62: β-Adrenergic Antagonists

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HISTORY

In 1948, Raymond Alquist postulated that the cardiovascular actions of epinephrine, hypertension and tachycardia, were best explained by the existence of two distinct sets of receptors that he generically named α and β receptors. At that time, the contemporary “antiepinephrine” xenobiotics such as phenoxybenzamine reversed the hypertension but not the tachycardia associated with epinephrine. According to Alquist’s theory these xenobiotics acted at the α receptors. The β receptors, in his schema, mediated catecholamine induced tachycardia. The British pharmacist, Sir James Black was influenced by Alquist’s work and recognized the potential clinical benefit of a β-adrenergic antagonist. In 1958, Black synthesized the first β-adrenergic antagonist, pronethalol. This drug was briefly marketed as Alderlin, named after Alderly Park, the research headquarters of ICI Pharmaceuticals. Pronethalol was discontinued because it produced thymic tumors in mice. Propranolol was soon developed and marketed as Inderal (an incomplete anagram of Alderlin) in the United Kingdom in 1964 and in the United States in 1973. Prior to the introduction of β-adrenergic antagonists, the management of angina was limited to medications such as nitrates, which reduced preload through dilation of the venous capacitance vessels and increased myocardial oxygen delivery by vasodilation of the coronary arteries. Propranolol gave clinicians the ability to decrease myocardial oxygen utilization. This new approach proved to decrease morbidity and mortality in patients with ischemic heart disease. New drugs soon followed and by 1979 there were ten β-adrenergic antagonists available in the United States. Unfortunately it soon became apparent that these medications were dangerous when taken in overdose and by 1979 cases of severe toxicity and death from β-adrenergic overdose were reported. Today there are nineteen β-adrenergic antagonists approved by the US Food and Drug Administration, and other β-adrenergic antagonists are available worldwide (Table 62–1). The pharmacology, toxicology, and poison management issues discussed in this chapter are applicable to all of these drugs. They are commonly used in the treatment of cardiovascular disease: hypertension, coronary artery disease, and tachydysrhythmias. Additional indications for β-adrenergic antagonists include congestive heart failure, migraine headaches, benign essential tremor, panic attack, stage fright, and hyperthyroidism. Ophthalmic preparations containing β-adrenergic antagonists are used in the treatment of glaucoma.

| TABLE 62–1. Pharmacologic Properties of the β-Adrenergic Antagonists |
| View Large |
**EPIDEMIOLOGY**

Intentional β-adrenergic antagonist overdose, although relatively uncommon, continues to account for a number of deaths annually. From 1985 to 1995, there were 52,156 β-adrenergic antagonist exposures reported to the American Association of Poison Control Centers (AAPCC; Chap. 136). These exposures accounted for 164 deaths of which β-adrenergic antagonists were implicated as the primary cause of death in 38. The other fatalities could not be clearly ascribed to β-adrenergic antagonists due to cardioactive coingestants such as calcium channel blockers or other factors. Children under the age of 6 accounted for 19,388 exposures, but no fatalities were reported in this age group. The youngest fatality reported in this series was aged 7 years. It is interesting to note that more than one-half of the fatalities developed cardiac arrest after reaching health care personnel. The number of exposures to β-adrenergic antagonists reported to the AAPCC has increased annually from 9500 in 1999 to more than 23,000 in 2010. Just under one-half of these exposures were single substance ingestions. Each year since 2006, single substance exposures to β-adrenergic antagonists have resulted in between 54 and 70 cases with major morbidity and three to six fatalities (Chap. 136).

Compared with the other β-adrenergic antagonists, propranolol accounts for a disproportionate number of cases of self-poisoning and deaths. This may be explained by the fact that propranolol is frequently prescribed to patients with diagnoses, such as anxiety, stress, hyperthyroidism, and migraine, who may be more prone to suicide attempts. Propranolol is also more lethal due to its lipophilic and membrane stabilizing properties.

**PHARMACOLOGY**

**Cardiac Cycle**

Normal cardiac electrical activity involves a complex series of ion fluxes that result in myocyte depolarization and repolarization. Cardiac electrical activity is coupled to myocyte contraction and relaxation respectively by increases and decreases in intracellular calcium concentrations. Cardiac electrical and mechanical activity is closely regulated by the autonomic nervous system.

Under normal conditions, heart rate is determined by the rate of spontaneous discharge of specialized pacemaker cells that comprise the sinoatrial (SA) node (Fig. 62–1). Pacemaker cells are also found in the atroventricular (AV) node and in Purkinje fibers. Spontaneous pacemaker cell depolarization has traditionally been ascribed to inward cation current through “pacemaker channels.” Recent research suggests that spontaneous depolarization of pacemaker cells involves several mechanisms including a “membrane clock,” consisting of “pacemaker channels” and other inward cation channels located on the cell membrane, and a “calcium clock,” which is driven by rhythmic release of calcium from the sarcoplasmic reticulum. β-Adrenergic stimulation significantly increases the rate of pacemaker cell depolarization by phosphorylating proteins within
the sarcoplasmic reticulum, thereby increasing the rate of the "calcium clock." There is also a direct, phosphorylation-independent action of cyclic adenosine monophosphate (cAMP) at the pacemaker channels, which increases the rate of the "membrane clock." Depolarization of cells in the SA node spreads to surrounding atrial cells where it triggers the opening of fast sodium channels. This initiates an electric current that spreads from cell to cell along specialized pathways to depolarize the entire heart. This depolarization, referred to as cardiac excitation, is linked to mechanical activity of the heart by the process of electrical–mechanical coupling described below (Chap. 16).

FIGURE 62–1.
Cardiac conduction system: A. The cardiac cycle begins when pacemaker cells in the sinoatrial node depolarize spontaneously. Traditionally, this depolarization has been attributed to inward "pacemaker" currents ($I_{f}$). There is recent evidence that pacemaker cell depolarization may also be driven by cyclical calcium release from a "calcium clock" in the sarcoplasmic reticulum (SR). β-Adrenergic stimulation increases both the frequency of the "calcium clock" by a phosphokinase A (PKA) mediated effect and the magnitude of the pacemaker current secondary to a direct effect of cAMP. These effects both increase the heart rate. Cholinergic stimulation has the opposite effects and results in bradycardia. Pacemaker cells lack fast sodium channels. Pacemaker cell depolarization triggers the opening of voltage sensitive L-type calcium channels ($I_{Ca,L}$) and the impulse is transmitted to surrounding cells.

B. Coordinated SA nodal depolarization generates an impulse sufficient to open fast sodium channels in surrounding atrial tissue and the impulse spreads along specialized pathways to depolarize the atria and ventricles.

