

CHAPTER 152

CARDIOVASCULAR DRUGS

Jon B. Cole and David J. Roberts

Cardiovascular drugs are a common cause of poisoning in the United States; in 2010, 97,336 exposures to cardiovascular drugs were reported to U.S. Poison Control Centers.¹ Cardiovascular drugs are the second most common cause, accounting for more than 10% of all poisoning deaths in the United States. Of the scores of cardiovascular drugs, three classes—cardioactive steroids (primarily digoxin), beta-adrenergic blockers, and calcium channel blockers—account for the majority of fatalities.

CARDIOACTIVE STEROIDS (DIGOXIN)

Perspective

Digoxin is derived from the Balkan foxglove plant, *Digitalis lanata* (Fig. 152-1), and the trade name for digoxin (Lanoxin) is derived from the Latin name of this plant.² Digitoxin, which is no longer in clinical use, comes from *Digitalis purpurea*.² Although William Withering was the first to describe the medicinal use of the foxglove plant,³ the ancient Egyptians reference medicinal use of foxglove. Despite centuries of experience with digitalis, chronic and acute poisonings still occur. Controversy about the therapeutic benefit of cardioactive steroids is not new. Benjamin Rush wrote in 1797, “I suspect the cases in which [digitalis preparations] were useful to have been either so few or doubtful and that the cases they had done harm were so much more numerous and unequivocal as justly to banish them from the *Materia Medica*.”⁴ Medication errors and toxic effects account for the most common causes (44%) of preventable iatrogenic cardiac arrests.

Principles of Disease

Pathophysiology

Digoxin is used therapeutically (1) to increase the force of myocardial contraction to increase cardiac output in patients with heart failure and (2) to decrease atrioventricular (AV) conduction to slow the ventricular rate in atrial fibrillation. The basis for its first effect is inhibition of membrane sodium-potassium-adenosine triphosphatase ($\text{Na}^+, \text{K}^+ \text{-ATPase}$), which increases intracellular sodium and extracellular potassium concentrations. This increase in intracellular sodium concentration results in dysfunction of the sodium-calcium ion exchanger, which normally extrudes intracellular calcium after systole. This subsequent increase in intracellular calcium concentration results in a larger amount of calcium pumped into the sarcoplasmic reticulum, so that on calcium-induced calcium release during subsequent action potentials, a larger amount of calcium is released into the cell, causing a more powerful contraction and thus increased cardiac output. Any

molecule with this effect is classified as a cardioactive steroid. Cardiac glycosides (such as digoxin) are merely cardioactive steroids with additional sugar moieties attached to their steroid nucleus. At therapeutic doses, the effects of digoxin on serum electrolyte levels are minimal. With toxic levels, digoxin paralyzes the $\text{Na}^+, \text{K}^+ \text{-ATPase}$ pump, potassium cannot be transported into cells, and serum potassium concentration can rise as high as 13.5 mmol/L.⁵

Digoxin exerts direct and indirect effects on sinoatrial (SA) and AV nodal fibers. At therapeutic levels, digoxin indirectly increases vagal activity. At toxic levels, digoxin can directly block the generation of impulses in the SA node, depress conduction through the AV node, and increase the sensitivity of the SA and AV nodes to catecholamines. Catecholamines, whether endogenous or administered to treat bradycardias or hypotension, probably play an important role in digoxin toxicity. Because bradycardias and tachycardias can appear and alternate in the same patient, administration of drugs to treat tachycardias may later contribute to more refractory bradycardias and AV block.

Digoxin also exerts three primary effects on Purkinje fibers: (1) decreased resting potential, resulting in slowed phase 0 depolarization and conduction velocity; (2) decreased action potential duration, which increases sensitivity of muscle fibers to electrical stimuli; and (3) enhanced automaticity resulting from increased rate of phase 4 repolarization and delayed afterdepolarizations. These mechanisms account for an increase in premature ventricular contractions, the most common manifestation of digoxin toxicity. At toxic extremes, these effects result in a dangerous sensitivity to mechanical and electrical stimulation. Interventions with pacemaker wires, catheters, and cardioversion can result in asystole, ventricular tachycardia, and ventricular fibrillation.⁶

Unlike most cardiovascular drugs, digoxin can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias (Box 152-1). Unfortunately, none is unique to digoxin, and because they can all occur in the setting of ischemic and other heart disease, digoxin toxicity remains a clinical rather than an electrocardiographic diagnosis.

The volume of distribution (V_d) of digoxin is 5 L/kg for adults but varies from 3.5 L/kg in premature infants to 16.3 L/kg in older infants.⁷ This indicates that only a small fraction of digoxin remains in the intravascular space, and the drug is highly concentrated in cardiac tissue. The myocardial-to-serum ratio at equilibrium ranges from 15:1 to 30:1. The V_d for digitoxin is only 0.5 L/kg, giving it a different pharmacokinetic profile.

The elimination half-life of digoxin, which is primarily excreted in the urine, is 36 hours, and the half-life of digitoxin, which is metabolized in the liver, is 7 days. Whereas digoxin undergoes only a small enterohepatic circulation, that for digitoxin is large, and



Figure 152-1. The Balkan foxglove plant, from which digoxin is derived.

Box 152-1 Dysrhythmias Associated with Digitalis Toxicity

Nonspecific

PVCs, especially bigeminal and multiform
 First-, second- (Wenckebach's), and third-degree AV block
 Sinus bradycardia
 Sinus tachycardia
 Sinoatrial block or arrest
 Atrial fibrillation with slow ventricular response
 Atrial tachycardia
 Junctional (escape) rhythm
 AV dissociation
 Ventricular bigeminy and trigeminy
 Ventricular tachycardia
 Torsades de pointes
 Ventricular fibrillation

More Specific but Not Pathognomonic

Atrial fibrillation with slow, regular ventricular rate (AV dissociation)
 Nonparoxysmal junctional tachycardia (rate 70-130 beats/min)
 Atrial tachycardia with block (atrial rate usually 150-200 beats/min)
 Bidirectional ventricular tachycardia

AV, atrioventricular; PVCs, premature ventricular contractions.

multiple-dose activated charcoal treatment has been used for digitoxin.

Protein binding varies from 20 to 30% for digoxin to 95% for digitoxin. The significant protein binding and large volumes of distribution suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective. The long half-lives suggest that temporizing measures such as pacemakers, atropine, and anti-dysrhythmic drugs would cost more time, money, and lives than simply giving Fab fragments initially.

Multiple drugs and disease states can negatively alter absorption, V_d , protein binding, and elimination and render the heart more susceptible to digoxin toxicity. The factors listed in Box 152-2 are especially important risk factors in chronic intoxication.

Clinical Features

The symptoms and signs of chronic digoxin toxicity are nonspecific. The most common symptoms, in more than 80% of cases,

Box 152-2 Factors Associated with Increased Risk of Digitalis Toxicity

Renal insufficiency
 Heart disease
 Congenital heart disease
 Ischemic heart disease
 Congestive heart failure
 Myocarditis
 Electrolyte imbalance
 Hypokalemia or hyperkalemia
 Hypomagnesemia
 Hypercalcemia
 Alkalosis
 Hypothyroidism
 Sympathomimetic drugs
 Cardiotoxic coingestants
 Beta-blockers
 Calcium channel blockers
 Tricyclic antidepressants
 Drug interactions
 Quinidine, amiodarone
 Erythromycin
 Verapamil, diltiazem, nifedipine
 Captopril
 Elderly woman

Box 152-3 Noncardiac Symptoms of Digitalis Intoxication

General

Weakness
 Fatigue
 Malaise

Gastrointestinal

Nausea and vomiting
 Anorexia
 Abdominal pain
 Diarrhea

Ophthalmologic

Blurred or snowy vision
 Photophobia
 Yellow-green chromatopsia (also red, brown, blue)
 Transient amblyopia, diplopia, scotomas, blindness

Neurologic

Dizziness
 Headache
 Confusion, disorientation, delirium
 Visual and auditory hallucinations
 Paranoid ideation, acute psychosis
 Somnolence
 Abnormal dreams
 Paresthesias and neuralgia
 Aphasia
 Seizures

are nausea, anorexia, fatigue, and visual disturbance, but a variety of gastrointestinal, neurologic, and ophthalmic disturbances also occur (Box 152-3). Digoxin intoxication should be considered in any patient receiving maintenance therapy who has consistent symptoms, especially with new conduction disturbances or dysrhythmias.

