Cardiac function and toxicity:
General principles:

Many chemicals cause structural and/or functional abnormalities in cardiac function. Factors that dictate the severity of toxicity include the concentration of the chemical, its inherent toxicity, and the duration of exposure. In particular, because cardiac tissue is intrinsically very excitable it is a sensitive target for toxic responses. Toxins may cause arrhythmias by altering impulse formation or conduction. Other toxins may alter contractile function directly, for example, by a cytotoxic mechanism, or indirectly, by an electrical disturbance. Metabolic alterations may also be caused by a toxin and these alterations are manifested by contraction and/or conduction abnormalities.

Cardiotoxicity can be both acute and chronic. Acute cardiac injury carries a high risk because of the indispensable character of heart action. Mechanisms associated with chronic injury have become better understood in recent years. Aspects of chronic cardiac injury include alterations in myocardial cell excitability, activation of pre-toxins, failed chemical detoxification, accumulation of an active toxin, and extension of toxic pharmacological effects.

BIOCHEMICAL MECHANISMS

From the perspective of biochemistry, toxicity to myocardial tissue may relate to one or more of several abnormal changes. These can, in turn, be classified into four categories; ionic changes, energy alterations, membrane disturbances, or cellular defense changes.

Inhibition of Na^+, K^+-ATPase

Na^+, K^+-ATPase reduces intracellular Na^+ in exchange for extracellular K^+. Inhibition of cardiac Na^+, K^+-ATPase increases resting intracellular Na^+ concentrations. This in turn increases intracellular Ca^{2+} concentrations through Na^+/Ca^{2+} exchange, and the elevated intracellular Ca^{2+} and Ca^{2+} stores thus contribute to the inotropic actions of these inhibitors.

Na^+ Channel Blockade

Agents that inhibit Na^+ channels in cardiac cells alter cardiac excitability by requiring greater membrane depolarization for the opening of Na^+ channels. The

effects of Na^+ channel blockade include a reduction of conduction velocity, prolonged QRS duration, and decreased automaticity.

K^+ Channel Blockade

Many different K^+ channels are expressed in the human heart. Blockade of K^+ channels increases the duration of the action potential and increases refractoriness (the cell undergoing repolarization is refractory to depolarization).

Ca^{2+} Channel Blockade

The L-type Ca^{2+} channel contributes to excitation-contraction coupling, whereas the T-type Ca^{2+} channels contribute to pacemaker potential in the SA node. Blockade of Ca^{2+} channels in the heart produces a negative inotropic effect as a result of reductions in Ca^{2+}-induced Ca^{2+} release.

β-Adrenergic Receptors and the Heart

β-Adrenergic receptors are divided into β1, β2, and β3 subtypes. The most prevalent subtype in the heart is the β1-adrenergic receptor, but there also are cardiac β2- and β3-adrenergic receptors. The relative density of cardiac β2-adrenergic receptors increases with heart failure. β1-Adrenergic receptors mediate increased inotropy by a well-described pathway involving cAMP and protein kinases. β1-Adrenergic receptors are coupled to Gs proteins that activate adenylate cyclase when the receptor is stimulated. This increases the intracellular production of cAMP, which binds to and activates protein kinase A and other cAMP-dependent protein kinases. Protein kinase A, in turn, phosphorylates important myocyte proteins, including phospholamban, voltage-sensitive calcium channels, and troponin. β1-Adrenergic receptors increase chronotropic by an incompletely understood mechanism that involves, at least in part, direct cAMP interaction with pacemaker channels. Like β1-adrenergic receptors, the cardiac β2-adrenergic receptors mediate increased inotropy and chronotropic; however, the subcellular mechanisms are less well understood than for β1-adrenergic receptors.