Myocyte Calcium Flow and Contractility
During systole, voltage sensitive slow calcium channels (L-type channels) on the myocyte membrane open in response to cell depolarization allowing calcium to flow down its concentration gradient into the myocyte (Fig. 62–2). Invaginations of the myocyte membrane, known as T-tubules, place L-type calcium channels in close approximation to calcium release channels (ryanodine receptors {RyRs}) on the sarcoplasmic reticulum (SR). The local increase in calcium concentration that follows the opening of a single L-type calcium channel on the cell membrane triggers the opening of the associated RyR channels, resulting in a large release of calcium from the SR, a phenomenon known as calcium-induced calcium release. Myocytes contain tens of thousands of $coup lons$, clusters of L-type calcium channels and RyR channels. The calcium released from one $coup l on$ is not sufficient to trigger firing of neighboring $coup l ons$. Organized myocyte contraction requires synchronized release of calcium from numerous $coup l ons$ throughout the myocyte. This process depends on membrane depolarization to synchronize opening of L-type channels and subsequent calcium release. This occurs rapidly throughout an extensive network of T-tubules that spans the myocyte. Following release from the sarcoplasmic reticulum, cytosolic calcium binds to troponin C and allows actin myosin interaction and subsequent myocyte contraction. The strength of contraction is proportional to the amount of calcium release from the SR during depolarization, which depends, in part, on the magnitude of SR calcium stores. Actin–myosin
interaction is also modulated by β-adrenergic–mediated troponin phosphorylation, ischemia, intracellular pH, and myofilament stretch. 8 17 20 209

FIGURE 62–2.
Fluctuations in calcium concentrations couple myocyte depolarization with contraction and myocyte repolarization with relaxation. [1] Depolarization causes voltage sensitive calcium channels to open and calcium to flow down its concentration gradient into the myocyte. [2] This calcium current triggers the opening of calcium release channels in the sarcoplasmic reticulum and calcium pours out of the sarcoplasmic reticulum (SR). The amount of calcium released from the SR is proportional to the initial inward calcium current and to the amount of calcium stored in the SR. [3] At rest, actin–myosin interaction is prevented by troponin. When calcium binds to troponin, this inhibition is removed, actin and myosin slide relative to each other, and the cell contracts. Following contraction, calcium is actively removed from the myocyte to allow relaxation. [4] Most calcium is actively pumped into the SR where it is bound to calsequestrin. Calcium stored in the SR is thus available for release during subsequent depolarizations. The sarcoplasmic calcium ATPase is inhibited by phospholamban (Fig. 62–3). [5] The calcium sodium antiporter couples the flow of three molecules of sodium flow in one direction to that of a single molecule of calcium in the opposite direction. This transporter is passively driven by electrochemical gradients which usually favor the inward flow of sodium coupled to the extrusion of calcium. Extrusion of calcium is inhibited by high intracellular sodium or extracellular calcium concentrations and by cell depolarization. Under these conditions, the pump may “run in reverse.” [6] Some calcium is actively pumped from the cell by a calcium ATPase. [7] As myocyte calcium concentrations fall, calcium is released from troponin and the myocyte relaxes.

During diastole, several ion pumps actively remove calcium from the cytoplasm (Fig. 62–2). The most important of these are the sarcoplasmic reticulum calcium ATPase that pumps cytosolic calcium into the SR, and the calcium–sodium transporter that exchanges one calcium ion for three sodium ions with the extracellular fluid. The SR calcium ATPase is important for maintaining SR calcium stores and is modulated by β-adrenergic stimulation (see below). When calcium concentrations drop during diastole, calcium dissociates from troponin and relaxation occurs. 15 17 18 187

β-Adrenergic Receptors and the Heart
β-Adrenergic receptors are divided into β₁, β₂, and β₃ subtypes. In the healthy heart, approximately 80% of human cardiac β₁-adrenergic receptors are β₁ and 20% are β₂. Human hearts may also contain a small number of β₂-adrenergic receptors. 28 60 61 159 177 The relative density of cardiac β₂-adrenergic receptors increases with heart failure. 24 100 β₁-Adrenergic receptors mediate increased inotropy by a well-described pathway involving cyclic AMP and protein kinases (Fig. 62–3). β₁-Adrenergic receptors are coupled to G protein that activate adenylate cyclase when the receptor is stimulated. This increases intracellular production of cAMP, which binds to and activates protein kinase A and other cAMP-dependent protein kinases. 128 Protein kinase A, in turn, phosphorylates important myocyte proteins, including phospholamban, the voltage sensitive calcium channels, the calcium release (RyR) channels, and troponin. 17 28 70 187 194 199 Phosphorylation of the L-type calcium channel increases contractility by increasing the influx of calcium during each cell depolarization triggering greater release of calcium from the sarcoplasmic reticulum. 189 199 200 Phospholamban inhibits
the SR calcium ATPase. Phosphorylation of phospholamban removes this inhibition and increases the activity of the sarcoplasmic calcium ATPase, resulting in increased SR calcium stores and hence enhanced contractility. Improved activity of the SR calcium ATPase will also result in more rapid removal of cytoplasmic calcium during diastole and aid in myocyte relaxation. Phosphorylation of the RyR channels results in more rapid release of calcium from SR stores.

Troponin phosphorylation facilitates calcium unbinding and thus improves cardiac performance by enhancing myocyte relaxation. β-Adrenergic receptors increase chronotropy by an incompletely understood mechanism that may involve phosphorylation of SR proteins, resulting in an increased rate of calcium discharge from the SR in addition to direct cAMP interaction with membrane bound pacemaker channels. Although β-adrenergic stimulation acutely improves cardiac function, chronic β-adrenergic stimulation, acting through β-adrenergic receptors, results in a number of detrimental effects, including calcium overload, increased risk of dysrhythmias, impaired excitation-contraction coupling, and myocyte apoptosis.

FIGURE 62–3.
β-adrenergic agonists are positive inotropes by virtue of their ability to activate protein kinase A (PKA). β-adrenergic receptors are coupled to Gs proteins, which activate adenyl cyclase when catecholamines bind to the receptor. This causes increased formation of cAMP from ATP. Increased cAMP concentrations activate PKA, which mediates the ultimate effects of β-adrenergic receptor stimulation by phosphorylating key intracellular proteins. Phosphorylation of phospholamban disinhibits the sarcoplasmic reticulum (SR) calcium ATPase resulting in increased SR calcium stores available for release during subsequent depolarizations and phosphorylation of SR calcium release channels enhances calcium release from SR stores during contraction. Phosphorylation of voltage sensitive calcium channels increases calcium influx through these channels during systole. Troponin phosphorylation improves cardiac performance by facilitating calcium unbinding during diastole. β2 Receptors are also coupled to Gi proteins and mediate positive inotropy through a cAMP mechanism. Increased cAMP directly increases heart rate (Fig. 62–1).

Cardiac β2-adrenergic receptors are dually linked to both excitatory Gs proteins and inhibitory Gi proteins. Under normal conditions, the Gs pathway predominates in human cardiac β2-adrenergic receptors and β2-adrenergic stimulation increases contractility, relaxation, and chronotropy through the protein kinase A pathway described above. However, in the failing heart, the inhibitory Gi protein pathway becomes dominant and β2-adrenergic stimulation inhibits cardiac function. Chronic β2-adrenergic stimulation may prevent myocyte apoptosis.

Noncardiac Effects of β-Adrenergic Receptor Activation
β-Adrenergic agonists have important noncardiac effects. β-Adrenergic receptors mediate smooth muscle relaxation in several organs. Relaxation of arteriolar smooth muscle predominately by β2-adrenergic stimulation reduces peripheral vascular resistance and decreases blood pressure. This counteracts α-adrenergic–mediated arteriolar constriction. In the lungs, β2-adrenergic receptors mediate bronchodilation. Unfortunately, chronic β-adrenergic stimulation may cause adverse
pulmonary effects, including mucous cell proliferation, hyperreactive airways, and inflammation. Third-trimester uterine tone and contractions are inhibited by β2-adrenergic agonists, and gut motility is decreased by both β1- and β2-adrenergic stimulation. Chronic, high-dose β2-adrenergic stimulation causes skeletal muscle hypertrophy.

β-Adrenergic receptors play a role in the immune system. Mast cell degranulation is inhibited by β2-adrenergic stimulation, explaining the role of epinephrine in aborting and treating severe allergic reactions. Polymorphonuclear leukocytes demarginate in response to β-adrenergic stimulation, resulting in the increased white blood cell counts with catecholamine infusions or with increased endogenous release of epinephrine that occurs with pain or physiologic stress.