There are significant differences between acute and chronic toxicity (Table 152-1). Chronic poisoning has an insidious onset and is accompanied by a higher mortality rate that is probably due in part to underlying heart disease and chronic accumulation of the

Table 152-1 Chronic versus Acute Digitalis Intoxication

CHRONIC	ACUTE
Higher mortality (LL ₅₀ 6 ng/mL)	Lower mortality
Ventricular dysrhythmias more common	Bradycardia and atrioventricular block more common
Usually elderly patients	Usually younger patients
Often need Fab fragment therapy	Often do well without Fab (<i>Caution</i> : many exceptions)
Underlying heart disease increases morbidity and mortality	Absence of heart disease decreases morbidity and mortality

toxin. In cases of chronic intoxication, the LL₅₀ (the level with a 50% mortality) is only 6 ng/mL.⁸ The LL₅₀ for acute intoxication is not known, but it is certainly much higher, especially in children. The association of hyperkalemia with acute toxicity is obvious given the mechanism of digoxin; either hypokalemia or hyperkalemia may occur with chronic toxicity.

Diagnostic Strategies

Diagnosis and management rely heavily on serum digoxin levels, but it is the steady state, rather than peak concentration, that correlates with tissue toxicity and is used to calculate antidote dosages. Peak concentrations after an oral dose of digoxin occur in 1.5 to 2 hours, with a range of 0.5 to 6 hours.⁹ Steady-state serum concentrations are not achieved until after distribution, or 6 to 8 hours after a dose or overdose, and may be only one fourth to one fifth of the peak concentration. The ideal serum digoxin concentration for patients with heart failure is considered to be 0.7 to 1.1 ng/mL,¹⁰ although laboratory “normals” are often reported up to 2.0 ng/mL. Serum steady-state digoxin levels of 1.1 to 3.0 ng/mL are equivocal; that is, levels as low as 1.1 ng/mL have been associated with increased mortality,¹¹ and patients with levels up to 3.0 ng/mL can be asymptomatic.¹² The incidence of digoxin-induced dysrhythmia reaches 10% at a level of 1.7 ng/mL and rises to 50% at a level of 2.5 ng/mL. Determination of a level too soon after the last maintenance dose falsely suggests toxicity, especially in cases of chronic intoxication, in which significant morbidity and mortality can occur at levels of 2 to 6 ng/mL.¹⁰ After an acute massive overdose in a patient who is rapidly becoming symptomatic, however, it may be impractical to wait 6 to 8 hours for the first reading.¹³ It is unlikely that early levels exceeding 10 to 20 ng/mL will fade to clinical insignificance at 6 to 8 hours after ingestion.

Differential Considerations

No sign or symptom, including dysrhythmia, is unique to digoxin poisoning, so the differential diagnosis is broad. Intrinsic cardiac disease as well as other cardiotoxic drugs should be considered. Central nervous system (CNS) depression or confusion may be due to various depressant drugs and toxins as well as infection, trauma, inflammation, and metabolic derangements. Visual disturbances should be binocular and are often not reported by the patient. Gastrointestinal disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

Management

Fab Fragments (DigiFab)

The treatment of significant digoxin poisoning is the administration of digoxin-specific fragment antigen-binding (Fab)

antibodies (DigiFab); all other interventions are considered complementary.

The mortality rate before Fab fragment therapy was 23% despite all of the interventions described.¹⁴ Fab fragment treatment is well established in both chronic and acute poisonings, with a 90% response rate.¹⁵ Nonresponders usually receive too little antibody or receive it too late. Other nonresponders are compromised by underlying heart or multisystem disease.

Digitalis antibodies are derived from sheep, but allergic reactions occur in less than 1% of cases.¹⁵ Reactions have included erythema, urticaria, and facial edema, all of which are responsive to the usual treatment. Other expected reactions when Fab fragments neutralize digitalis include hypokalemia, exacerbation of congestive heart failure, and increase in ventricular rate with atrial fibrillation. Two Fab fragment preparations were previously available; however, Digibind has been discontinued, leaving DigiFab as the only available product in the United States. If vials of Digibind are still available at a given institution, they require a 0.22- μ m membrane filter for proper use; such a filter is not required for DigiFab.

Fab fragment treatment is best reserved for cases of serious cardiovascular toxicity rather than for routine or prophylactic administration with higher than expected serum levels. In acute poisoning, antibody treatment should be used for a serum potassium level above 5.0 mEq/L or unstable dysrhythmias, such as symptomatic sinus bradycardia, ventricular dysrhythmias, or second- or third-degree heart block unresponsive to atropine. Although toxicity increases with greater body load, there is no clear correlation with amount ingested, especially in children, and many patients with large ingestions or high serum levels become only mildly symptomatic.⁸ Fab fragment therapy should be used before transvenous pacing, which carries significant risk.

The median time to initial response is 19 minutes after completion of the Fab infusion, but complete resolution of digitalis toxic rhythms may require hours.^{16,17} Late administration of Fab fragments has resuscitated 54% of patients who have suffered cardiac arrest.¹⁸ This antidote should be considered whenever hemodynamic compromise attends a digitalis toxic dysrhythmia or heart block (Box 152-4).¹⁹

Current formulas for calculation of DigiFab doses are found in the package insert. There are at least three approaches. The first is empirical. A patient has a history of digitalis ingestion, consistent symptoms, and life-threatening dysrhythmias. There is no time to assess serum digoxin levels, and 10 vials should be administered over 30 minutes for the average acute ingestion, 4 to 6 vials for the average chronic ingestion. In cardiac arrest, 20 vials can be administered undiluted by intravenous bolus. The second approach uses a simple calculation when the ingested dose is known with reasonable certainty. One vial of Digibind or DigiFab contains 38 mg or 40 mg, respectively, of Fab fragments, which bind 0.5 mg of digoxin or digitoxin (Box 152-5). A third approach is to base the dosage on the steady-state serum digoxin or digitoxin level after 6 to 8 hours (Boxes 152-6 and 152-7). Because most assays measure both bound and unbound drug, digoxin levels will be elevated for up to 1 week, with values often greater than 100 ng/mL once Fab fragments have been administered. Newer methods can measure free digoxin, but it is more meaningful to follow the patient clinically.

Electrolyte Correction

In cases of chronic toxicity, which may be exacerbated by hypokalemia, maintenance of the serum potassium level to at least 3.5 to 4 mEq/L is an important early treatment. Potassium can be administered orally (which is safer) or intravenously (IV) at a rate of less than 40 mEq/hr.

In acute poisoning, serum potassium concentration may begin to rise rapidly within 1 to 2 hours of ingestion. Potassium should be withheld, even if mild hypokalemia is measured initially. The initial serum potassium concentration may in fact be a better predictor of mortality than the initial digoxin concentration. In a study of 91 patients with acute digoxin poisoning, nearly 50% of the patients with serum potassium concentrations between 5.0 and 5.5 mmol/L died. No patients with a potassium level of less than 5.0 mEq/L died, and all 10 patients with serum potassium concentrations exceeding 5.5 mmol/L perished.²⁰ Because of these findings, a serum potassium concentration greater than 5 mmol/L alone warrants treatment with Fab fragments. Even with Fab fragments, severe hyperkalemia should be treated with intravenous administration of glucose, insulin, and sodium bicarbonate as needed.

