

Cardiovascular Challenges in Toxicology

Christopher P. Holstege, MD*,
Stephen Dobmeier, BSN, CSPI

Blue Ridge Poison Center, Division of Medical Toxicology, Department of Emergency Medicine, University of Virginia, P.O. Box 800774, Charlottesville, VA 22908-0774, USA

The diagnoses and subsequent treatment of poisoned patients manifesting cardiovascular compromise challenges the most experienced emergency physician. Numerous drugs and chemicals cause cardiac and vascular disorders. Despite widely varying indications for therapeutic use, many agents share a common cardiovascular pharmacologic effect if taken in overdose. Standard advanced cardiac life support protocol care of these patients may not apply and may even result in harm if followed [1]. This chapter discusses common cardiovascular toxins and groups them into their common mechanisms of toxicity.

Epidemiology

Emergency physicians routinely evaluate and manage poisoned patients. In 2003, more than 2.3 million human exposure cases were reported to poison centers throughout the United States [1]. Of those cases, more than 500,000 (22%) were treated at health care facilities, with most of those cases evaluated in the emergency department. Cardiovascular drugs were listed as the seventh most frequently encountered human exposure in adults (40,896 cases) and the fifth leading cause of poisoning deaths. When taken in overdose, numerous other products can also produce cardiovascular toxic effects. Emergency physicians should consider the cardiac complications of specific agents at the time they are evaluating poisoned patients.

Cardiac physiology

To understand the cardiac complications of various agents, physicians must have a clear understanding of basic myocardial cell function. The

* Corresponding author.

E-mail address: ch2xf@virginia.edu (C.P. Holstege).

myocardial cell membrane in its resting state is impermeable to Na^+ . The $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ actively pumps three Na^+ ions out of cardiac cells while pumping in two K^+ ions to maintain a negative electric potential in the myocyte of approximately -90 mV (phase 4). Depolarization of the cardiac cell membrane is a result of the rapid opening of Na^+ channels and the subsequent massive Na^+ influx (phase 0). This Na^+ influx causes the rapid upstroke of the cardiac action potential because it is conducted through the ventricles and is directly responsible for the QRS interval of the EKG. The peak of the action potential is marked by the closure of Na^+ channels and the activation of K^+ efflux channels (phase 1). Calcium influx then occurs allowing for a plateau in the action potential (phase 2) and continued myocardial contraction. The cardiac cycle ends with closure of the Ca^{++} channels and activation of K^+ efflux channels causing the potential to again approach -90 mV (phase 3). It is this K^+ efflux from the myocardial cell that is directly responsible for the QT interval of the EKG.

General management of agents that cause cardiovascular toxicity

All patients who present to the emergency department (ED) following an overdose of agents that could result in cardiovascular toxicity should be closely monitored. The patient's airway should be patent and adequate ventilation assured. If necessary, endotracheal tube intubation should be performed. Too often physicians are lulled into a false sense of security at the time a patient's oxygen saturations are adequate on high-flow oxygen. If the patient has inadequate ventilation, the patient may be at risk for subsequent CO_2 narcosis, declining mental status, and development of a respiratory acidosis. The patient who has a poor gag reflex is at risk for the development of aspiration and prolonged hospitalization [2]. In those patients, intubation should be performed. Because laryngoscopy has been reported to induce a vagal response, administration of atropine should be considered in the bradycardic patient before intubation [3,4].

Patients who have overdosed on potential cardiovascular toxins should be placed on continuous cardiac monitoring with pulse oximetry. All patients should receive a large bore peripheral intravenous (IV) line and all symptomatic patients should have a second line placed peripheral or central. If the patient is a potential candidate for an IV pacemaker, central line placement should be placed in the right internal jugular or the left subclavian [5]. The initial treatment of hypotension consists of IV fluids. Close monitoring of the patient's pulmonary examination should be performed to assure that pulmonary edema does not develop as fluids are infused. Frequent neurologic checks should be made. In patients who experience altered mental status, the patient's glucose should be checked. Placement of a urinary catheter should be considered early in the care of symptomatic patients to monitor urinary output as an indicator of adequate renal perfusion.

Gastrointestinal decontamination should be considered only after initial supportive care has been provided and airway control has been assured. Activated charcoal (1g/kg) may be considered. Because many cardiovascular agents have sustained release preparations, multidose charcoal administration (1 g/kg first dose and 1/2 g/kg every 4 hours) should be considered along with whole bowel irrigation (Golytely at 500 mL/h for children and up to 2 L/h for adults) [6,7]. Ipecac syrup should not be administered in the ED and is contraindicated after overdose with the agents listed in this article because of the potential for rapid clinical deterioration [8]. Gastric lavage has not been shown to change outcome after overdose of these agents and can induce an unwanted vagal response [9].

Calcium channel blocker toxicity

Various calcium channel blockers (CCBs) are available by prescription. This group of agents includes derivatives from four structural classes: (1) the dihydropyridines (nicardipine, nifedipine, isradipine, amlodipine, felodipine, and nimodipine), (2) the phenylalkylamines (verapamil), (3) the benzothiazepines (diltiazem) and (4) the diarylaminopropylamine ethers (bepridil). As each agent has become available on the market over the past decade, the number of exposures has dramatically increased [1,10]. In 2003, there were 9650 CCB exposures reported to poison centers in the United States, with more than 1000 of those exposures categorized as moderate or major outcomes accounting for 57 deaths [1].