β-Adrenergic agonists also have important metabolic effects. Insulin secretion is increased by β2-adrenergic receptor stimulation. Despite increased insulin concentrations, the net effect of β2-adrenergic receptor stimulation is to increase glucose due to increased skeletal muscle glycogenolysis and hepatic gluconeogenesis and glycogenolysis. β-Adrenergic receptors also cause glucagon secretion from pancreatic α cells. β-Adrenergic agonists act at fat cells to cause lipolysis and thermogenesis. Stimulation of adipocyte β-adrenergic receptors results in breakdown of triglycerides and release of free fatty acids. Skeletal muscle potassium uptake is increased by β2-adrenergic stimulation resulting in hypokalemia, explaining the role of β2-adrenergic agonists in the treatment of hyperkalemia. Finally, renin secretion is increased by β1-adrenergic stimulation, resulting in increased blood pressure.

Effects of β-Adrenergic Antagonists

β-Adrenergic antagonists competitively antagonize the effects of catecholamines at β-adrenergic receptors and blunt the chronotropic and inotropic response to catecholamines. Bradycardia and hypotension may be severe in patients who take additional medications that impair cardiac conduction or contractility or in those with underlying cardiac or medical conditions that make them reliant on sympathetic stimulation. In addition to slowing the rate of SA node discharge, β-adrenergic antagonists inhibit ectopic pacemakers and slow conduction through atrial and AV nodal tissue. β-Adrenergic antagonists block the detrimental effects of chronic adrenergic overstimulation and have become standard of care for patients with all stages of compensated chronic heart failure, including patients with stable NYHA (New York Heart Association) class III or IV disease. β-Adrenergic blockade may exacerbate symptoms in patients with decompensated congestive heart failure but, in the absence of cardiogenic shock or symptomatic bradycardia, β-adrenergic antagonists should not be routinely discontinued in heart failure patients admitted to hospital. β-Adrenergic antagonists prevent adverse cardiac events in patients with recent myocardial infarctions but may be ineffective in patients with prior myocardial infarction, stable coronary artery disease, or risk factors for coronary artery disease.

The antihypertensive effect of β-adrenergic antagonists is counteracted by a reflex increase in peripheral vascular resistance. This effect is augmented by the β2-adrenergic antagonism of nonselective β-adrenergic antagonists. By causing increased peripheral vascular resistance, β2-adrenergic antagonists may rarely worsen peripheral vascular disease.
Patients with reactive airways disease may suffer severe bronchospasm after using β-adrenergic antagonists due to loss of β₂-adrenergic–mediated bronchodilation. Catecholamines inhibit mast cell degranulation through a β₂-adrenergic mechanism. Interference with this may predispose to life-threatening effects following anaphylactic reactions in atopic individuals. β₂-Adrenergic antagonists impair the ability to recover from hypoglycemia and may mask the sympathetic discharge that serves to warn of hypoglycemia. This combination of effects is dangerous for patients with diabetes at risk for hypoglycemic episodes.

β₁-Adrenergic antagonism inhibits catecholamine-mediated potassium uptake at skeletal muscle. This may cause slight elevations in serum potassium especially after exercise. Although β₂-adrenergic stimulation augments insulin release, β₁-adrenergic antagonists seldom lower insulin concentrations and may actually cause hypoglycemia by interference with glycogenolysis and gluconeogenesis. These effects are important in patients with diabetes at risk for hypoglycemia. β₁-Adrenergic antagonists also alter lipid metabolism. Although the release of free fatty acids from adipose tissue is inhibited, patients taking nonselective β-adrenergic antagonists typically have increased plasma concentrations of triglycerides and decreases in high-density lipoproteins.

**PHARMACOKINETICS**

The pharmacokinetic properties of the β-adrenergic antagonists depend in large part on their lipophilicity. Propranolol is the most lipid soluble of the β-adrenergic antagonists and atenolol is the most water soluble. The oral bioavailability of the β-adrenergic antagonists ranges from approximately 25% for propranolol to almost 100% for pindolol and penbutolol.

The highly lipid-soluble drugs cross lipid membranes rapidly and concentrate in adipose tissue. These properties allow rapid entry into the central nervous system (CNS), and typically result in large volumes of distribution. In contrast, highly water-soluble drugs, cross lipid membranes slowly, distribute in total body water, and tend to have less CNS toxicity. Volumes of distribution range from about 1 L/kg for atenolol to more than 100 L/kg for carvedilol.

The highly lipid soluble β-adrenergic antagonists are highly protein bound and poorly excreted by the kidneys. They require hepatic biotransformation before they can be eliminated and accumulate in patients with liver failure. By contrast, the water-soluble β-adrenergic antagonists tend to be slowly absorbed, poorly protein bound, and renally eliminated. They accumulate in patients with kidney failure. Esmolol, although water-soluble, is rapidly metabolized by red blood cell esterases and does not accumulate in patients with kidney failure. The half-life of esmolol is about 8 minutes. Half-lives of the other β-adrenergic antagonists range from about 2 hours for oxprenolol to as much as 32 hours for nebivolol. The β-adrenergic antagonists also differ in their β₁-adrenergic selectivity, intrinsic sympathomimetic activity, and vasodilatory properties (Table 62–1).

β, Selectivity (Acebutolol, Atenolol, Betaxolol, Bisoprolol, Celiprolol, Esmolol, Metoprolol, Nebivolol)

β₁-Selective antagonists may avoid some of the adverse effects of the non-selective antagonists. Short-term use of β₁-adrenergic selective antagonists appears to be safe in patients with mild to
moderately severe reactive airways. These drugs may be safer for patients with diabetes mellitus or peripheral vascular disease and may be more effective antihypertensives. Their $\beta_1$-adrenergic selectivity, however, is incomplete, and adverse reactions secondary to $\beta_2$-adrenergic antagonism may occur with therapeutic dosage as well as in overdose.

Membrane Stabilizing Effects (Acebutolol, Betaxolol, Carvedilol, Oxprenolol, Propranolol)
$\beta$-Adrenergic antagonists that inhibit fast sodium channels (also known as type I antidysrhythmic activity) are said to possess membrane-stabilizing activity. No significant membrane stabilization occurs with therapeutic use of $\beta$-adrenergic antagonists, but this property can contribute to toxicity in overdose.

Intrinsic Sympathomimetic Activity (Acebutolol, Carteolol, Oxprenolol, Penbutolol, Pindolol)
These medications act as partial agonists at $\beta$-adrenergic receptors and are said to have intrinsic sympathomimetic activity (ISA). This property is unrelated to $\beta_1$-adrenergic selectivity. These drugs may avoid the dramatic decrease in resting heart rate that occurs with $\beta$-adrenergic antagonism in susceptible patients, but their clinical benefit is not demonstrated in controlled trials.

Potassium Channel Blockade (Acebutolol, Sotalol)
Sotalol is a nonselective $\beta$-adrenergic antagonist with low lipophilicity, no membrane stabilizing effect, and no ISA. Sotalol is unique because of its ability to block the delayed rectifier potassium current responsible for repolarization. This prolongs the action potential duration and is manifested on the electrocardiogram (ECG) by a prolonged QT interval. The prolonged QT interval predisposes to torsade de pointes and ventricular dysrhythmias may complicate the therapeutic use of sotalol. In patients taking sotalol therapeutically, torsade de pointes is most common in those who have kidney failure, use other drugs that prolong the QT interval, or have predisposing factors for QT prolongation such as hypokalemia, hypomagnesemia, bradycardia, or congenital QT prolongation. Some authors suggest that QT dispersion is a better predictor of sotalol induced torsade de pointes than QT prolongation alone (Chap. 17). A difference between the longest and shortest QT interval on 12-lead ECG of more than 100 milliseconds indicates an increased risk of torsade de pointes. Acebutolol also prolongs the QT interval presumably secondary to blockade of outward potassium channels.