The decision to administer calcium to patients with hyperkalemia and digoxin poisoning represents a clinical dilemma. Classic teaching is that in the setting of the increased intracellular calcium concentration from digoxin poisoning, administration of exogenous calcium will result in “stone heart” from excessive intracellular calcium.²¹ This concept has been in the literature since 1927,²² based on animal studies.²³ Documented cases of cardiac arrest after calcium administration are exceedingly rare in the literature, and the temporal relationship is dubious.²⁴ More recent data indicate that the intravenous administration of calcium can be safe for hyperkalemia in the setting of digoxin toxicity.²⁵ Unequivocally, however, the best treatment of hyperkalemia due to acute digoxin toxicity is Fab fragments. The treatment of hyperkalemia in the setting of chronic digoxin toxicity and renal failure is less clear; however, the evidence that calcium salts will be harmful is dubious at best. Calcium salts should be administered during several minutes through a secure peripheral intravenous site or through a central venous catheter. Indications are identical to those for hyperkalemia, including but not exclusive to a widened QRS duration on the electrocardiogram. A reasonable starting dose would be 3 g of calcium gluconate or 1 g of calcium chloride. Calcium salts should be followed immediately with other pharmacologic measures to lower serum potassium concentration.

Many patients receiving diuretic therapy are also magnesium depleted, even when the measured serum magnesium level is normal. If significant magnesium depletion is suspected (e.g., if electrocardiographic changes such as QTc prolongation are present), 1 to 2 g of magnesium sulfate can be given during 10 to 20 minutes (child: 25 mg/kg), followed by a constant infusion of 1 to 2 g/hr. Patients should be closely monitored for respiratory depression, which is usually preceded by progressive loss of deep tendon reflexes. Hypermagnesemia can exacerbate digitalis toxicity, but magnesium has been reported to reverse digoxin-induced tachydysrhythmias.²⁶ It is prudent to infuse magnesium slowly and to stop the infusion if heart block or bradycardia develops. Avoid magnesium in patients with renal failure. The role of magnesium in bradydysrhythmias and conduction blocks is less clear but probably dangerous because hypermagnesemia can impair impulse formation and AV conduction.

Atropine

Atropine is generally used for severe bradycardia and advanced AV block, with mixed results. Standard dosing (0.02 mg/kg in children with a minimum of 0.1 mg; 1 mg IV in adults) should be used. In general, an external or transvenous pacemaker should be readied when bradycardia or AV block appears.

Pacing

Transvenous pacing has been a mainstay of treatment for several decades, but the catheter may induce ventricular

Box 152-4 Recommendations for Administration of Digitalis Antibody Fragments

Adults

1. Ventricular dysrhythmias more severe than premature ventricular contractions
2. Progressive and hemodynamically significant bradydysrhythmias unresponsive to atropine
3. Serum potassium level above 5.0 mEq/L
4. Rapidly progressive rhythm disturbances or rising serum potassium level
5. Coingestion of cardiotoxic drugs such as beta-blockers, calcium channel blockers, or tricyclic antidepressants
6. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)
7. Acute ingestion of more than 10 mg *plus* any one of factors 1 through 6 above
8. Steady-state serum digoxin concentration above 6 ng/mL *plus* any one of factors 1 through 6 above

Children

1. Ingestion of more than 0.1-0.3 mg/kg or steady-state digoxin concentration above 5 ng/mL *plus* rapidly progressive symptoms or signs of digitalis intoxication or potentially life-threatening dysrhythmias or conduction blocks or serum potassium concentration above 6 mmol/L
2. Coingestion of other cardiotoxic drugs with additive or synergistic toxicity
3. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)

Box 152-5 Sample Calculation of Digibind or DigiFab Based on Ingested Dose of Digoxin or Digitoxin*

Case: A toxic-appearing 40-year-old woman has ingested fifty 0.25-mg digoxin tablets.

$$\begin{aligned} \text{Body load} &= \text{amount ingested} \\ &\quad \times 0.8 \text{ (bioavailability of digoxin tablets)} \\ &= 12.5 \text{ mg} \times 0.8 = 10 \text{ mg} \end{aligned}$$

$$\begin{aligned} \text{Dose of digoxin Fab} &= 10 \text{ mg} \div 0.5 \text{ mg bound per vial} \\ \text{fragments (in vials)} &= 20 \text{ vials} \end{aligned}$$

*Formula from GlaxoSmithKline, 2008.

Box 152-6 Sample Calculation of Digibind or DigiFab Based on Steady-State Digoxin Concentration*

Case: A toxic-appearing 4-year-old child weighing 20 kg has a digoxin level of 16 ng/mL 8 hours after ingestion of an unknown number of digoxin tablets.

$$\begin{aligned} \text{Dose (in number of vials)} &= (\text{serum digoxin concentration} \\ &\quad \times \text{weight in kg}) \div 100 \\ &= (16 \times 20) \div 100 \\ &= \text{approximately } 3 \text{ vials} \end{aligned}$$

*Formula from GlaxoSmithKline 2008; assumes $V_d = 5 \text{ L/kg}$.

Box 152-7 Calculation of Digibind or DigiFab Based on Steady-State Digitoxin Concentration*

Case: A toxic-appearing 70-year-old man weighing 80 kg has a digitoxin level of 200 ng/mL (therapeutic = 10 to 35 ng/mL).

$$\begin{aligned} \text{Dose (in number of vials)} &= (\text{serum digitoxin concentration} \\ &\quad \times \text{weight in kg}) \div 1000 \\ &= (200 \times 80) \div 1000 \\ &= 16 \text{ vials} \end{aligned}$$

*Formula from GlaxoSmithKline 2008; $V_d = 5 \text{ L/kg}$.

tachydysrhythmias in a myocardium made irritable by digoxin. Iatrogenic accidents of cardiac pacing are frequent (14 of 39, 36%) and often fatal (5 of 39, 13%).²⁷ We recommend avoidance of transvenous pacing unless external pacing fails. Pacing usually is required only temporarily while waiting for Fab fragments to take effect. Cardioversion for tachydysrhythmia also may be hazardous in the setting of digoxin intoxication. If it is deemed necessary, such as when the tachydysrhythmia is thought to be causing severe hypotension, we recommend use of lower than usual energy settings, such as 25 to 50 J, although there is no proof that this is less hazardous.

Carotid Sinus Massage

Carotid sinus massage may result in bradycardia and cardiac arrest in the setting of digoxin toxicity and is rarely if ever indicated.

Phenytoin and Lidocaine

Phenytoin and lidocaine are believed to be the safest of the anti-dysrhythmic drugs for control of tachydysrhythmias in the setting of digoxin toxicity. Indications include unstable tachydysrhythmias when Fab fragments are unavailable and unstable tachydysrhythmias that occur while waiting for Fab fragments to take effect. Phenytoin may enhance AV conduction. Phenytoin has been infused at 25 to 50 mg/min to a loading dose of 15 to 20 mg/kg; it may also be administered in 100-mg boluses every 5 minutes until arrhythmias improve or 1000 mg is administered. Lidocaine can be given initially at a dosage of 1 to 1.5 mg/kg during several minutes, followed by an infusion of 1 to 4 mg/min (30-50 µg/kg/min).²⁸ Most other cardiac drugs (isoproterenol, procainamide, amiodarone, beta-blockers, calcium antagonists) may worsen dysrhythmias or depress AV conduction. Digoxin immune Fab fragments are the preferred therapy for dysrhythmias.

Pediatric Considerations

Children at greatest risk are those receiving chronic digoxin therapy for heart disease. Children with healthy hearts can tolerate massive acute oral ingestions without Fab treatment.²⁸ This excludes therapeutic errors, children who are taking digoxin therapeutically, and children with heart disease.

Dosage calculation and administration errors account for more pediatric digoxin intoxication and death than does accidental oral ingestion. Therapeutic errors, especially accidental intravenous overdoses, often result in death within 1 to 4 hours.

Signs and symptoms in children with digoxin poisoning are somewhat different (Table 152-2). Vomiting, somnolence, and

obtundation are more common than in adults.¹⁸ CNS depression, in the absence of a history, might lead the clinician to suspect narcotic or sedative-hypnotic overdose or nontoxicologic causes, such as head injury, metabolic disorder, and CNS infection. Conduction disturbances and bradycardias are more common than ventricular dysrhythmias in children, especially with acute ingestion.^{9,18}

Disposition

All patients who are symptomatic for digoxin toxicity with hyperkalemia, dysrhythmia, AV block, or significant comorbidity should be admitted to an intensive care unit or coronary care unit after treatment with Fab. Asymptomatic patients reporting an acute ingestion of a large quantity of digoxin should be admitted to an intensive care unit or coronary care unit for at least 12 hours of continuous cardiac monitoring to determine the need for Fab.