Pathophysiology

The CCBs discussed earlier inhibit the voltage sensitive L-type calcium channel within the cell membrane [11]. This channel resides in heart and vascular smooth muscle cell membranes. The inhibition of this channel prevents movement of Ca^{++} from extracellular sites through the cell membrane to intracellular sites. The inhibition of Ca^{++} influx within the conduction system results in slowing of conduction; potential first-, second-, and third-degree heart blocks; bradycardia; bundle branch blocks; and junctional and ventricular escape rhythms [12]. Decreased intracellular Ca^{++} within the myocardial cells results in decreased contractility and decreased cardiac output. Blockade of Ca^{++} influx within the vascular smooth muscle cells results in vasodilation. Decreased cardiac output coupled with vasodilation may result in profound hypotension [12].

The CCBs have also been associated with profound hyperglycemia refractory to standard doses of insulin [13]. CCB-mediated blockade of insulin release and the blockade of peripheral insulin receptors have been suggested as the possible etiology [14].

In animal models and human case series, verapamil and diltiazem have also been associated with cardiac Na^+ channel blockade [13,15]. This

blockade can result in a delay of phase 0 of depolarization, subsequent QRS prolongation, and further potential for dysrhythmias [13].

Clinical features

Hypotension is a common sign associated with toxicity from CCBs. Initially, the patient may complain of lightheadedness or dizziness, especially upon standing. Depending on the agent ingested, reflex tachycardia may not be seen. As levels of CCBs increase, the patient may develop marked hypotension, various heart blocks, bradydysrhythmias, acute mental status changes, oliguria, hyperglycemia, acidosis, syncope, asystole, and death [16,17]. Symptomatic CCB-overdose patients are prone to development of pulmonary edema, and frequent pulmonary reassessments should be made [18].

Management

A symptomatic acute CCB overdose can be one of the most challenging poisonings encountered by the emergency physician. Initial management of all CCB-toxic patients should be treated in the manner discussed in the section Entitled “General Management of Agents That Cause Cardiovascular Toxicity.” Atropine may be considered in an attempt to reverse symptomatic bradycardia at doses of 1 to 2 mg IV for adults (0.02 mg/kg in children, minimum of 0.15 mg and a maximum of 1 mg); however, atropine may be ineffective at reversing the bradycardia [16,19].

In symptomatic CCB poisonings, an IV calcium infusion should be considered early in the care [20]. Before central venous access, calcium gluconate may be infused through peripheral line access. Recall that 10 mL of 10% calcium gluconate (93 mg Ca^{2+} or 4.6 mEq Ca^{2+}) provides less bioavailable calcium than 10 mL of 10% calcium chloride (272 mg Ca^{2+} or 13.6 mEq Ca^{2+}). However, calcium chloride has been reported to cause marked tissue necrosis if it extravasates while being infused through peripheral venous access [21]. After central venous access is obtained, calcium chloride may be infused. The exact infusion doses of calcium and targeted calcium levels have not been well delineated [22]. An initial dose of 10 mL of 10% or 1 g in adults (20 mg/kg or up to 1 g in children) administered IV is an appropriate starting dose. This dose may be repeated and titrated to clinical effect. Increasing the patient’s ionized calcium may lead to further sedation, nausea, and vomiting.

Glucagon may be beneficial in the management of the CCB overdose [23–26]. Glucagon raises intracellular cyclic adenosine monophosphate (cAMP) concentrations that in turn open cell membrane calcium channels. A starting dose of 5 mg (50 $\mu\text{g/kg}$ in children) of IV glucagon (diluted in 10 mL and infused over 1–2 minutes) should be considered, with repeat dosing administered as needed. A glucagon infusion at 5–10 mg/hr (50 $\mu\text{g/kg/h}$ in children) may be considered. Glucagon at this dosage may induce emesis that could lead to aspiration in the sedate, nonintubated patient. When

mixing glucagon, use normal saline and avoid using the glucagon package diluent. The package diluent contains 0.2% phenol and might hypothetically result in toxicity in high doses.

High-dose insulin drips have been advocated in CCB overdose. Experimental models suggest a superior effect of this therapy in the canine model compared with other therapies [27]. Human case reports also suggest the efficacy of these drips [13,28–30]. The optimal dose of insulin is unclear [31]. Insulin infusions can be initiated at 0.2 U/kg/h and titrated upward every hour to euglycemic effect and hemodynamic effect. Supplemental glucose may be necessary to maintain euglycemia. Serum glucose and potassium levels should be monitored closely during therapy.

Catecholamine infusions may be considered after the above therapies fail to give adequate response. Epinephrine and norepinephrine have been used in the management of CCB toxicity [32,33]. Dobutamine, a direct β_1 -adrenergic agonist, may be of benefit, but adequate studies of its effect in CCB toxicity are lacking [33]. The phosphodiesterase inhibitors, amrinone and milrinone, have also been reported to be of benefit following CCB toxicity.

Recently, sodium bicarbonate infusions have been advocated in the management of CCB toxicity [13,15]. Patients with prolonged QRS (>100 ms), acidosis, or persistent hypotension despite the above methods should be considered candidates for a trial of sodium bicarbonate in doses noted in the section entitled “Sodium Channel Blocker Toxicity.”