Vasodilation (Betaxolol, Bucindolol, Carteolol, Carvedilol, Celiprolol, Labetalol, Nebivolol)
Labetalol and the newer “third-generation” $\beta$-adrenergic antagonists (betaxolol, bucindolol, carteolol, carvedilol, celiprolol, nebulol) are also vasodilators. Labetalol and carvedilol are nonselective $\beta$-adrenergic antagonists that also possess $\alpha$-adrenergic antagonist activity. Nebivolol is a selective $\beta_1$-adrenergic antagonist that causes vasodilation by release of nitric oxide. Bucindolol, carteolol, and celiprolol vasodilate because they are agonists at $\beta_2$-adrenergic receptors. Celiprolol and carteolol also vasodilate because of nitric oxide mediated effects. Bucindolol and celiprolol are not FDA approved. Carteolol is currently available as an ocular preparation. Betaxolol and carvedilol also have calcium channel blocking properties that result in vasodilation (Table 62–1). $\beta$-Adrenergic antagonists with vasodilating properties may be particularly beneficial for patients with congestive heart failure. These drugs may also have a role in managing patients with coronary artery disease.
or peripheral vascular disease. Those drugs with β2-adrenergic agonist activity may prove useful for patients with reactive airways.

β-Adrenergic antagonists should not be given without appropriate α-adrenergic blockade in situations of catecholamine excess such as pheochromocytoma. In these conditions, β- adrenergic–mediated vasodilation is essential to counteract α-adrenergic–mediated vasoconstriction. β-Adrenergic antagonists would result in “unopposed α” adrenergic effect causing dangerous increases in vascular resistance. Even agents with combined α- and β-adrenergic antagonist properties can cause this problem. Labetalol, for example, is five to ten-fold more potent as a β- adrenergic antagonist than as an α-adrenergic antagonist. Theoretically, xenobiotics with β2- adrenergic agonist properties may avoid the “unopposed α” effect, but their use in this situation has not yet been investigated. 48, 63, 114, 210, 223

Other Preparations (Ophthalmic Preparations, Sustained Release, Combined Products)
Therapeutic use of ophthalmic solutions containing β-adrenergic antagonists may cause systemic adverse effects such as bradycardia, high-grade AV block, heart failure, and bronchospasm. 24, 46, 152, 189, 216, 223

An extended-release tablet containing a combination of the calcium channel blocker, felodipine, and metoprolol has been studied as an antihypertensive medication. 45, 69 This medication (Logimax, AstraZeneca) is marketed in more than 35 countries worldwide but is not available in the United States or Canada. Another combined β-adrenergic and calcium channel antagonist containing atenolol and nifedipine (Nif–Ten, AstraZeneca) is also used as an antihypertensive. 45

PATHOPHYSIOLOGY

Most of the toxicity of β-adrenergic antagonists is due to their ability to competitively antagonize the action of catecholamines at cardiac β-adrenergic receptors. The peripheral vascular effects of β-adrenergic antagonism are less prominent in overdose. β-Adrenergic antagonists also appear to have toxic effects independent of their action at catecholamine receptors. In catecholamine depleted, spontaneously beating isolated rat hearts, propranolol, timolol and sotalol all decreased heart rate and contractility. 42 Surprisingly, these effects were similar in catecholamine depleted and nondepleted hearts. 114 A membrane depressant effect likely contributes to the cardiac depressant effects of propranolol but not to that of timolol or sotalol. It may be concluded that β-adrenergic antagonists cause myocardial depression at least in part by an action independent of catecholamine antagonism or membrane depressant activity. 114 This effect may be mediated by interference with calcium handling in the sarcoplasmic reticulum.

Other investigators studied the role of extracellular ions and cardiac membrane potential in modulating β-adrenergic antagonist toxicity. β-Adrenergic antagonists interfere with calcium uptake into intracellular organelles. This interference with cytosolic calcium handling may stimulate calcium sensitive outward potassium channels and result in myocyte hyperpolarization and subsequent refractory bradycardia. Lowering extracellular potassium or raising extracellular sodium
concentrations was conjectured to counteract this effect and, in fact, partially reversed propranolol and atenolol toxicity in isolated rat hearts. In another series of experiments with isolated rat hearts, calcium improved the function of rat hearts poisoned with β-adrenergic antagonists. This may have been due to a nonspecific positive inotropic action of calcium.

Although cardiovascular effects are most prominent in overdose, β-adrenergic antagonists also cause respiratory depression. This effect is centrally mediated and appears to be an important cause of death in spontaneously breathing animal models of β-adrenergic antagonism toxicity. There is evidence that propranolol is concentrated in synaptic vessels and may impair synaptic function by inhibition of membrane ion pumps, including the sodium–potassium ATPase, the calcium ATPase, and the magnesium ATPase. These actions may explain some of the CNS effects noted in propranolol overdose.

**CLINICAL MANIFESTATIONS**

Symptoms of toxicity generally occur within hours after β-adrenergic antagonist overdose. Propranolol overdose, in particular, may be complicated by the rapid development of hypoglycemia, seizures, coma, and dysrhythmias. In a retrospective review of published reports of adult β-adrenergic antagonist overdose there were 39 symptomatic patients with well documented times from ingestion to symptom onset. Only one patient had ingested a sustained release product. Thirty-one patients were symptomatic at 2 hours, all but one developed symptoms at 4 hours, and everyone developed symptoms within the first 6 hours. The authors conclude that there have been no well documented reports of immediate release β-adrenergic antagonist overdose resulting in toxicity delayed more than 6 hours after ingestion. The authors of an Australian series also noted that, in their 58 patients with β-adrenergic antagonist overdose, all major symptoms began within 6 hours of ingestion. These observations do not apply to sotalol, which is well known to cause delayed toxicity in overdose, or to sustained-release preparations.

Isolated β-adrenergic antagonist overdose in healthy people is often benign. In several series, one-third or more of patients reporting a β-adrenergic overdose remained asymptomatic. This is partially explained by the fact that β-adrenergic antagonism is often well tolerated in healthy persons who do not rely on sympathetic stimulation to maintain cardiac output. In particular, unintentional ingestions in children rarely result in significant toxicity. In fact, a review of published cases found a few reports of hypoglycemia but no deaths or serious cardiovascular morbidity following β-adrenergic antagonist ingestion in children younger than 6 years of age.

β-Adrenergic antagonists severely impair the ability of the heart to respond to peripheral vasodilation, bradycardia, or decreased contractility caused by other xenobiotics. Therefore even relatively benign vasoactive xenobiotics may cause catastrophic toxicity when coingested with β-adrenergic antagonists. According to one author, the most important predictor of toxicity in β-adrenergic antagonist overdose is likely to be the presence of a cardioactive coingestant. Isolated β-adrenergic antagonist overdose is most likely to cause symptoms in persons with congestive heart
failure, sick sinus syndrome, or impaired AV conduction who rely on sympathetic stimulation to maintain heart rate or cardiac output. Nevertheless, severe toxicity and death may still occur in healthy persons who have ingested β-adrenergic antagonists alone. This may be explained by an increased susceptibility of certain persons to β-adrenergic antagonism or by special properties that increase the toxicity of certain β-adrenergic antagonists (see below). In patients without a coingestant, toxicity is most likely to occur in those who ingest a β-adrenergic antagonist with membrane stabilizing activity.

