however, is that they are available only at tertiary care facilities.[90]

The use of albumin dialysis with molecular adsorbents recirculating system therapy has also been reported because of its unique ability to selectively remove from circulation protein-bound toxins (and potentially drugs) that are not cleared by conventional hemodialysis. The use of molecular adsorbents recirculating system (MARS) therapy is under current investigation with *Amanita* poisoning, but reportedly was successfully used in three patients with severe CCB poisoning.[91]

Urgent consultation with a medical toxicologist or regional poison control center is recommended in cases of cardiotoxicity, because standard guidelines for non–drug-related emergency cardiovascular care may not apply to the management of acute overdose.[92,93] Rather, administering an atypical life-saving antidote or specific continuous monitoring may be deciding factors for whether or not a patient survives a severe overdose. Unfortunately, many recommendations for emergency care of drug-related cardiovascular events lack firm scientific foundation, and further research is needed.[94]

Disposition

Patients who manifest any signs or symptoms of BAA or CCB toxicity should be admitted to an intensive care setting. Because of the potential for delayed toxicity, patients ingesting sustained-release products should be admitted for 24 hours to a monitored setting, even if asymptomatic. This is particularly important for toddlers and small children in whom even one or a few tablets may produce significant toxicity. Activated charcoal and WBI should be strongly considered in those with a history of sustained-release product ingestion.

SUMMARY

The hallmarks of BAA and CCB toxicity include bradydysrhythmias, hypotension, and shock, which are an extension of the pharmacologic effects of these agents. Most patients with immediate-release ingestions develop symptoms of hypoperfusion, such as lightheadedness, nausea, or fatigue, within hours of a significant ingestion; while sustained-release formulations may result in significant delays to hemodynamic consequences and prolonged toxicity. Aggressive decontamination of patients with exposures to sustained-release products should begin as soon as possible and should not be delayed by waiting for signs of toxicity. The use of high-dose insulin therapy should be instituted early due to the temporal delay in its efficacy. In cases of severe toxicity, the use of ILE therapy should be considered. Patients who fail to respond to all pharmaceutical interventions should be considered for extracorporeal mechanical support whenever available.

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