Pacemakers, intra-aortic balloon pump, extracorporeal membrane oxygenation, and cardiopulmonary bypass may all be considered in cases not responding to pharmacologic therapy [33,34]. Vasopressin has been reported to reverse hypotension following some overdoses, but a recent study does not support the use of vasopressin monotherapy in shock secondary to CCB toxicity [35]. None of the CCBs are amenable to hemodialysis or hemoperfusion because of their large size, high protein binding, or large volume of distribution.

Disposition

Asymptomatic CCB overdose patients with normal ECGs and ingestions of nonsustained release products may be observed in the ED for 4 hours [36]. If they remain asymptomatic and the ECG remains unchanged, they may be discharged to a nonmonitored setting. An asymptomatic patient acutely overdosing on a sustained release product should be admitted to a monitored bed for observation [36,37]. Any symptomatic CCB patient should be admitted to a monitored setting until complete resolution of symptoms occurs [38].

Beta-blocker toxicity

β -adrenergic receptor antagonists are increasingly used because of their efficacy in the treatment of hypertension, ischemic heart disease, and

arrhythmias. Numerous beta-blockers (BBs) are available on the market. These agents share in common the mechanism of competitive β -adrenergic receptor antagonism. Some of these agents have equal affinity for β_1 and β_2 receptors (ie, propranolol), whereas others are selective and have greater β_1 than β_2 -receptor–blocking activity (ie, metoprolol). Some agents also block other receptors, such as α -adrenergic receptors (ie, labetalol), cardiac Na^+ channels (ie, propranolol), and cardiac potassium efflux channels (ie, sotalol) [39,40].

Pathophysiology

BBs competitively inhibit the β -adrenergic receptor. Inhibition of β_1 -receptors results in a decrease in the force and rate of myocardial contraction, a decrease in AV node conduction velocity, and a decrease in renin secretion. Inhibition of β_2 -receptors results in a decrease in glycogenolysis, decrease in gluconeogenesis, and decrease in relaxation of smooth muscles in blood vessels, bronchi, and the gastrointestinal tract.

Clinical features

In acute overdose (OD), BBs most pronounced effect is on the cardiovascular system [25,41]. Bradycardia, heart blocks, and hypotension are the hallmarks of significant BB toxicity [42]. Dyspnea may occur and be the result of congestive heart failure or bronchospasm. Coma, grand mal seizures, and changes in mental have been reported. Hypoglycemia may occur, especially in young children [43].

Management

The initial management of all patients presenting after an acute overdose of BBs or presenting with significant toxicity should be treated as in the manner discussed above in the “General Management of Agents That Cause Cardiovascular Toxicity” section. Atropine may be considered in an attempt to reverse bradycardia at doses of 1–2 mg IV (0.02 mg/kg in children, minimum of 0.15 mg and a maximum of 1 mg). In previous BB intoxications, atropine has shown inconsistent effects in reversing bradycardia and hypotension [44].

Glucagon infusion should be considered in symptomatic BB-toxic patients [25,26,44]. β -adrenergic stimulation raises intracellular cAMP concentrations that in turn regulate ion channels. When β -adrenergic receptors are inhibited, intracellular cAMP levels decrease. Glucagon increases intracellular cAMP through nonadrenergic pathways [45]. A starting dose of 5–10 mg in adults (50 $\mu\text{g/kg}$ in children) of IV glucagon (diluted in 10 mL and infused over 1–2 minutes) should be considered and can be repeated if necessary. Glucagon can be infused at 5 mg/h for adults

(50 $\mu\text{g/kg/h}$ in children). For further information on glucagon therapy, see the section entitled “Calcium Channel Blocker Toxicity.”

Calcium demonstrates efficacy at reversing the hypotensive effects of toxicity in animal models and human case reports [25,46–48]. Dosing of calcium should be performed at dosage noted in the CCB section.

Insulin infusions have been advocated for BB toxicity based on an animal model [49]. The exact mechanism of this therapy is unclear, but it is believed to be secondary to increased myocardial glucose use resulting from the high-dose insulin drips.

Catecholamine infusions may be considered after the therapies discussed earlier fail to give adequate response. Epinephrine and norepinephrine have been used in the management of BB toxicity. Dopamine has been used. Recall that dopamine at low concentrations (1–5 $\mu\text{g/kg/min}$) effects dopamine receptors in renal, mesenteric, and coronary beds leading to vasodilation. At somewhat higher concentrations (5–10 $\mu\text{g/kg/min}$), dopamine exerts positive inotropic effects by acting on β_1 -adrenergic receptors. It is not until dopamine is infused at high concentrations (>10 $\mu\text{g/kg/min}$), that dopamine effects β_1 -adrenergic receptors and leads to vasoconstriction and elevated blood pressure. Unlike the direct β_1 -adrenergic agonist activity of epinephrine and norepinephrine, dopamine does not have significant direct activity and instead induces norepinephrine release at the β_1 -adrenergic receptor. Dobutamine, a direct β_1 -adrenergic agonist, may be of benefit but adequate studies of its effect in BB toxicity are lacking [32]. Isoproterenol is a potent, nonselective β -adrenergic agonist and may also be considered [46,50].