BETA-ADRENERGIC BLOCKERS

Perspective

Beta-adrenergic blocking drugs became widely used in Europe in the 1960s for treatment of dysrhythmias. Their antihypertensive effects were later appreciated, and, by the 1970s, they were one of the most widely prescribed classes of drugs in the United States. Current indications include supraventricular dysrhythmias, hypertension (although the drugs have fallen out of favor for this indication), angina, thyrotoxicosis, migraine, and glaucoma. Of the numerous beta-blockers available, propranolol is the most deadly. In 2010, U.S. Poison Control Centers received more than 23,000 calls regarding beta-blocker exposures.¹

Principles of Disease

Pathophysiology

Beta-blockers structurally resemble isoproterenol, a pure beta-agonist. They competitively inhibit endogenous catecholamines such as epinephrine at beta-adrenergic receptors, blocking the catecholamine effects on augmentation of myocardial contraction (inotropy), enhancing cardiac conduction (dromotropy), and accelerating heart rate (chronotropy). These are all beta₁ effects. Complex beta₂ effects include vascular (smooth muscle relaxation and vasodilation), liver (glycogenolysis, gluconeogenesis), lung (bronchodilation), adipose tissue (release of free fatty acids), and uterus (smooth muscle relaxation) effects. Equally important properties, which vary from one beta-blocker to another, include cardioselectivity (beta₁ selectivity), membrane-stabilizing effect (fast cardiac sodium channel blocking properties), lipophilicity, and intrinsic sympathomimetic activity (Table 152-3). Although cardioselectivity is lost in overdose, cardioselective beta-blockers such as atenolol, metoprolol, and esmolol still have a lower mortality rate than that of propranolol.

Beta-blockers are rapidly absorbed after oral ingestion, and the peak effect of normal-release preparations occurs in 1 to 4 hours. Hepatic metabolism on first pass results in significantly less bioavailability after oral dosing than with intravenous injection (e.g., 1:40 for propranolol). Because volume of distribution for most beta-blockers generally exceeds 1 L/kg, hemodialysis is not efficacious for most beta-blockers. Protein binding varies from 0% for sotalol to 93% for propranolol. Elimination half-lives vary from 8 to 9 minutes for esmolol to as long as 24 hours for nadolol and others (see Table 152-3).

Table 152-2 Age Differences in Digitalis Intoxication

ADULT	PEDIATRIC
Toxic at lower levels	Asymptomatic at higher levels
Nausea, fatigue, and visual disturbances most common	Obtundation and vomiting more common than in adults
Tachydysrhythmias as common as blocks and bradycardias	Bradycardias and blocks most common
Allergic reactions to Fab fragments uncommon (<1%)	Allergic reactions extremely rare
V _d less variable (5-7.5 L/kg)	V _d more variable (3.5-6.0 L/kg in premature infants, 8.0-16.3 L/kg in infants 2-24 months)

Table 152-3 Selected Characteristics of Common Beta-Blockers

	V _d (L/kg)	ISA	ELIMINATION HALF-LIFE (hr)	LIPOPHILIC	PROTEIN BINDING (%)	MSE	COMMENTS
Nonselective Beta-Blockers							
Propranolol	4	0	4	+	93	+	Most fatalities
Nadolol	1.9	0	10-20	0	20	0	Dialyzable
Timolol	1.4-3.5	0	3-5	+	10	0	Dialyzable
Pindolol	3-6	+	3-4	+	51	+	
Labetalol	10	0	4-6	0	50	+	Alpha-blockade also
Oxprenolol	1.3	+	2	+	78	+	
Sotalol	1.6-2.4	0	7-18	+	0	0	Class III and class II antidysrhythmic; torsades de pointes; dialyzable
Carvedilol	1.5-2	0	6-10	+	95	0	
Selective Beta-Blockers							
Metoprolol	5.5	0	3-4	+	12	0	
Atenolol	0.7	0	5-8	0	5	0	Dialyzable
Esmolol	2	0	0.13	0	55	0	
Acebutolol	1.2	+	2-4	+	26	+	QT prolongation, VT, dialyzable
Practolol	1.6	+	10-11	+		0	
Bisoprolol	2.9	0	10-12	0	30	0	
Betaxolol	5-13	0	12-22	0	55	0	

ISA, intrinsic sympathomimetic activity; MSE, membrane-stabilizing effect; VT, ventricular tachycardia.

Box 152-8 Manifestations and Complications of Beta-Blocker Overdose in Order of Decreasing Frequency*

1. Bradycardia (65/90 cases)
2. Hypotension (64/90)
3. Unconsciousness (50/90)
4. Respiratory arrest or insufficiency (34/90)
5. Hypoglycemia (uncommon in adults)
6. Seizures (common only with propranolol, 16/90)
7. Symptomatic bronchospasm (uncommon)
8. VT or VF (6/90)
9. Mild hyperkalemia (uncommon)
10. Hepatotoxicity, mesenteric ischemia, renal failure (rare or single case reports)

VF, ventricular fibrillation; VT, ventricular tachycardia.

*Intoxication with beta-sympatholytics.

Clinical Features

The most common initial sign remains bradycardia, which should suggest the possibility of cardiac drug overdose. Hypotension and unconsciousness are the second and third most common signs (Box 152-8). Much of propranolol's unique toxicity derives from its lipophilic nature, which allows it to penetrate the CNS, causing obtundation, respiratory depression, and seizures. Seizures probably result from a combination of hypotension, hypoglycemia, hypoxia, and direct CNS toxicity. Other beta-blockers are not lipophilic and do not have these effects. Surprisingly, bronchospasm is rarely a problem in cases of beta-blocker overdose, even with nonselective beta-blockers. The few cases of symptomatic bronchospasm respond to the usual bronchodilator nebulizations.

Propranolol, nadolol, betaxolol, and acebutolol have a membrane-stabilizing effect that impairs SA and AV node function and leads to bradycardia and AV block. Ventricular

conduction is also depressed, leading to QRS widening, occasional ventricular dysrhythmias such as ventricular tachycardia and ventricular fibrillation, and cardiogenic shock. The intrinsic sympathomimetic activity of some beta-blockers, such as pindolol, oxprenolol, acebutolol, and carteolol, can lead to some unusual manifestations, such as ventricular dysrhythmias and sinus tachycardia instead of bradycardia. Labetalol and carvedilol also block alpha₁-adrenergic receptors, giving an additional mechanism for hypotension and distributive shock. However, labetalol's beta-blockade is three (oral route) to seven (intravenous route) times more potent than its alpha-blockade. Nebivolol is a cardioselective beta-adrenergic blocker that also causes vasodilation through a unique mechanism: induction of endothelium-dependent vasodilation by stimulation of nitric oxide bioactivity.

In contrast to digitalis, beta-blocker toxicity has a more rapid onset; life-threatening CNS and cardiovascular effects can occur 30 minutes after oral overdose. Patients ingesting delayed-release preparations may remain asymptomatic for several hours, affording a valuable therapeutic window.