Patients with symptomatic β-adrenergic antagonist overdose will most often be hypotensive and bradycardic. Decreased SA node function results in sinus bradycardia, sinus pauses, or sinus arrest. Impaired atrioventricular conduction manifested as prolonged PR interval or high-grade AV block occurs rarely. Prolonged QRS and QT intervals may occur and severe poisonings may result in asystole. Congestive heart failure often complicates β-adrenergic antagonist overdose. Delirium, coma, and seizures occur most commonly in the setting of severe hypotension but may also occur with normal blood pressure, especially with exposure to the more lipophilic xenobiotics such as propranolol. Respiratory depression and apnea may have an additional role in toxicity. In a review of reported cases, 18% of patients with propranolol toxicity and 6% of those with atenolol toxicity had a respiratory rate fewer than 12 breaths/min. Respiratory depression following β-adrenergic antagonist overdose typically occurs in patients who are hypotensive and comatose but is reported in awake patients. Hypoglycemia may complicate β-adrenergic antagonist poisoning in children but is uncommon in acutely poisoned adults. In a series of 15 cases of β-adrenergic antagonist overdose, none of the 13 adults were hypoglycemic whereas both of the two children had symptomatic hypoglycemia. Bronchospasm is relatively uncommon following β-adrenergic antagonist overdose and appears to occur only in susceptible patients. In the series mentioned above, only two of the 15 patients developed bronchospasm and in a recent review of 39 cases of symptomatic adults with β-adrenergic antagonist overdose, only one patient developed bronchospasm. Clinical use of β-adrenergic antagonists slightly increases serum potassium; however, significant hyperkalemia is rare.

**β, Selectivity (Acebutolol, Atenolol, Betaxolol, Bisoprolol, Esmolol, Metoprolol, Nebivolol)**

In overdose, cardioselectivity is largely lost and deaths due to the β₁-adrenergic selective agents including acebutolol, atenolol, betaxolol, and metoprolol are reported. There have been single reports of minor toxicity following overdose with bisoprolol and nebivolol. Propranolol possesses the most membrane stabilizing activity of this class and propranolol poisoning is characterized by coma, seizures, hypotension, bradycardia, impaired atrioventricular conduction, and widened QRS interval. A Brugada-pattern on ECG may occur following propranolol overdose (Chap. 16). Ventricular tachydysrhythmias may also occur. Hypotension may be out of proportion to bradycardia and deaths from propranolol overdose are well reported. Acebutolol, betaxolol and oxprenolol also possess significant membrane stabilizing activity and have caused fatalities when taken in overdose.
Lipid Solubility
In overdose, the more lipophilic β-adrenergic antagonists may cause delirium, coma, and seizures even in the absence of hypotension.\textsuperscript{54, 167} Atenolol, the least lipid soluble of β-adrenergic antagonists, appears to be one of the safer β-adrenergic antagonists when taken in overdose.\textsuperscript{54} In fact, in one series of β-adrenergic antagonist overdoses, none of the 18 patients with atenolol overdose had seizures compared with eight out of 28 patients with propranolol overdose.\textsuperscript{167} Nevertheless, atenolol overdose may result in severe toxicity and cardiovascular death.\textsuperscript{133, 161, 202}

Intrinsic Sympathomimetic Activity (Acebutolol, Carteolol, Oxprenolol, Penbutolol, Pindolol)
There is little experience with overdose of these agents, but ISA would theoretically make these drugs safer than the other β-adrenergic antagonists. Sympathetic stimulation with mild tachycardia or hypertension often predominates in pindolol overdose, and this class of medications appears to be relatively safe in overdose.\textsuperscript{54, 109, 166} In addition to ISA, acebutolol and oxprenolol have significant membrane-stabilizing activity, making them dangerous in overdose, and deaths due to acute toxicity from these β-adrenergic antagonists are reported.\textsuperscript{54, 75, 125, 165} Overdose with carteolol or penbutolol has not been reported.

Potassium Channel Blockade (Acebutolol, Sotalol)
In six patients with sotalol overdose, the average QT interval was 172% of normal and five patients had ventricular dysrhythmias, including multifocal ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation.\textsuperscript{156} Sotalol overdose may also be complicated by hypotension, bradycardia, and asystole,\textsuperscript{5, 156} and fatalities are well documented.\textsuperscript{152, 160}

Sotalol overdose may cause delayed and prolonged toxicity although ECG changes appear to occur early. In a series of six patients with sotalol overdose, all had prolonged QT interval noted on the initial ECG taken 30 minutes to 4.5 hours after ingestion. It is not clear whether these patients were taking sotalol therapeutically prior to the overdose so it is possible that the prolonged QT on the initial ECG was present prior to the overdose. The greatest QT prolongation occurred 4 to 15 hours after ingestion, and the risk of ventricular dysrhythmias was highest between 4 and 20 hours. All four patients who developed ventricular tachycardia did so after 4 hours, and in two patients ventricular dysrhythmias first occurred 9 hours after ingestion. One patient continued to have ventricular dysrhythmias at 48 hours, and abnormally prolonged QT intervals were noted as long as 100 hours after ingestion. In this series the average sotalol half-life was 13 hours, and the average time until normalization of the QT interval was 82 hours.\textsuperscript{156} Acebutolol-induced QT interval prolongation may partially explain the ventricular tachydysrhythmias that occur with severe acebutolol toxicity.\textsuperscript{44, 125, 133}

Vasodilation (Betaxolol, Bucindolol, Carteolol, Carvedilol, Celiprolol, Labetolol, Nebivolol)
The vasodilatory properties of these drugs would theoretically act in synergy with β-adrenergic antagonism to increase toxicity. Conversely, the low membrane-stabilizing effect of these drugs may make them relatively safe in overdose. Betaxolol is the sole drug in this class with membrane stabilizing properties. Overdose with labetalol appears to be similar to that of other β-adrenergic antagonists with hypotension and bradycardia as prominent features.\textsuperscript{169, 195, 196} Experience with overdose of the newer vasodilating β-adrenergic antagonists is limited. Similar to conventional β-
adrenergic antagonists, carvedilol overdose causes hypotension and bradycardia.\textsuperscript{23, 68, 205} In a case report from Germany, nebivolol overdose was complicated by bradycardia, lethargy, and hypoglycemia. The patient received standard treatment and had a benign outcome.\textsuperscript{74} Another patient became hypotensive and bradycardic and then experienced cardiac arrest following nebivolol overdose. That person was successfully resuscitated with lipid emulsion and high-dose insulin.\textsuperscript{211} Severe toxicity and death have occurred following betaxolol\textsuperscript{20, 21} and celiprolol\textsuperscript{176} poisoning. Overdoses with bucindolol or carteolol have not been reported.

**Other Preparations (Ophthalmic Preparations, Sustained Release, Combined Products)**

There is very little published experience with overdoses of the sustained release β-adrenergic antagonists, but it is reasonable to expect that overdose with these agents will result in both a delayed onset and prolonged duration of toxicity. Acute overdose of ophthalmic β-adrenergic antagonists has not been reported. Patients who take mixed overdoses with calcium channel antagonists and β-adrenergic antagonists are difficult to manage because of synergistic toxicity.\textsuperscript{180, 188, 195} Overdoses with combined β-adrenergic antagonist and calcium channel blocker preparations such as felodipine and metoprolol or atenolol and nifedipine have not been reported, but these combinations would be expected to be quite dangerous in overdose.

**DIAGNOSTIC TESTING**

All patients with an intentional overdose of a β-adrenergic antagonist should have a 12-lead ECG and continuous cardiac monitoring. Serum glucose should be measured regardless of mental status because β-adrenergic antagonists can cause hypoglycemia. A chest radiograph and assessment of oxygen saturation should be obtained if the patient is at risk for or suffering symptoms of congestive heart failure. For patients with bradycardia of uncertain etiology, measurement of thyroid function, potassium, kidney function, cardiac enzymes, and digoxin concentration may prove helpful. Serum concentrations of β-adrenergic antagonists are not readily available for routine clinical use but may prove helpful in making a retrospective diagnosis in selected cases. Lactate concentrations may be elevated in patients with β-adrenergic antagonist poisoning but are poor predictors of survival.\textsuperscript{147}

**MANAGEMENT**

Airway and ventilation should be maintained with endotracheal intubation if necessary. Because laryngoscopy may induce a vagal response, it is reasonable to give atropine prior to intubation of the bradycardic patient. This is particularly true for children who are more susceptible to this complication. The initial treatment of bradycardia and hypotension consists of atropine and intravenous fluids. These measures will likely be insufficient in patients with severe toxicity but may suffice in patients with mild poisoning or other etiologies for bradycardia.