Sodium bicarbonate infusions have been advocated in the management of propranolol toxicity because of propranolol's cardiac Na^+ channel-blockading activity [8,51]. Propranolol overdoses with prolonged QRS (>100 milliseconds), acidosis, or persistent hypotension despite the above therapies should be considered candidates for a trial of sodium bicarbonate in doses noted in the section entitled “Sodium Channel Blocker Toxicity.”

The phosphodiesterase inhibitors (ie, amrinone, milrinone) and aminophylline increase cAMP concentrations and, therefore, would theoretically be useful in BB toxicity. Animal models and case reports suggest improved survival with their use, but their efficacy beyond the use of glucagon is questionable [52,53]. Pacemaker insertion, balloon pump, and bypass may all be considered in cases not responding to pharmacologic therapy [54]. Extracorporeal removal has been reported with specific BBs with small volumes of distribution and low protein binding (atenolol, nadolol, and acebutolol), but removal is technically difficult if there is coexisting hypotension [55,56].

Disposition

Asymptomatic BB overdose patients who produce normal ECGs and ingestions of nonsustained release BB should be observed in the ED for at

least 6 hours [8,41]. If they remain asymptomatic and the ECG remains unchanged, they may be discharged to a nonmonitored setting. Asymptomatic patients acutely overdosing on a sustained release BB or sotalol should be admitted to a monitored bed for observation. Symptomatic BB-toxic patient should be admitted to a monitored setting until complete resolution of symptoms occurs.

Sodium channel blocker toxicity

The ability of drugs to block cardiac Na^+ channels has been well described in several previous literature reports [57]. This Na^+ channel-blocking activity has been described as a membrane stabilizing effect, a local anesthetic effect, or a quinidinelike effect. Agents associated with myocardial Na^+ channel blockade are listed in Table 1.

Pathophysiology

Cardiac voltage-gated Na^+ channels reside in the cell membrane and open in response to depolarization of the cell. The Na^+ channel blockers bind to the transmembrane Na^+ channels and decrease the number available for depolarization. This binding creates a delay of Na^+ entry into the cardiac myocyte during phase 0 of depolarization. As a result, the upstroke of depolarization is slowed and the QRS complex widens.

Clinical features

Myocardial Na^+ channel-blocking drugs comprise a diverse group of pharmaceutical agents (see Table 1). As a result, patients poisoned with these agents have various clinical presentations. For example, cyclic antidepressants, propoxyphene, and cocaine may result in anticholinergic, opioid, and sympathomimetic syndromes respectively. In addition, these agents may affect not only the myocardial Na^+ channels, but also other myocardial ion channels, such as the Ca^{++} influx and K^{++} efflux channels. EKG changes and rhythm disturbances not related entirely to the drug's Na^+ channel-blocking activity may result.

Sodium channel blockers result in widening of the QRS complex [58,59]. In some cases, the QRS complexes may take the pattern of recognized bundle branch blocks. In the most severe cases, the QRS prolongation becomes so profound that it is difficult to distinguish between ventricular and supraventricular rhythms [60]. Continued prolongation of the QRS may result in a sine wave pattern and eventual asystole. Sodium channel blockers may also induce a monomorphic ventricular tachycardia. Theoretically, the Na^+ channel blockers can cause slowed intraventricular conduction, unidirectional block, the development of a re-entrant circuit, and a resulting ventricular tachycardia, which can degenerate into ventricular fibrillation. Because many of the Na^+ channel-blocking agents are also anticholinergic

Table 1

Potassium and sodium channel blocking drugs and sodium-potassium-ATPase-blocking agents

K ⁺ efflux channel-blocking drugs	Na ⁺ channel-blocking drugs	Na ⁺ – K ⁺ ATPase-blocking agents
Antihistamines	Amantadine	Bufadienolides
astemizole	Carbamazepine	Digoxin
clarithromycin	Chloroquine	Digitoxin
diphenhydramine	Class IA antiarrhythmics	Foxglove
loratidine	disopyramide	Lily of the valley
terfenadine	quinidine	Oleander
Antipsychotics	procainamide	Red squill
chlorpromazine	Class IC antiarrhythmics	
droperidol	encainide	
haloperidol	flecainide	
mesoridazine	propafenone	
pimozide	Citalopram	
quetiapine	Cocaine	
risperidone	Cyclic antidepressants	
thioridazine	amitriptyline	
ziprasidone	amoxapine	
Arsenic trioxide	desipramine	
Bepridil	doxepin	
Chloroquine	imipramine	
Cisapride	nortriptyline	
Citalopram	maprotiline	
Clarithromycin	Diltiazem	
Class IA antiarrhythmics	Diphenhydramine	
disopyramide	Hydroxychloroquine	
quinidine	Loxapine	
procainamide	Orphenadrine	
Class IC antiarrhythmics	Phenothiazines	
encainide	medoridazine	
flecainide	thioridazine	
moricizine	Propranolol	
propafenone	Propoxyphene	
Class III antiarrhythmics	Quinine	
amiodarone	Verapamil	
dofetilide		
ibutilide		
sotalol		
Cyclic antidepressants		
Erythromycin		
Fluoroquinolones		
Halofantrine		
Hydroxychloroquine		
Levomethadyl		
Pentamidine		
Quinine		
Tacrolimus		
Venlafaxine		

or sympathomimetic agents, bradydysrhythmias are rare. However, the Na^+ channel-blocking agents can affect cardiac pacemaker cells. Bradycardia may occur as a result of slowed depolarization of pacemaker cells that depend upon entry of Na^+ . In Na^+ channel blocker poisoning by anticholinergic and sympathomimetic drugs, the combination of a wide QRS complex and bradycardia is an ominous sign and may indicate that the Na^+ channel blockade is so profound that a tachycardia cannot be mounted in response to muscarinic antagonism or adrenergic agonism.