Diagnostic Strategies

Diagnosis and management depend entirely on the clinical picture. Blood levels of beta-blockers correlate poorly with severity of intoxication and are not readily available. Most urine toxicology screens do not identify antidysrhythmic drugs and are not helpful.²⁹ Hypoglycemia is common in children, and bedside determination of glucose concentration should be done if CNS depression is noted. Known access of the patient to a beta-blocker and consistent clinical features such as obtundation, seizures, hypotension, bradydysrhythmias, and occasionally tachydysrhythmias should lead the clinician to consider beta-blocker intoxication. Whereas some authors believe that a serum lactate concentration can help predict mortality in overdose patients,³⁰ this has not held true in pure beta-blocker ingestions.³¹

Differential Considerations

The combination of bradycardia and hypotension suggests beta-blockade or calcium channel blockade. Centrally acting alpha₂-adrenergic agonists, such as clonidine and tizanidine, or imidazolines, such as tetrahydrozoline and oxymetazoline, may also cause this constellation of symptoms. Without a history of beta-blocker ingestion, the diagnosis can be challenging, especially when noncardiac effects such as CNS depression and seizures predominate. Sodium channel poisoning with QRS widening can occur, suggesting other antidysrhythmic drugs or cyclic antidepressants. The differential diagnosis also includes sedative-hypnotic drug overdose, hypoglycemic drug ingestion, opiate overdose, CNS injury or infection, endocrine-metabolic disorder, sepsis, and acute myocardial infarction.

Management

Immediate measures include intravenous fluids, supplemental oxygen, and monitoring of cardiac rhythm and respirations. Activated charcoal has been used in the first hour after overdoses as a theoretic but unproven treatment, but theoretic advantages should be weighed against the very real risk of aspiration if obtundation or seizure ensues. Management of dysrhythmias and hypotension should not be delayed by administration of charcoal. Evidence for improved outcome is also lacking, but whole-bowel irrigation has been commonly used for sustained-release preparations with a polyethylene glycol solution (GoLYTELY), administered orally or by nasogastric tube at 2 L/hr in adults or 20 mL/kg initially in children. Again, risks and benefits make a clear recommendation impossible. Gastric lavage also carries procedural risks, and yet morbidity and mortality from beta-blockers are high and consideration of lavage in patients who present within 1 hour of ingestion is reasonable. With currently available evidence, gastric decontamination by activated charcoal, whole-bowel irrigation, or gastric lavage can neither be recommended nor criticized. Onset of toxicity is so uniformly early that absence of symptoms 4 hours after ingestion implies a low risk for subsequent morbidity unless a delayed-release preparation is involved.

Hypotension, Bradycardia, and Atrioventricular Block

The first step in the treatment of beta-blocker overdose is bolus administration of crystalloid fluids. In hypotensive patients, 20 to 40 mL/kg of normal saline or lactated Ringer's solution can be infused and repeated. Atropine at standard doses may be used for bradycardia but is rarely effective. Infusion of more potent drugs or cardiac pacing is usually necessary. Atropine should be given before vagal stimuli, such as tracheal or gastric intubation. Early placement of a central venous catheter may be prudent as these patients frequently require central venous pressure monitoring, additional intravenous access, and administration of medications necessitating central access.

Calcium

Because the final common pathway for stimulation of adrenergic receptors is an increase in intracellular calcium concentration and deleterious effects on calcium transport may contribute to beta-blocker toxicity, intravenous administration of calcium has been suggested for treatment of hypotension. One gram of calcium gluconate contains 4.5 mEq of elemental calcium, whereas 1 g of calcium chloride contains 13.6 mEq of elemental calcium. Calcium chloride is an acidifying salt and can cause significant tissue damage and necrosis if extravasation occurs. Thus it should be administered through a central venous catheter or a secure

large-bore antecubital peripheral line. Indications for calcium include hypotension and bradycardia. We recommend an initial dose of 13 to 25 mEq of calcium in adults (1-2 g calcium chloride, 3-6 g calcium gluconate) during 10 minutes. Patients in extremis may receive the initial dose during 1 minute. If a response is observed, repeated doses may be given every 20 minutes, or a constant infusion may be started at 0.5 mEq/kg/hr. It is prudent to raise the total serum calcium level no higher than 14 mg/dL, which the endocrine and oncology literature defines as the threshold of "severe" hypercalcemia; if ionized calcium is measured, we recommend not to exceed twice-normal levels. Children can receive 0.15 to 0.3 mEq/kg of calcium IV initially (10 to 30 mg/kg [0.1-0.3 mL/kg]) of 10% calcium chloride or 30-60 mg/kg calcium gluconate. The serum calcium level can be as high as 18.2 mg/dL within 15 minutes after a bolus of just 5 mL of 10% calcium chloride, so levels should be measured later during the constant infusion.

Glucagon

Because glucagon has both inotropic and chronotropic effects and does not depend on beta receptors for its action, it has long been used for beta-blocker toxicity. It stimulates the production of intracellular cyclic adenosine monophosphate independently of the beta-adrenergic receptor.³² Furthermore, it helps counteract the hypoglycemia induced by beta-blocker overdose. The dosing of glucagon is not well studied, but the drug is frequently used as a 5- to 10-mg IV bolus (0.05-0.1 mg/kg for children). If a response occurs to glucagon, the "response dose" should be started as an infusion at a rate of response dose during 1 hour. Glucagon has a very short (20-minute) half-life, and unfortunately its effect is often transient. Vomiting is a common complication of glucagon, so the airway should be secured or monitored closely to prevent aspiration. With cumulative large doses, glucagon should be diluted in 5% glucose in water for constant infusion. Side effects also include hypokalemia and allergic reactions. The response to glucagon alone is often inadequate, and glucagon is likely to be less effective than high-dose insulin.³³ Furthermore, hospitals may not be adequately stocked for treatment beyond a few hours.³⁴ From clinical experience, we find glucagon most useful as a transient therapy to bridge patients to high-dose insulin.

High-Dose Insulin

Despite glucagon's longer history for treatment of beta-blocker toxicity, high-dose insulin (HDI) is probably a better agent. HDI is not a vasopressor; it is a profound inotrope³⁵ with vasodilating properties.^{36,37} The mechanism for HDI is not fully known, but it probably involves both optimization of the use of carbohydrates for fuel by cardiac myocytes and modulation of intracellular calcium.³⁸ HDI improves cardiac output significantly in beta-blocker toxicity from an increase in stroke volume more than heart rate. Dosing of HDI is not agreed on; dosing in humans successfully treated with HDI has ranged from 0.5 to 21.8 U/kg/hr.³⁹ In the largest human case series to date of patients receiving HDI for poison-induced cardiogenic shock, 11 of 12 patients survived; the only death occurred when HDI was terminated early because of a protocol violation.⁴⁰ Mean maximal HDI dosing in this series was 8.7 U/kg/hr. Previous recommendations for dosing of HDI were a bolus of 1 U/kg of regular insulin IV, followed by a drip at 1 U/kg/hr.⁴⁰ On the basis of animal data,⁴¹ some authors start HDI at 10 U/kg/hr in severely toxic patients with the belief that the glucose use from insulin saturates before the inotropic effect. Regardless of HDI dosing, patients should receive a bolus of dextrose before insulin and a dextrose infusion should be started thereafter, such as a bolus of 25 g glucose (1 traditional "amp" of D50) if the serum glucose concentration is below 200 mg/dL.

(11.1 mmol/L), followed by concentrated dextrose solutions (such as D25, D50, or even D70) through a central line because patients receiving HDI therapy are at risk of fluid overload. Glucose concentration should be monitored as frequently as every 10 minutes until a steady state of glucose use is achieved. Potassium concentration should also be monitored closely and potassium replaced as needed because patients may become hypokalemic.⁴⁰

Sodium Bicarbonate

Sodium channel blockade from beta-blockers with membrane-stabilizing activity, such as propranolol, occasionally causes QRS widening, which should respond to sodium bicarbonate. Bicarbonate should be dosed at 1 to 2 mmol/kg IV as a bolus repeated every 3 to 5 minutes until the QRS narrows.

Vasopressors and Other Inotropes

If hypotension or bradycardia persists, other cardioactive drugs are indicated. The use of vasopressors is not without risk; HDI is probably safer.³⁷ Vasopressors may be useful to transiently maintain mean arterial pressure (MAP) high enough to ensure adequate cerebral perfusion pressure (CPP). A MAP of 65 mm Hg is often quoted as the minimum MAP required to ensure adequate CPP.⁴² If the patient is not intubated and has a normal mental status, lower MAP readings are probably adequate. The more difficult situation of an intubated patient with a MAP slightly below 65 mm Hg represents a clinical dilemma. It is our practice to accept an MAP of 60 mm Hg if all other signs point to adequate organ perfusion.