Gastrointestinal decontamination is warranted for all persons who have ingested significant amounts of a β-adrenergic antagonist. Induction of emesis is contraindicated because of the potential for catastrophic deterioration of mental status and vital signs in these patients, and since vomiting
increases vagal stimulation and may worsen bradycardia. Orogastric lavage is recommended for patients with significant effects such as seizures, hypotension, or bradycardia if the patient presents in a time frame when the drug is still expected to be in the stomach. Orogastric lavage is also recommended for all patients who present shortly after ingestion of large (gram amount) ingestions of propranolol or one of the other more toxic β-adrenergic antagonists (ie, acebutolol, betaxolol, metoprolol, oxprenolol, sotalol). Orogastric lavage causes vagal stimulation and carries the risk of worsening bradycardia so it is reasonable to pretreat patients with standard doses of atropine. We recommend activated charcoal alone for persons with minor symptoms following an overdose with one of the more water-soluble β-adrenergic antagonists who present later than one hour following ingestion. Whole bowel irrigation with polyethylene glycol should be considered in patients who have ingested sustained release preparations (Antidotes in Depth: A2).

Seizures or coma associated with cardiovascular collapse is treated by attempting to restore circulation. Seizures in the patient with relatively normal vital signs should be treated with benzodiazepines followed by barbiturates if benzodiazepines fail. Refractory seizures are rare in β-adrenergic antagonist overdose.

Specific Management
Patients who fail to respond to atropine and fluids require management with the inotropics discussed below (Fig. 62–4). When time permits, it is preferable to introduce new medications sequentially so that the effects of each may be assessed. We recommend glucagon followed by calcium, and high-dose insulin euglycemia therapy. In the critically ill patient, there may not be enough time for this approach and multiple treatments may be started simultaneously. If these therapies fail, we suggest starting a catecholamine pressor and phosphodiesterase inhibitors. Advanced hemodynamic monitoring, when available, is advisable to guide therapy for all patients receiving catecholamine pressors or phosphodiesterase inhibitors. Lipid emulsion therapy should be given to patients with severe toxicity or cardiac arrest. Mechanical life support with intra-aortic balloon pump or extracorporeal circulation may be lifesaving when medical management fails and is most effective when started early.

FIGURE 62–4.
Positive inotropes improve cardiac function by a number of mechanisms, which usually result in increased intracellular calcium. Xenobiotics that [1] increase cAMP: Glucagon receptors and β-adrenergic receptors are coupled to Gs proteins so that receptor binding increases cAMP by activation of adenyl cyclase. Phosphodiesterase inhibitors increase cAMP by inhibiting its breakdown. [2] increase calcium influx: Calcium salts increase calcium influx through L-type calcium channels by a direct mass effect. [3] inhibit extrusion of calcium via the sodium-calcium exchange pump: Those that increase intracellular sodium such as digoxin and sodium channel agonists (eg, aconitine) and those such as 4-aminopyridine that prolong the action potential duration alter the electrochemical gradients in a way that hinders the extrusion of calcium. [4] increase the sensitivity of the contractile elements to calcium: Angiotensin II and endothelin do this by inducing an intracellular alkalosis. The calcium sensitizers, levsimendan and pimobendan are used to treat heart failure in some countries.
Glucagon
Cardiac glucagon receptors, like β-adrenergic receptors, are coupled to Gs proteins. Glucagon binding increases adenyl cyclase activity independent of β-adrenergic receptor binding. The inotropic effect of glucagon is enhanced by its ability to inhibit phosphodiesterase and thereby prevent cAMP breakdown.

There are no controlled trials of glucagon in humans with β-adrenergic antagonist poisoning. Nevertheless, with more than 30 years of clinical use, glucagon is still recognized as a useful treatment of choice for severe β-adrenergic antagonist toxicity. This is supported by animal models and a case series suggesting that glucagon is also effective in correcting symptomatic bradycardia and hypotension secondary to therapeutic β-adrenergic antagonist use. Glucagon is a vasodilator, and in animal models of propranolol poisoning it is more effective in restoring contractility, cardiac output, and heart rate than in restoring blood pressure.

The initial adult dose of glucagon for β-adrenergic antagonist toxicity is 3 to 5 mg given slowly over 1 to 2 minutes. The initial pediatric dose is 50 µg/kg. If there is no response to the initial dose, higher doses up to a total of 10 mg may be used. Once a response occurs, a glucagon infusion is started. Most authors recommend using an infusion of 2 to 5 mg/h, although many authorities recommend glucagon infusions as high as 10 mg/h. We suggest that the glucagon infusion be started at the “response dose” per hour. Thus, for example, if the patient receives 7 mg of glucagon before a response occurs, the glucagon infusion should be started at 7 mg/h. When a full 10 mg dose of glucagon fails to restore blood pressure and heart rate and the diagnosis of β-adrenergic antagonist toxicity is probable, we still recommend starting an infusion of glucagon at 10 mg/h as glucagon will have synergistic effects with subsequent antidotes. Glucagon may cause vomiting with risk of aspiration. Other adverse events of glucagon in this setting include hyperglycemia and mild hypocalcemia and these should be treated appropriately if they develop. Patients also develop rapid tachyphylaxis to glucagon, and the need for increasing doses and additional therapies should be expected, even when patients initially respond (Antidotes in Depth: A18).

Calcium
Calcium salts effectively treat hypotension but not heart rate in animal models of β-adrenergic antagonist toxicity. Calcium chloride successfully reverses hypotension in patients with β-adrenergic antagonist overdose and in combined calcium channel blocker and β-adrenergic antagonist toxicity. The adult starting dose of calcium gluconate is 3 g of the 10% solution given intravenously. We recommend using up to 9 g of calcium gluconate if needed. The initial dose of calcium gluconate in children is 60 mg/kg up to 3 g. This may be repeated up to a total of 180 mg/kg (Antidotes in Depth: A29).

Insulin and Glucose
High-dose insulin, euglycemia therapy improves cardiac function following cardiac surgery and survival following myocardial infarction. There is evidence that high-dose insulin combined
with sufficient glucose to maintain euglycemia is beneficial in β-adrenergic antagonist poisoning. In a canine model of propranolol toxicity, all six animals treated with insulin and glucose survived compared with four out of six in the glucagon group, one of six in the epinephrine group, and no survivors in the sham treatment group. Insulin plus glucose was markedly more effective than vasopressin plus epinephrine in a porcine model of propranolol toxicity. In that experiment, all five animals in the insulin group survived the 4-hour protocol and all five in the vasopressin plus epinephrine group died within 90 minutes. In a rabbit model of severe propranolol toxicity, high-dose insulin was more effective than lipid emulsion in restoring blood pressure and heart rate, but there was no difference in survival. Clinical experience with high-dose insulin for β-adrenergic antagonist poisoning is increasing but still limited to case reports and case series. Improvements in heart rate and blood pressure following high-dose insulin are reported in patients with isolated overdoses of metoprolol, nebivolol, and propranolol. High-dose insulin was also effective in combined poisoning with β-adrenergic antagonists and calcium channel blockers.