Management

The initial management of all patients presenting after an acute overdose of Na^+ channel-blocking agents or presenting with significant toxicity from these agents should be treated as discussed in the above section entitled “General Management of Agents That Cause Cardiovascular Toxicity.” The management of Na^+ channel-blocking agents consists of administration sodium or alkalosis [61–63]. Infusion of sodium bicarbonate by intermittent bolus or by continuous infusion has been advocated. Hypertonic sodium infusion has also been shown to be effective [64]. A sodium bicarbonate infusion should be considered if any of the following criteria are met: QRS duration is greater than 100 milliseconds, persistent hypotension despite adequate hydration occurs, or dysrhythmias. Recall that a single ampule of sodium bicarbonate contains 50 mEq of Na^+ and multiple doses may be necessary to achieve clinical improvement of the patient. Sodium bicarbonate infusions can be created by mixing at least 3 ampules of sodium bicarbonate in 1 L of D5W and with the rate infused at two times maintenance. Consider adding potassium (40 mEq to a liter of D5W) to the sodium bicarbonate drip to prevent the development of hypokalemia (caused by the excretion of potassium in exchange for hydrogen ions as the kidneys attempt to correct the alkalosis). The infusion can then be adjusted to maintain a blood pH between 7.5 and 7.55. During infusions of sodium bicarbonate, close monitoring of electrolyte, pH, and fluid balance should be performed.

Hyperventilation has been shown to be effective in reversing sodium channel-blocking activity, most likely secondary to the induced respiratory alkalosis [65,66]. Lidocaine has been suggested in the treatment of ventricular dysrhythmias, though clear evidence is lacking [67]. Class IA and IC antiarrhythmics should be avoided because of their ability to block cardiac sodium channels.

Disposition

Any symptomatic patient who has ingested a potential Na^+ channel-blocking agent should be admitted and observed in a monitored setting. In the asymptomatic patient who has ingested a Na^+ channel-blocking agent, the length of observation varies. For example, a patient who has ingested

amitriptyline should be observed for a minimum of 6 hours. If that patient remains asymptomatic and develops no ECG changes during that time period, they can be discharged to an unmonitored setting. Other poisonings, such as diphenhydramine, can be discharged if asymptomatic after a 4-hour postingestion observation period.

Potassium efflux blocker toxicity

Definition

Studies suggest that approximately 3% of total noncardiac prescriptions are associated with the potential for QT prolongation [68]. Potassium efflux-blocking agents competitively inhibit cellular potassium efflux during cellular repolarization; therefore, a delay in repolarization occurs corresponding with an increase in the QT interval [69]. The patient may then be at risk for polymorphic ventricular tachycardia or torsades de pointes [70]. Drugs, such as sotalol, are prescribed specifically for this mechanism [71]. Other medications possess this activity as an unwelcome side effect at therapeutic doses. Many medications, such as terfenadine and cisapride, have been removed from the United States market because of reports of torsades de pointes and sudden death in patients taking these drugs [72,73]. Other medications have rarely been reported to cause QT prolongation except when taken in massive overdose. Agents associated with QT prolongation are listed in Table 1 [68,74]. Other etiologies of prolongation of the QT interval include: (1) congenital long QT syndrome, (2) hypokalemia, (3) hypomagnesemia, (4) hypocalcemia, (5) myocardial ischemia, (6) neurological catastrophes, and (7) hypothyroidism [75].

Pathophysiology

The primary problem with K^+ channel-blocking drugs is that they prolong cardiac action potentials [76], which may lead to early after-depolarizations (EAD), related triggered activity, and the possibility of torsades de pointes. Patients at increased risk are those with familial QT prolongation, patients who develop electrolyte abnormalities, patients on multiple agents with K^+ efflux channel-blocking activity, or patients on drugs that inhibit the metabolism of K^+ efflux channel-blocking agents resulting in the build-up to toxic levels.

Clinical features

Syncope may be associated with drug-induced QT prolongation. Palpitations, dyspnea, and sudden death may also be associated with QT prolongation. After acute overdose, the presenting signs and symptoms may not be related to the cardiac effects but to the other mechanisms of those drugs.

Management

If a patient has a prolonged QT interval caused by a potassium efflux-blocking agent, therapy should focus on immediate withdrawal of the potential cause and correction of any coexisting hypoxia or electrolyte abnormalities. The initial management of all patients presenting after an acute overdose of an agent associated with K^+ efflux blockade should be treated as discussed in the section entitled “General Management of Agents That Cause Cardiovascular Toxicity.” IV magnesium sulfate is a highly effective intervention to suppress occurrence of dysrhythmias associated with QT prolongation, even though Mg^{++} does not typically result in shortening of the QT interval itself [77]. A starting dose of 2 g diluted in 10 mL D5W may be infused and titrated to effect.