A single drug of choice after HDI and glucagon has not emerged, but some clinicians favor isoproterenol (isoprenaline in Europe), dopamine, or epinephrine.²⁸ Other catecholamines that have been successfully used include norepinephrine, dobutamine, and phenylephrine. Often, norepinephrine or dopamine is added to beta-agonists such as isoproterenol that lack vasopressor activity. In the selection of cardioactive medications to supplement HDI and glucagon, we recommend early assessment of systemic vascular resistance and cardiac output by either indirect measurements with a pulse contour analysis-based hemodynamic monitoring tool such as the FloTrac device (Edwards Lifesciences; Irvine, Calif.) or Swan-Ganz catheter and choosing of appropriate drugs if either cardiogenic (inotropic drugs such as norepinephrine, dobutamine, dopamine) or distributive shock (pressors such as norepinephrine, phenylephrine, vasopressin) exists. Refractory cases of bradycardia may respond to an external or transvenous pacemaker. A pacemaker is particularly useful when the heart rate is the predominant cause of decreased cardiac output.

Intravenous Fat Emulsion (Intralipid)

Intravenous fat emulsion (IFE) is a promising new therapy for poison-induced cardiogenic shock. This therapy was first described for treatment of toxicity from local anesthetics such as bupivacaine.⁴³ IFE is proposed to work by three separate mechanisms: (1) the lipid sink, (2) modulation of intracellular metabolism, and (3) activation of ion channels.⁴⁴ The lipid sink theory posits that fat-soluble drugs are soaked up and removed from the site of toxicity, effectively increasing the volume of distribution for a fat-soluble drug. This is the predominant theory behind the use of IFE. A second theory involves optimization of cardiac metabolism. The heart under physiologic circumstances prefers free fatty acids; in times of stress it switches to glucose metabolism for energy. A dose of IFE theoretically provides a large supply of free fatty acids to optimize energy use in the heart. The final proposed mechanism involves direct activation of cardiac calcium channels. Animal evidence exists to support the use of IFE for both

lipid-soluble beta-blockers (such as propranolol)⁴⁵ and non-lipid-soluble beta-blockers (such as atenolol).⁴⁶ Dramatic human case reports of successful resuscitations exist for propranolol,⁴⁷ nebivolol,³⁹ and metoprolol.⁴⁸ Although IFE was originally indicated for patients in cardiac arrest only, in 2011 the American College of Medical Toxicology released a position statement stating that “in circumstances where there is serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, lipid resuscitation therapy (IFE) is viewed as a reasonable consideration for therapy, even if the patient is not in cardiac arrest.”⁴⁹ Dosing for IFE is not agreed on. We recommend an initial bolus of 1.5 mL/kg of 20% lipid solution given during 2 to 3 minutes, followed immediately by an infusion of 0.25 mL/kg/min.⁴⁹ The bolus can be repeated up to two additional times for refractory patients. Response is typically within minutes of the bolus. We use IFE in patients with persistent bradycardia or hypotension not responding to intravenous fluids, calcium, and HDI.

Ventricular Dysrhythmias

Although it is uncharacteristic, ventricular tachydysrhythmias do occur sometimes. Cardioversion and defibrillation are indicated for ventricular tachycardia and ventricular fibrillation, respectively, following American Heart Association guidelines. Pulsatile ventricular tachycardia or frequent ventricular ectopy can most safely be treated with lidocaine. Other antidysrhythmic drugs, especially of classes IA and IC, should be avoided; they may potentiate AV block or be pro-dysrhythmic because of an additive membrane-stabilizing effect. Sotalol, unlike other beta-blockers, has class III as well as class II effects; that is, it prolongs the QT interval and can cause torsades de pointes and other ventricular dysrhythmias. Overdrive pacing with isoproterenol or a pacemaker and magnesium sulfate are specific therapies for torsades de pointes.

Extracorporeal Elimination and Circulatory Assistance

Hemodialysis or hemoperfusion may be beneficial for atenolol, acebutolol, nadolol, sotalol, and timolol, the beta-blockers with lower V_d , lower protein binding, and greater hydrophilicity.⁵⁰

Unlike overdoses of acetaminophen and iron, overdoses of cardiovascular drugs do not destroy tissue, and if circulation can be supported, complete recovery can be expected. An intra-aortic balloon pump or cardiopulmonary bypass can be lifesaving in cases of refractory hypotension.^{51,52} A percutaneous left ventricular assist device, although it has not been studied in beta-blocker toxicity, may also be useful. The relatively short half-lives (hours rather than days) of beta-blocking and calcium-blocking drugs fall within the temporal range of such interventions. To be successful, such heroic measures should be taken before prolonged hypotension leads to multiorgan ischemic injury (Box 152-9). Because most patients recover with just supportive care, these expensive and invasive interventions should be reserved for drugs and circumstances, such as propranolol, verapamil, and mixed cardiotoxic overdoses, that are associated with higher rates of mortality.

Pediatric Considerations

Severe pediatric beta-blocker poisonings are rare. In the cases reported, CNS, cardiac, and metabolic toxicities are similar.⁵³ Symptomatic hypoglycemia, however, is much more common in children and occurs even after therapeutic doses. Therefore, serum glucose concentration should be measured in children. Risk factors include young age, fasting state, and diabetes mellitus. Obtunded children should receive empirical glucose, 1 to 2 mL/

Box 152-9 Treatment of Beta-Blocker Poisoning**Phase 1 (Resuscitation)**

Boluses of intravenous isotonic fluids, calcium, atropine, glucagon

Phase 2 (Stabilization)

Infusions of

High-dose insulin/glucose

Glucagon

Catecholamines (epinephrine, norepinephrine, isoproterenol, dobutamine, dopamine, metaraminol)

Phosphodiesterase inhibitors (amrinone)

Early cardiac pacing if no prompt response to chronotropic or dromotropic drugs

Peripheral arterial and pulmonary artery catheter monitoring if refractory hypotension

Consider hemodialysis of hydrophilic beta-blockers with low protein binding and low V_d

Phase 3 (Salvage Therapies)

Intravenous fat emulsion (e.g., Intralipid)

Intra-aortic balloon counterpulsation

Consider percutaneous left ventricular assist device or cardiac bypass

kg of 25% glucose IV. In general, 5% glucose infusions have been sufficient to maintain euglycemia, especially with concomitant use of glucagon and catecholamines, which stimulate glucose release. Because glycogen mobilization is a β_2 effect, hypoglycemia may be less common with the cardioselective (β_1) blockers.

Seizures also occur in cases of pediatric beta-blocker overdose, but hypoglycemia is probably an important contributing factor. They are more common with the lipid-soluble beta-blockers propranolol and oxprenolol. Benzodiazepines are generally effective.

Children generally fare well after beta-blocker ingestion, with symptoms in only 8 of 378 (2%) potential beta-blocker exposures in children.⁵⁰

Disposition

Patients who remain completely asymptomatic for 6 hours after an oral overdose of normal-release preparations can be safely referred for psychiatric evaluation, with medical consultation for the first 24 hours. Patients ingesting sustained-release preparations should be admitted to a monitored bed, but those who remain asymptomatic 8 hours after ingestion are very unlikely to have toxicity. Those who have been hypotensive, who have more than first-degree heart block, or who have hemodynamically significant dysrhythmias should be admitted to an intensive care unit.