High-dose insulin is simple to use, safe (with appropriate monitoring of glucose and potassium), and does not require invasive monitoring. For these reasons, we recommend using high-dose insulin and glucose infusions for patients with β-adrenergic antagonist toxicity who have not responded to fluids, atropine, and glucagon. Although the dose of insulin is not definitively established, therapy typically begins with a bolus of 1 unit/kg of regular human insulin along with 0.5 g/kg of dextrose. If blood glucose is greater than 300 mg/dL (16.7 mmol/L), the dextrose bolus is not necessary. An infusion of regular insulin should follow the bolus starting at 1 unit/kg/h. A continuous dextrose infusion, beginning at 0.5 g/kg/h should also be started. Glucose should be monitored every 15 to 30 minutes until stable and then every 1 to 2 hours and titrated to maintain the blood glucose between 100 and 250 mg/dL. Cardiac function should also be reassessed every 10 to 15 minutes, and if it remains depressed, the insulin infusion can be increased up to 10 units/kg/h as required (rarely higher). The goal of therapy includes improved organ perfusion with improvements in cardiac output, mental status, urine output, and acid-base abnormalities. The response to insulin is typically delayed for 15 to 60 minutes so it will usually be necessary to start a catecholamine infusion before the full effects of insulin are apparent. It is important to continue monitoring glucose and electrolytes for several hours after insulin is discontinued (Antidotes in Depth: A17).

Catecholamines
Patients who do not respond to the preceding therapies usually require a catecholamine infusion. The choice of catecholamine is somewhat controversial. Theoretically, the pure β-adrenergic agonist isoproterenol would seem to be the ideal agent because it can overcome β-adrenergic blockade without causing any α-adrenergic effects. Unfortunately, this therapy has several potential drawbacks, which limit its efficacy. In the presence of β-adrenergic antagonism, extraordinarily high doses of isoproterenol and other catecholamines are frequently required. Individual case reports document isoproterenol infusions as high as 800 µg/min. At these high doses, the β-adrenergic effects of isoproterenol cause peripheral vasodilation and may actually lower blood pressure. Nevertheless, in some animal models, isoproterenol is the most effective catecholamine...
and is even more effective than glucagon in reversing β-adrenergic antagonist toxicity. However, clinical experience has not shown this to be the case. In a review of reported cases, glucagon increased heart rate 67% of the time and blood pressure 50% of the time. In contrast, isoproterenol was effective in increasing heart rate only 11% of the time and blood pressure only 22% of the time. Epinephrine was more effective than isoproterenol. Prenalterol would be expected to be especially effective following overdose of the cardioselective β-adrenergic antagonists. Prenalterol is not FDA approved and prenalterol therapy is limited as its relatively long half-life (~ 2 hours) makes titration difficult. Dobutamine is a β1-adrenergic agonist with relatively little effect on vascular resistance that may be useful in this setting. However, experience is limited and dobutamine is not always effective in patients with β-adrenergic antagonist overdose. In the setting of β-adrenergic antagonism, catecholamines with substantial α-adrenergic agonist properties may increase peripheral vascular resistance without improving contractility, resulting in acute cardiac failure. Severe hypertension due to lack of β2-adrenergic–mediated vasodilation is another potential adverse reaction from this so-called “unopposed α-adrenergic” effect. Because of these potential problems, we recommend that catecholamine use be guided by hemodynamic monitoring using noninvasive techniques such as bioimpedance or echocardiographic monitoring or direct invasive measures of determining cardiac performance. Catecholamine infusions should be started at the usual rates and then increased rapidly until a clinical effect is obtained. If advanced monitoring is impossible and the diagnosis of β-adrenergic antagonist overdose is fairly certain, it is reasonable to begin an isoproterenol or epinephrine infusion with careful monitoring of the patient’s blood pressure and clinical status. The infusion should be stopped immediately if the patient becomes more hypotensive or develops congestive heart failure.

Lipid Emulsion
Lipid emulsion is a promising antidote that has a role in selected cases of severe β-adrenergic antagonist overdose. Intravenous administration of lipid emulsion is hypothesized to reduce the toxicity of lipid-soluble xenobiotics by lowering free serum concentrations of these compounds, because they partition into the lipemic component of blood and improve the bioenergetics of the heart. Lipid emulsion has proven effective in animal models of poisoning with propranolol, a highly lipid soluble β-adrenergic antagonist, but not those that are water-soluble such as atenolol or metoprolol. Lipid emulsion was less effective than high-dose insulin in restoring heart rate and blood pressure in a rabbit model of propranolol poisoning. Human experience with the use of lipid emulsion in β-adrenergic antagonist overdose is limited, but cases of dramatic recovery from cardiac arrest have been reported. It is reasonable to administer intravenous lipid emulsion in patients with severe toxicity from a lipid-soluble β-adrenergic antagonist that does not respond to usual therapy. The optimal dose and formulation of lipid emulsion for this purpose is unknown. One protocol calls for a 1.5 mL/kg of 20% Intralipid followed by an infusion of 0.25 mL/kg/min. The bolus can be repeated in 3 to 5 minutes if necessary. The total dose should be less than 8 mL/kg (Antidotes in Depth: A20).
Phosphodiesterase Inhibitors
The phosphodiesterase inhibitors amrinone, milrinone, and enoximone are theoretically beneficial in β-adrenergic antagonist overdose since they inhibit the breakdown of cAMP by phosphodiesterase and hence increase cAMP independently of β-adrenergic receptor stimulation. Phosphodiesterase inhibitors increase inotropy in the presence of β-adrenergic antagonism in both animal models and in humans. Although these agents appear to be as effective as glucagon in animal models of β-adrenergic antagonist toxicity, controlled dog models were unable to demonstrate an additional benefit of these agents over glucagon. Phosphodiesterase inhibitors might be useful in selected patients who fail glucagon therapy, and have been used clinically to treat β-adrenergic antagonist poisoned patients. Therapy with phosphodiesterase inhibitors is often limited by hypotension secondary to peripheral vasodilation. Furthermore, these drugs are difficult to titrate because of relatively long half-lives (30–60 minutes for milrinone, 2–4 hours for amrinone, and ~2 hours for enoximone). For these reasons the phosphodiesterase inhibitors should generally only be considered for patients who have arterial and pulmonary artery pressure monitoring.

Ventricular Pacing
Ventricular pacing is not a particularly useful intervention in patients with β-adrenergic antagonist toxicity, but it will increase the heart rate in some patients. Unfortunately, there will frequently be failure to capture or pacing may increase the heart rate with no increase in cardiac output or blood pressure. In fact, some authors have noticed that ventricular pacing occasionally decreases blood pressure perhaps secondary to loss of organized atrial contraction or due to impaired ventricular relaxation.

Extracorporeal Removal
Extracorporeal removal is ineffective for the lipid-soluble β-adrenergic antagonists due to their large volumes of distribution. Hemodialysis may remove water-soluble renally eliminated β-adrenergic antagonists such as atenolol and acebutolol. Because hemodialysis is often technically difficult in poisoned patients due to hypotension and bradycardia, it is rarely utilized in patients with β-adrenergic antagonist overdose but may be considered in selected cases.

Mechanical Life Support
It is important to remember that the patient with circulatory failure from an acute overdose will typically recover without sequelae if ventilation and circulation are maintained until the xenobiotic is eliminated. When the preceding medical treatment fails, it is appropriate to consider the use of an intra-aortic balloon pump or extracorporeal life support (ECLS). Several case reports describe remarkable recoveries following the use of these therapies for refractory β-adrenergic antagonist toxicity or combined β-adrenergic antagonist and calcium channel blocker overdose. In one report, a neonate who developed refractory circulatory collapse from an iatrogenic overdose of propranolol was supported with extracorporeal membrane oxygenation (ECMO) for 5 days and survived neurologically intact. A case series documents experience with ECMO for patients with cardiac arrest caused by cardiovascular drug poisoning. In this series of six patients, two deaths were attributed to delayed institution of ECMO. The other four patients survived...
without sequelae. In another series, ECLS was used in 17 patients with circulatory failure following a drug overdose. Eight patients had taken β-adrenergic antagonists either alone or in combination with other cardiovascular toxins. Thirteen of the 17 patients had long-term survival. The authors conclude that ECLS is efficient and relatively safe as a last resort treatment for patients with cardiac arrest or refractory shock following a drug overdose. More recently, researchers compared survival with ECLS versus conventional therapy in poisoned patients with circulatory failure. Six patients in the ECLS group and ten in the conventional therapy group had ingested β-adrenergic antagonists. In this series, 12 out of 14 (86%) of the ECLS patients survived compared with 23 out of 48 (48%) in the conventional therapy group. The authors concluded that ECLS is helpful in critically ill poisoned patients who do not respond to conventional therapy.