In patients who experience intermittent runs of torsades not responsive to magnesium therapy, electrical overdrive pacing should be considered [78]. Pacing at rates up to 100 to 120 beats per minute is often effective at terminating torsades de pointes. In the presence of a nonperfusing rhythm, such as ventricular fibrillation, pulseless ventricular tachycardia, or torsades de pointes, unsynchronized electrical defibrillation should be performed.

Disposition

Patients with newly diagnosed prolongation of their QT interval or torsades de pointes should be admitted to a monitored setting. Symptomatic patients who have ingested these agents should also be admitted to a monitored setting.

Sodium-Potassium-ATPase—Blocker Toxicity

Cardiac glycosides (CGs) are agents that inhibit the sodium-potassium adenosine triphosphosphate ($Na^+ - K^+ - ATPase$) pump. Digoxin is the most widely encountered CG, but numerous other similar acting agents also exist (see Table 1). Digoxin has been historically administered to treat supraventricular tachydysrhythmias and congestive heart failure, but its use has been decreasing as newer agents have been developed. Cardiac glycosides that are not prescription medications have also been associated with human toxicity, such as after ingestion of specific plants and contaminated herbal products [79–82].

Pathophysiology

The CGs inhibit active transport of Na^+ and K^+ across cell membranes by inhibiting the $Na^+ - K^+ - ATPase$, which results in an increase in extracellular potassium and intracellular Na^+ . An increased intracellular Na^+ results in a reduced transmembrane Na^+ gradient and subsequent increased activity of the $Na^+ - Ca^{++}$ exchanger. Intracellular calcium rises. The increased intracellular Ca^{++} augments myofibril activity in cardiac myocytes and causes

a positive inotropic action. CGs also increase vagal tone that may lead to a direct atrioventricular depression and produce conduction disturbances.

Clinical features

Cardiac glycoside toxicity may result in the following dysrhythmias [83]: (1) excitant activity (atrial, junctional and ventricular premature beats and tachydysrhythmias); (2) suppressant activity (sinus bradycardia, bundle branch blocks, first-, second-, and third-degree blocks); and (3) combination of excitant and suppressant activity (atrial tachycardia with atrioventricular block, second-degree block with junctional premature beats). The most common dysrhythmia associated with toxicity induced by these agents is frequent premature ventricular beats. Bidirectional ventricular tachycardia is specific for digitalis toxicity but is rarely seen.

In addition to the cardiac manifestations, noncardiac signs and symptoms may occur in CG toxicity and vary widely depending on whether the toxicity is acute or chronic. Anorexia, nausea, vomiting, headache, fatigue, depression, dizziness, confusion, memory loss, delirium, and hallucinations have all been noted. Visual disturbances, including seeing yellow halos around objects (xanthopsia), have been reported. Not uncommonly, chronic digoxin intoxication may be misdiagnosed as a more common illness, such as influenza or gastroenteritis.

Patients suspected of having CG toxicity should have an ECG performed and a chemistry obtained. Acute toxicity most closely correlates with hyperkalemia as the $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ is inhibited and extracellular K^+ rises. In chronic toxicity, hyperkalemia may not be seen because of the slow increase in K^+ , allowing the kidneys to correct the imbalance. Many of those patients on chronic digoxin therapy are also on diuretics that further promote potassium excretion. Chronic toxicity associated with renal failure may result in hyperkalemia caused by the kidneys' inability to compensate.

A serum digoxin level should be obtained with therapeutic levels reported between 0.5 to 2.0 ng/mL. Serum digoxin levels should be interpreted with caution. In acute exposure, digoxin is absorbed into the plasma and then slowly redistributes into the tissues. As a result, high acute digoxin levels are not always associated with toxicity. Levels greater than 10 ng/mL at any time may be associated with significant toxicity and treatment with digoxin-specific Fab should be considered. Other CGs can cross-react with the digoxin assay, though the degree of this cross-reaction is not known. A false positive assay may result in the presence of digoxinlike immunoreactive substance seen in neonates, pregnancy, renal insufficiency, liver disease, congestive heart failure, acromegaly, and stress [84].

Management

Cardiac glycoside toxicity should always be considered in patients taking digoxin and presenting with new onset dysrhythmias, gastrointestinal

complaints, or altered mental status. Meticulous attention to supportive care and a search for easily correctable conditions, such as hypoxia, hypovolemia, and electrolyte disturbances, are top priorities. Patients should always be treated as discussed in the section entitled "General Management of Agents That Cause Cardiovascular Toxicity."

In CG-poisoned patients, Fab fragments are the first-line therapy in patients who have symptomatic cardiac dysrhythmias [83,85,86]. Atropine use in animal models decreased the total percent of digoxin induced arrhythmias, delayed their onset, and changed the type of arrhythmias [87]. Cardiac pacing has been advocated for bradydysrhythmias unresponsive to atropine, but care should be exercised because the pacing wire itself may induce ventricular fibrillation. The classic antiarrhythmic of choice for ventricular dysrhythmias is phenytoin because it increases the ventricular fibrillation threshold in the myocardium and enhances conduction through the AV node. Lidocaine has been advocated for treatment of ventricular dysrhythmias caused by digitalis toxicity, although it does not affect AV nodal conduction. Few reports exist of the use of amiodarone for digoxin toxicity. Amiodarone has been reported to be effective in case reports of digoxin induced dysrhythmias [88]. Quinidine and procainamide are contraindicated in digitalis toxicity because they depress AV nodal conduction and may worsen cardiac toxicity. Electrical cardioversion of the digitalis-toxic patient must be performed with extreme caution and considered only as a last resort. A low energy setting (eg, 10–25 W/s) should be used and preparations made to treat potential ventricular fibrillation.