CALCIUM CHANNEL BLOCKERS**Perspective**

Verapamil and nifedipine, the earliest calcium channel antagonists, were introduced in Europe in the 1970s and in the United States in the early 1980s. Calcium antagonists have found many clinical applications: angina pectoris, hypertension, supraventricular dysrhythmias, hypertrophic cardiomyopathy, and migraine prophylaxis. Most fatalities occur with verapamil, but severe toxicity and death have been reported for most drugs of this class. In 2010, U.S. Poison Control Centers received more than 10,000 calls about calcium channel blockers.¹

Pathophysiology

Calcium channel antagonists block the slow L-type calcium channels in the myocardium and vascular smooth muscle, leading to coronary and peripheral vasodilation. They also reduce cardiac contractility, depress SA nodal activity, and slow AV conduction. In cases of overdose, verapamil has the deadliest profile, combining severe myocardial depression and peripheral vasodilation. Both verapamil and diltiazem act on the heart and blood vessels, whereas dihydropyridines such as nifedipine cause primarily vasodilation and subsequent reflex tachycardia. As with beta-blockers, selectivity is lost after overdose, and toxicity is fourfold; the calcium antagonists have negative effects on heart rate, contractility, conduction, and vascular tone, with the exception of dihydropyridines, which tend to result in tachycardia even in severe toxicity.⁵⁴

All calcium channel blockers are rapidly absorbed, although first-pass hepatic metabolism significantly reduces bioavailability (Table 152-4). Onset of action and toxicity ranges from less than 30 minutes to 60 minutes. Peak effect of nifedipine can occur as early as 20 minutes after ingestion, but peak effect of sustained-release verapamil can be delayed for many hours. High protein binding and V_d greater than 1 to 2 L/kg make hemodialysis or hemoperfusion ineffective. Fortunately (except with sustained-release preparations), their half-lives are relatively short, limiting toxicity to 24 to 36 hours.

Clinical Features

Severe calcium antagonism eventually affects multiple organ systems, but cardiovascular toxicity is primarily responsible for morbidity and mortality. Hypotension and bradycardia occur early, and other rhythm disturbances include AV block of all degrees, sinus arrest, AV dissociation, junctional rhythm, and asystole. Dihydropyridines, such as nifedipine, often cause reflex sinus tachycardia from peripheral vasodilation. Calcium channel blockade has little effect on ventricular conduction, so QRS widening is not seen early on. Ventricular dysrhythmias are also uncommon.

Diagnostic Strategies

Serum levels of calcium antagonists are not readily available, nor do urine toxicology screens reliably detect this class of drugs. Glucose and electrolytes (including calcium and magnesium) should be measured. Hyperglycemia secondary to insulin inhibition occurs occasionally, but the elevation is usually mild (150-300 mg/L), is usually short-lived (<24 hours), and generally requires no treatment. Some authors suggest that hyperglycemia is a predictor of poor outcomes in verapamil and diltiazem toxicity.⁵⁵ A metabolic (lactic) acidosis occurs with hypotension and hypoperfusion.

An electrocardiogram should be promptly obtained, with special attention to atrial and ventricular rates and PR, QRS, and QT intervals.

Differential Considerations

Differential diagnosis is similar to that of beta-blocker cases. Until characteristic rhythm disturbances supervene, many other toxic, metabolic, traumatic, and cardiovascular disorders can cause hypotension but less commonly cause bradycardia. Like the beta-blockers, calcium antagonists cause early toxicity, and symptoms can be expected within 6 hours of ingestion of normal-release preparations. Toxicity can be delayed 12 to 24 hours with sustained-release preparations.

As with beta-blockade, CNS depressive effects are common and include lethargy, confusion, and coma. Unlike beta-blockers,

Table 152-4 Selected Characteristics of Some Calcium Channel Blockers

	V _d (L/kg)	HALF-Life (hr)	PROTEIN BINDING (%)	COMMENTS
Verapamil	4	3-12	90	Most fatalities; impairs contractility and cardiac conduction more than most other calcium antagonists
Diltiazem	1.7-5.3	3-7.9	70-80	Suppression of atrioventricular node similar to verapamil; myocardial depression otherwise less
Nifedipine	1.4-2.2	1-5	92-98	Vasodilation greatest effect
Nicardipine	0.64	8-9	95	Vasodilation
Nimodipine	0.94-2.3	1-2	95	Vasodilation
Amlodipine	21	30-50	98	Vasodilation
Bepridil	8	33-42	99	Class I as well as class IV antidysrhythmic; prolongs QT: torsades de pointes
Felodipine	10	10	99	Vasodilation
Isradipine	3	1.9-16	95	Vasodilation
Nisoldipine	4-5	7-12	99	Vasodilation

Box 152-10 Manifestations of Calcium Channel Blocker Poisoning

Cardiovascular: Hypotension, sinus bradycardia, sinus arrest, AV block, AV dissociation, junctional rhythm, asystole; ventricular dysrhythmias uncommon except with bepridil
Pulmonary: Respiratory depression, apnea; pulmonary edema; adult respiratory distress syndrome
Gastrointestinal: Nausea, vomiting, bowel infarction (rare)
Neurologic: Lethargy, confusion, slurred speech, coma; seizures (uncommon); cerebral infarction (rare)
Metabolic: Metabolic (lactic) acidosis; hyperglycemia (mild); hyperkalemia (mild)
Dermatologic: Flushing, diaphoresis, pallor, peripheral cyanosis

AV, atrioventricular.

calcium antagonists seldom induce seizures. Pulmonary effects include noncardiogenic pulmonary edema, and apnea can also occur. As with digitalis and beta-blocker overdose, nausea and vomiting are common (Box 152-10).

Management

Initial management includes rapid establishment of vascular access, supplemental oxygen, cardiac monitoring, and frequent blood pressure measurement. Gastrointestinal decontamination is controversial. For this class of highly lethal overdoses, activated charcoal at 1 g/kg can be considered if the airway is secure and if the patient presents in less than 1 or 2 hours. Multidose activated charcoal can be considered for sustained-release preparations and if a bezoar is suspected. Some authors have argued against the use of whole-bowel irrigation⁵⁶; however, calcium channel blockers cause significant morbidity and mortality, and risks should be weighed against potential benefits. Gastric lavage may be considered for patients presenting early, but pills are often large, and safe performance of this procedure requires a secure airway. No evidence exists that gastrointestinal decontamination improves mortality in general overdoses or in calcium channel blocker toxicity. With the lack of currently available evidence, gastric decontamination can neither be recommended nor criticized and has its proponents and detractors.

Hypotension and Bradycardia

Hypotension can be caused by myocardial depression, inadequate heart rate, or peripheral vasodilation. Atropine can be

administered in the standard doses. Atropine's effect has often been disappointing and short-lived, and multiple doses risk anticholinergic poisoning. A bolus of crystalloid fluid (20-40 mL/kg or more) should also be infused early. Intravenous calcium salts have traditionally been given to most patients. Their effect on contractility is considerable, but their effect on bradycardia, AV block, and peripheral vasodilation is often poor. The optimal dose of calcium is unknown. See the earlier discussion of calcium in the section on beta-blockers for our dosing recommendations. Adverse effects of hypercalcemia include lethargy, coma, anorexia, nausea, vomiting, pancreatitis, polyuria, dehydration, and nephrocalcinosis. Most of these effects have been reported after weeks or months of hypercalcemia from malignant disease or hyperparathyroidism. It is doubtful that hours or days of acutely induced hypercalcemia would be detrimental in the setting of massive calcium channel blockade. However, with *rapid* intravenous injection in animals and humans, bradycardia, AV block, AV dissociation, junctional tachycardia, ventricular ectopy, and ventricular fibrillation have been reported.

As with beta-blocker poisoning, a monotherapeutic approach will probably succeed only for trivial overdoses. If patients treated with isotonic fluids, calcium, and atropine have persistent hypotension or bradycardia, we next recommend HDI. HDI is thought to act by improving myocardial carbohydrate metabolism, thereby augmenting myocardial contraction. Serum glucose and potassium levels should be checked frequently to ensure that normal levels are maintained, although transient hyperglycemia is acceptable. Enthusiasm for HDI treatment is growing, and this therapy may prove safer and more efficacious than vasopressors.⁵⁷ See the earlier discussion for our dosing recommendations.

Most severely poisoned patients require the addition of catecholamines to accelerate the heart rate (chronotropy), to enhance AV conduction (dromotropy), and to restore tone to peripheral vessels (vasotropy). As with beta-blocker toxicity, in the selection of cardioactive medications to supplement HDI and glucagon, we recommend early assessment of systemic vascular resistance and cardiac output by either indirect measurements with a pulse contour analysis-based hemodynamic monitoring tool such as the FloTrac device (Edwards Lifesciences) or Swan-Ganz catheter and choosing of appropriate drugs for cardiogenic (epinephrine, norepinephrine, dopamine, dobutamine) or distributive shock (phenylephrine, vasopressin). Dosing of catecholamines in calcium channel blocker toxicity is not different from that in other clinical situations requiring their use. As long as dysrhythmias are not induced, catecholamine infusions should be aggressively titrated to effect (Box 152-11).