Experimental Treatment

Vasopressin is a hypothalamic hormone that acts at G protein–coupled receptors to mediate vasoconstriction (at V₁ receptors), water retention (at V₂ receptors), and corticotropin secretion (at V₃ receptors), and may also increase the response to catecholamines. Vasopressin analogues have been used as vasopressors clinically in shock states and for patients in cardiopulmonary arrest. Vasopressin was as effective as glucagon but less effective than high-dose insulin in a porcine model of propranolol toxicity. There are no reports of vasopressin use for human β-adrenergic antagonist toxicity.

The calcium sensitizers, levosimendan and pimobendan, interact with the contractile proteins to improve cardiac function and are used clinically to treat heart failure. Levosimendan is both a positive inotrope and a vasodilator and has a better safety profile than pimobendan. It is approved in Europe for use in heart failure patients and is as effective as dobutamine in increasing contractility. Levosimendan infusions allow uptitration of β-adrenergic antagonists in patients with severe heart failure. Levosimendan improved survival in a porcine model of propranolol toxicity and improved cardiac output in a murine model of metoprolol toxicity but was not beneficial in a murine model of propranolol toxicity. Calcium sensitizers are not available in the United States or Canada. They may prove to have a role in managing patients poisoned with β-adrenergic antagonists.

Fructose 1,6-diphosphate (FDP) is an intermediate in the glycolytic pathway. FDP is able to cross cell membranes and it increases cardiac contractility. Compared with glucose infusion, FDP infusion resulted in improved survival in murine models of propranolol toxicity and verapamil toxicity. FDP may prove to have a role in the management of β-adrenergic antagonist poisoning, but it cannot be recommended at this time.

Special Circumstances

The preceding discussion applies to the generic management of β-adrenergic antagonists. Certain β-adrenergic antagonists have unique properties that modify their toxicity. The management considerations for these unique agents are discussed as follows.

Sotalol
In addition to bradycardia and hypotension, sotalol toxicity may result in a prolonged QT interval and ventricular dysrhythmias including torsade de pointes. Sotalol induced bradycardia and hypotension should be managed as with other β-adrenergic antagonists. Specific management of patients with sotalol overdose includes correction of hypokalemia and hypomagnesemia. Overdrive pacing and magnesium infusions may be effective for sotalol-induced torsade de pointes. In the future, potassium channel openers such as the cardioprotective drug nicorandil may prove effective for sotalol-induced torsade de pointes.

Lidocaine is also effective for sotalol-induced torsade de pointes.

Peripheral Vasodilation (Betaxolol, Bucindolol, Carteolol, Carvedilol, Celiprolol, Labetalol, Nebivolol)
Treatment of patients who have overdosed with one of the vasodilating β-adrenergic antagonists is similar to that for patients who ingest other β-adrenergic antagonists. Decisions about the need for vasopressors should be guided by clinical findings. If vasodilation is a prominent feature, high doses of vasopressors with α-adrenergic agonist properties (eg, norepinephrine or phenylephrine) may be required. Conversely, if β-adrenergic antagonism is prominent, xenobiotics that act to increase intracellular cAMP, like glucagon, may be needed.

Membrane Stabilizing Effects (Acebutolol, Betaxolol, Carvedilol, Oxprenolol, Propranolol)
It might be expected that hypertonic sodium bicarbonate would be beneficial in treating the ventricular dysrhythmias that occur with these β-adrenergic antagonist. Unfortunately there is limited experience with the use of sodium bicarbonate in this situation, and the experimental data are mixed. Sodium bicarbonate was not beneficial in a canine model of propranolol toxicity, although there was a trend toward QRS interval narrowing in the sodium bicarbonate group. In models with propranolol poisoned isolated rat hearts, however, hypertonic sodium bicarbonate proved beneficial. Perhaps most compelling is the fact that sodium bicarbonate appeared to reverse ventricular tachycardia in a human case of acebutolol poisoning. Because sodium bicarbonate is a relatively safe and simple intervention, we would recommend that it be used in addition to standard therapy for β-adrenergic antagonist poisoned patients with QRS widening, ventricular dysrhythmias, or severe hypotension. Sodium bicarbonate would not be expected to be beneficial in sotalol induced ventricular dysrhythmias and, by causing hypokalemia, may actually increase the risk of torsade de pointes. The usual dose of hypertonic sodium bicarbonate is 1 to 2 mEq/kg given as an intravenous bolus. This may be followed by an infusion or repeated boluses may be given as needed. Care should be taken to avoid severe alkalosis or hypokalemia (Antidotes in Depth: A5).

Observation
All patients who have bradycardia, hypotension, abnormal ECG findings, or CNS toxicity following a β-adrenergic antagonist overdose should be observed in a intensive care setting until these findings resolve. Toxicity from regular release β-adrenergic antagonist poisoning other than with sotalol almost always occurs within the first 6 hours. Therefore patients without any findings of toxicity following an overdose of a regular release β-adrenergic antagonist other than sotalol may be discharged from medical care after an observation time of 6 to 8 hours if they remain asymptomatic with normal vital signs and normal ECG and have had gastrointestinal decontamination with
activated charcoal. Ingestion of extended-release preparations may be associated with delayed toxicity, and these patients should be observed for 24 hours in an intensive care unit. Patients who may have delayed absorption because of a mixed overdose or underlying gastrointestinal disease may also require longer observation. Sotalol toxicity may also be delayed with ventricular dysrhythmias first occurring as late as 9 hours after ingestion. We recommend that all patients with sotalol overdose be monitored for at least 12 hours. Patients who remain stable without QT prolongation may then be discharged from a monitored setting.

SUMMARY

- β-Adrenergic antagonists are commonly used to treat hypertension, angina, tachydysrhythmias, tremor, migraine, and panic attacks.
- Overdoses of β-adrenergic antagonists are relatively uncommon but continue to cause deaths worldwide.
- Patients who develop symptoms after ingesting regular release β-adrenergic antagonists do so within the first 6 hours. Sotalol ingestions are an exception to this and may cause delayed and prolonged toxicity. Extended release formulations may also result in delayed toxicity and require 24 hour observation.
- Patients with consequential β-adrenergic antagonist overdose typically develop bradycardia and hypotension.
- Propranolol and other β-adrenergic antagonists with membrane- stabilizing properties and high lipid solubility are the most toxic in overdose. These xenobiotics cause prolongation of the QRS interval, severe hypotension, coma, seizures, and apnea.
- Sotalol is unique in its ability to prolong the QT interval and its toxicity often results in refractory ventricular dysrhythmias, which may respond to overdrive pacing or to magnesium infusions.
- In addition to supportive care, the most important therapy for β-adrenergic antagonist toxicity is glucagon. High doses of insulin together with glucose provide a promising new treatment modality. Catecholamine infusions may also be helpful but should be closely monitored and large doses are typically required. Patients who fail treatment with glucagon, insulin, and catecholamines are critically ill and may respond to intravenous fat emulsion therapy, phosphodiesterase inhibitors, or mechanical support of circulation. Fortunately, most patients respond to simpler measures and this aggressive therapy is rarely required.

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