Supplemental potassium may be beneficial in chronic digitalis toxicity when diuretic-induced hypokalemia is a factor. It should be given cautiously because renal failure may be the cause of chronic digitalis toxicity. Potassium should not be routinely administered to the acutely poisoned patient because hyperkalemia is common. Patients who have acute CG poisoning and exhibit hyperkalemia may be treated with IV glucose, insulin, and sodium bicarbonate or continuous inhaled beta agents, such as albuterol (if no tachydysrhythmia or ectopy), although these therapies may be ineffective. The exchange resin, sodium polystyrene sulfonate, also may be considered. However, the increased serum potassium level reflects a change in potassium distribution and not an increase in total body potassium stores. The use of agents such as exchange resins may lead to total body potassium depletion and subsequent problems once the digitalis toxicity has abated. Hemodialysis may be of benefit in a CG-poisoned patient who has uncontrolled hyperkalemia. A theoretical concern exists that treating CG-induced hyperkalemia with IV calcium may enhance digitalis cardiac toxicity and should probably be avoided until further data is available.

Hypomagnesemia has been reported in a significant number of patients who are chronically CG-toxic. IV administration of magnesium has been shown to counteract ventricular irritability from digitalis toxicity [89]. The

recommended dose of magnesium for malignant ventricular dysrhythmias is 2 to 4 g (10–20 mL of a 20% solution) given IV for longer than 1 minute. Magnesium should be infused more slowly in patients who are ectopic and are hemodynamically stable. Magnesium may also be helpful in treating hyperkalemia. It should be used with extreme caution in renal failure patients.

A milestone in the treatment of CG poisoning has been the development of drug-specific antibodies. Digoxin-specific Fab fragments (Digibind or DigiTab) are antibody fragments produced by enzymatic cleavage of sheep immunoglobulin (IgG) antibodies to digoxin. Fab fragments can reverse digitalis-induced dysrhythmias, conduction disturbances, myocardial depression, and hyperkalemia in severely poisoned patients. Most patients have an initial response to CG-toxic dysrhythmias within 30 minutes of Fab administration and those who respond have complete resolution by 4 hours. Animal studies and case reports have demonstrated the efficacy of Fab fragments to the CGs contained in plants. Adverse reactions to Fab administration have been few and include rare but mild hypersensitivity reactions, precipitous drops in serum potassium, and supraventricular tachydysrhythmias previously controlled by digoxin.

Fab fragment therapy is indicated for severely intoxicated patients who do not immediately respond to conventional therapies, have CG-induced dysrhythmias that threaten or result in hemodynamic compromise, and have hyperkalemia ($K^+ \geq 5.0$ mEq/L). Often, chronically poisoned patients can be managed by discontinuing digoxin and close observation. However, the threshold for treatment with Fab should be lower in chronically poisoned patients who exhibit signs of cardiac toxicity or who have any of the predisposing conditions: (a) chronic pulmonary disease, (b) hypokalemia, (c) hypothyroidism, (d) renal insufficiency, or (e) underlying cardiac disease [90]. If patients are managed conservatively, the Fab dose to be administered should be calculated (Box 1) and the Fab fragments made available at the bedside while the patient is monitored for worsening toxicity.

Although serum digoxin levels should not be the sole factor in determining the need to administer Fab, dosage calculations for Fab are based on the serum digoxin level or estimated body load of digoxin. Equimolar doses of antibody fragments are required to achieve neutralization. Forty milligrams of Fab (1 vial) binds 0.6 mg of digoxin. A severely toxic patient in whom the quantity ingested is unknown should be given 5 to 10 vials at a time and the clinical response observed. If cardiac arrest is imminent or has occurred, the dose can be given as a bolus. Otherwise, it should be infused over 30 minutes. In contrast, patients who experience chronic therapeutic overdose often have only mildly elevated digoxin levels and respond to 1 to 2 vials of Fab. The recommended dose for a given patient can be determined using the tables in the package insert or by contacting a regional poison center or toxicology consultant.

Box 1. Digoxin-specific Fab fragment dosing calculations

- 1) If the patient has chronic toxicity where the digoxin level is at steady state:

$$\text{Number of vials of Fab} = [(\text{serum digoxin level}) \times (\text{patient's weight in kg})] / 100$$

- 2) If the patient has an acute overdose and the exact amount taken is known:

$$\text{Number of vials of Fab} = [(\text{amount of digoxin ingested in mg}) \times (0.80)] / 40$$

- 3) If the amount ingested is unknown and Fab is indicated, 5–10 vials should be given.

Free digoxin levels are decreased to zero within 1 minute of Fab fragment administration, but total serum digoxin levels are markedly increased. Because most assay methods measure bound and free digoxin (total), high digoxin levels are seen after Fab fragment therapy but have no correlation with toxicity. Serum levels may be unreliable for several days after Fab treatment. The digoxin-Fab complex is excreted in the urine and in patients who undergo renal failure, elimination of the digoxin-Fab complex is prolonged, and free digoxin levels gradually increase over hours after Fab administration. Rebound CG toxicity is rare but has been reported. Hemodialysis does not enhance elimination of digoxin-Fab complex.