Treatment of Calcium Channel Blocker Intoxication

Phase 1 (Resuscitation)

Boluses of intravenous isotonic fluids, calcium, atropine

Phase 2 (Stabilization)

Calcium infusion
High-dose insulin/glucose infusion
Catecholamine infusions
Transcutaneous or transvenous cardiac pacing
Invasive monitoring

Phase 3 (Salvage Therapies)

Intravenous fat emulsion (e.g., Intralipid)
Intra-aortic balloon counterpulsation
Consider percutaneous left ventricular assist device or cardiac bypass

Glucagon has also been used for its inotropic and chronotropic effects in doses similar to those advocated for beta-blocker poisoning. Anecdotal human cases exist of calcium channel blocker poisonings responding to glucagon.⁵⁸ No controlled human studies exist. It is our practice to omit the use of glucagon in the treatment of calcium channel blocker toxicity.

IFE (e.g., Intralipid) has been described in the use of calcium channel blockers. The proposed mechanisms are discussed earlier. Animal evidence exists that IFE may be effective especially for the treatment of verapamil toxicity.⁵⁹ Dramatic human case reports exist of successful resuscitation of toxicity from diltiazem⁴⁸ and verapamil.⁶⁰ Dosing and indications are identical to those for beta-blocker toxicity.

Pediatric Considerations

Nifedipine and probably other drugs in its class join the short list of medications that can kill a child with ingestion of a single tablet.⁶¹ Seizures may be more common in children than in adults and should be treated with diazepam, lorazepam, or calcium.

Overall, death after calcium antagonist ingestion in children is rare. The intravenous route of administration, as with digitalis, is much more dangerous. Even therapeutic doses of intravenous verapamil are considered contraindicated in infants with supra-ventricular tachycardia because of case reports of cardiovascular collapse and cardiac arrest after injection.⁶²

Hyperglycemia occasionally occurs in children, but the elevation is usually short-lived. Although insulin has been administered in a handful of cases, it is generally not necessary unless HDI is being used therapeutically because the hyperglycemia usually resolves spontaneously within 24 to 36 hours.

A small number of children in refractory shock secondary to drug toxicity have been treated with intra-aortic balloon counterpulsation or cardiac bypass. Circulatory support during the day or two required for hepatic or renal elimination of the drug is potentially beneficial for a drug that does not cause irreversible damage. Aside from the differences previously noted, the presentation in children is similar to that in adults: rapid onset of toxicity with CNS depression, bradydysrhythmias, hypotension, and metabolic acidosis.

Disposition

Because the peak effect of normal-release calcium channel blockers commonly occurs in 90 minutes to 6 hours, patients who are totally asymptomatic for 6 hours after an ingestion of immediate-release medication can be safely discharged according

to psychiatric needs. Symptomatic patients or those who ingested delayed-release preparations should be admitted to a medical or toxicology service for at least 24 hours of continuous cardiac monitoring.

NITRATES AND NITRITES

Nitrates (nitroglycerin, isosorbide mononitrate and dinitrate) are widely used as vasodilators in the treatment of heart failure and ischemic heart disease. They augment coronary blood flow as well as reduce myocardial oxygen consumption by reducing afterload. At lower doses nitrates primarily dilate veins, but at higher doses they also dilate arteries. Hypotension is a common complication but usually responds to supine positioning, intravenous fluids, and reduction of dose. Hypotension is usually transient. Low-dose pressors are occasionally needed, but it is best to avoid them in the setting of acute coronary syndromes.

Intravenous nitroglycerin infusions are being used commonly in patients with acute pulmonary edema for afterload reduction. Infusions are usually initiated at 5 to 10 $\mu\text{g}/\text{min}$, but rates as high as 200 to 300 $\mu\text{g}/\text{min}$ may be used. These doses may be beneficial in patients with pulmonary edema accompanied by acute hypertension, but hypotension may develop suddenly. Intravenous nitroglycerin has a rapid offset of action, so excessive fall in blood pressure usually responds to reduction or termination of the infusion. Use of nitrates is contraindicated in patients who have recently taken sildenafil (Viagra). Sildenafil and related drugs (vardenafil [Levitra] and tadalafil [Cialis]) inhibit type 5 phosphodiesterase, relaxing vascular smooth muscle. These agents can prolong and intensify the vasodilating effects of nitrates, resulting in severe hypotension. If blood pressure does not rise with intravenous fluids, dopamine should be cautiously titrated, beginning at 5 $\mu\text{g}/\text{kg}/\text{min}$.

Nitrates are occasionally found in rural well water contaminated by livestock or fertilizer runoff. Oral nitrates may be converted to nitrites in the gastrointestinal tract, especially in infants, whose hemoglobin is also more susceptible to oxidation. However, most exposures are encountered in young adults, usually male, who inhale various alkyl nitrites (amyl, butyl, isobutyl, or ethyl nitrite) in the hope of enhancing or prolonging sexual pleasure. Because of the sound they make when broken open, these products are best known to abusers as poppers. The popularity of poppers has waned in recent years as sales of sildenafil and related products have soared. Nitrites and nitrates are both potent vasodilators, and excessive use can cause headache, skin flushing, and orthostatic hypotension. Nitrites are also oxidizing agents that convert hemoglobin to methemoglobin, impairing oxygen delivery. Although most exposure is by inhalation, unintentional ingestion may occur because nitrites are also used legitimately as food preservatives. A family of five had methemoglobinemia after consuming a meal seasoned with sodium nitrite mislabeled as table salt.⁶³

Patients with glucose-6-phosphate dehydrogenase deficiency are especially susceptible to the oxidative stress of nitrite exposure, and they may even have hemolysis. When methemoglobin levels exceed 15%, a venous blood sample appears chocolate brown, and the skin appears blue even while patients look remarkably comfortable. Unlike in most cases of cyanosis, supplemental oxygen does not improve the patient's color. Pulse oximetry is not reliable, and the partial pressure of oxygen remains normal in mild to moderate cases. This rare complication can be treated with intravenous administration of methylene blue, but this antidote is usually not needed unless methemoglobinemia approaches 30% or the patient has clinical signs of distress, such as tachypnea, tachycardia, acidosis, and hypotension. The usual dose of methylene blue in adults is 1 to 2 mg IV during 5 minutes.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

KEY CONCEPTS

Digitalis

- Consider digoxin intoxication in any patient with gastrointestinal or visual disturbance and a new dysrhythmia or conduction disturbance.
- Dose digitalis Fab antibody fragments by body load of digitalis, not by body weight of the patient.
- Use digitalis Fab fragments before pacing or other antidysrhythmic drugs.
- Hyperkalemia in digitalis toxicity is best treated with Fab fragments. Conventional treatment with sodium bicarbonate, insulin, and glucose as well as with calcium is also appropriate, especially when Fab fragment preparations are not immediately available.

Beta-Adrenergic Blockers

- Beta-blocker intoxication usually causes bradycardias and occasionally AV block.
- Noncardiac symptoms such as obtundation, seizures, and hypoglycemia may predominate, especially early in the course and particularly with propranolol.
- Volume expansion, atropine, calcium, and glucagon are early treatment measures, but absent a response, begin a high-dose insulin/glucose infusion.

Calcium Channel Blockers

- Signs and symptoms of calcium channel blocker intoxication occur early after overdose.
- CNS depression is common; seizures are not.
- AV block and bradycardias predominate, except with bepridil.
- Volume expansion, calcium, and vasopressors have been the mainstays of treatment, but high-dose insulin/glucose infusion probably offers the most therapeutic benefit in cases of severe intoxication.

Nitrates and Nitrites

- Hypotension and methemoglobinemia are common presentations.

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