Disposition

All patients who receive Fab fragments require continued monitoring in an intensive care unit for at least 24 hours. For the chronically poisoned elderly patient, modifying the outpatient treatment regimen by discontinuing the use of a CG or providing a more reliable method of drug administration with close clinical follow-up may avert further toxic episodes.

Methylxanthine toxicity

The methylxanthines comprise a class of agents consisting of theophylline and caffeine. Theophylline used in treatment of lung disease has decreased over the past decade and, therefore, toxicity from this class of agents has

also decreased. However, because of the potential for rapid cardiovascular compromise, emergency physicians should also be aware of these agents.

Pathophysiology

At least four mechanisms have been proposed for the pro-arrhythmic potential of methylxanthine overdoses. First, methylxanthines increase circulating catecholamines [91–94]. Second, methylxanthines inhibit phosphodiesterase [95]. Increased circulating catecholamines after methylxanthine overdose increases β_1 -receptor stimulation. Stimulation of β_1 -receptors increases intracellular cAMP by G-protein stimulation of adenylate cyclase. The activity of cAMP is prolonged because of its decreased metabolism because phosphodiesterase is inhibited by methylxanthines. Subsequently, β_1 -receptor effects are exaggerated and tachydysrhythmias are induced. Third, methylxanthines increase myocardial intracellular calcium. Methylxanthines induce release of calcium from the sarcoplasmic reticulum and block calcium's re-uptake into the sarcoplasmic reticulum [96–98]. This resulting increase in cytosolic calcium may provoke dysrhythmias. Methylxanthines, therefore, block cardiac A2 receptors that are antiarrhythmic [99].

Hypotension is also commonly seen following overdoses of methylxanthines and is believed to be caused by two mechanisms [100]. First, methylxanthine-induced tachydysrhythmias lead to inadequate filling of the heart and subsequent decrease in cardiac output. Second, increased catecholamines stimulate β_2 -receptors that increase intracellular cAMP. Augmentation of β_2 -stimulation and phosphodiesterase inhibition leads to a prolonged effect of cAMP and subsequent vasodilation with resulting hypotension.

Clinical effects

Clinically, methylxanthine intoxication is associated with nausea, vomiting, tremors, mental status changes, and seizures. Reports of methylxanthine-induced cardiac dysrhythmias abound in the literature [101–105]. Hypotension can be profound and resilient to standard therapies.

Management

All methylxanthine-intoxicated patients should be managed as discussed earlier. For patients manifesting signs of excitation of the central nervous system (ie, tremors, clonus, hyperreflexia), phenobarbital or benzodiazepines should be administered early before frank seizures occur.

Persistent hypotension unresponsive to IV fluids should be treated with a direct alpha-one agonist such as phenylephrine. Vasopressin has been used in a case of refractory hypotension from a caffeine overdose [106]. Two vasopressin-receptor subtypes. V1 receptors are located on vascular smooth muscle and mediate vasoconstriction. This V1-receptor activation mediates

vasoconstriction by receptor-coupled activation of phospholipase C and release of calcium from intracellular stores, by way of the phosphoinositide cascade, and extracellular stores, by way of calcium channels located on the cell membrane. Vasopressin is a potent vasoconstrictor for skin, skeletal muscle, fat, pancreas, and thyroid gland. Vasopressin causes less vasoconstriction in mesenteric, coronary, and cerebral circulations probably because of a nitrous oxide (NO)-mediated vasodilating effect of vasopressin on these circulations [107]. In addition, vasopressin potentiates the contractile effects of catecholamines. V2 renal receptors, which cause the antidiuretic effects of vasopressin, are present in the renal collecting duct system and endothelial cells. Kidney V2 receptors interact with adenylyl cyclase to increase intracellular cAMP and trigger the release of more water channels to appear on the cell surface with resultant increased re-absorption of water in the collecting duct [108]. The reported rate of the vasopressin infusions vary, with most infusions beginning at 0.03–0.07 units/min and are titrated to effect. Potential adverse side effects of vasopressin include organ ischemia, myocardial infarction, hypersensitivity reactions, skin necrosis, and rhabdomyolysis.

Various techniques to enhance elimination of methylxanthines have been reported in the literature. Multidose activated charcoal has been advocated in the treatment of methylxanthine toxicity to prevent further absorption of drug and to enhance elimination by gut dialysis [109]. Hemodialysis has been shown to significantly enhance elimination following theophylline and caffeine overdose. Cases of severe methylxanthine toxicity have been treated with peritoneal dialysis, but this modality is less efficient at drug clearance than hemodialysis [110–112]. The use of charcoal hemoperfusion has been reported in theophylline poisoning. However, no clear indication exists demonstrating that charcoal hemoperfusion provides increased methylxanthine clearance over hemodialysis [113].

Summary

Multiple agents exist that can result in human cardiovascular toxicity. The management of the toxicity of each agent should follow a rationale approach. Many agents have multiple mechanisms of toxicity. The first step in the care of poisoned patients focuses on good supportive care.

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