Non-cardiac Effects of β-Adrenergic Receptor Activation

β2-Adrenergic receptors mediate smooth muscle relaxation in several organs. Relaxation of arteriolar smooth muscle 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. β Receptors play a role in the immune system. Mast cell degranulation is inhibited by β2-adrenergic stimulation β-Adrenergic agonists

also have important metabolic effects. Insulin secretion is increased by β2-adrenergic receptor stimulation. Despite increased insulin levels, the net effect of β2-adrenergic receptor stimulation is to increase glucose as a result of increased skeletal muscle glycogenolysis and hepatic gluconeogenesis and glycogenolysis. β2-Adrenergic receptors also cause glucagon secretion from pancreatic alpha cells. β-Adrenergic agonists act on fat cells to cause lipolysis and thermogenesis. Stimulation of adipocyte β-adrenergic receptors results in the breakdown of triglycerides and the 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.

PATHOPHYSIOLOGY

Most of the toxicity of β-adrenergic antagonists is a result of their ability to competitively antagonize the action of catecholamines at cardiac β-adrenergic receptors. The peripheral effects of β-adrenergic antagonism are more prominent in overdose; β-Adrenergic antagonists interfere with calcium uptake into the SR. This interference with cytosolic calcium handling may stimulate calcium-sensitive outward potassium channels, and result in myocyte hyperpolarization and subsequent refractory bradycardia. 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.

CLINICAL MANIFESTATIONS

Toxicity generally occurs early following β-adrenergic antagonist poisoning. Propranolol overdose, in particular, may be complicated by the rapid development of seizures, coma, and dysrhythmias. Pure 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, Patients with symptomatic β-adrenergic antagonist overdose are usually 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 QTc intervals may occur, and severe poisonings may result in asystole. 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 more lipophilic agents. Respiratory depression and

apnea may have an additional role in toxicity, Hypoglycemia may complicate β-adrenergic antagonist poisoning in children but is uncommon in acutely poisoned adults. Bronchospasm is relatively uncommon following β-adrenergic antagonist overdose and appears to occur only in susceptible patients. Clinical use of β-adrenergic antagonists slightly increases serum potassium; however, significant hyperkalemia rarely complicates acute overdose.

DIAGNOSTIC TESTING

All patients who intentionally overdose with a β-adrenergic antagonist should have a 12-lead electrocardiogram and continuous cardiac monitoring. Serum glucose should be measured regardless of mental status because β-adrenergic antagonists can cause hypoglycemia. A chest radiograph and measurement of oxygen saturation should be obtained if the patient appears to be at risk for congestive heart failure. For patients with bradycardia of uncertain etiology, measurement of potassium, renal function, cardiac enzymes, and digoxin concentrations 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.

Management of Patients with β-Adrenergic Antagonist Poisoning

Asymptomatic

1. Activated charcoal
2. Consider orogastric lavage within the first-hour post ingestion
3. Consider whole-bowel irrigation with polyethylene glycol electrolyte lavage solution for the management of ingested sustained-release preparations

Mild Toxicity

Mild hypotension (BP <100 mmHg systolic) or bradycardia (HR <60 beats/minute) without hypoperfusion
1. All of the above plus:
2. Atropine 1 mg for bradycardia
3. Fluid boluses (20-40 mL/kg of 0.9% NaCl solution) for hypotension (monitor closely to avoid pulmonary edema)

Moderate Toxicity

Failure of the above therapy, or severe bradycardia (HR < 40 beats/minute), or hypotension (BP < 80mmHg systolic), or clinical evidence of hypoperfusion: for example, congestive heart failure or decreased consciousness

1. All of the above plus:
2. Monitor ventilation and intubated if necessary
3. Glucagon: 3-5 mg IV over 1-2 minutes (may give up to 10 mg) then 2-5 mg/h (up to 10 mg/h)
4. Atropine up to 3 mg for bradycardia
5. Calcium salts for hypotension: 1-3 g calcium chloride slow IV push (alternatively, 3-9 g calcium gluconate)
6. High-dose insulin: regular insulin 1 unit/kg bolus followed by regular insulin 0.5-1.0 unit/kg/h intravenously with dextrose 1 g/kg/h glucose should be monitored every 30 min and the infusion tapered, or increased, as required

Severe Toxicity

Failure of the above therapy, or evidence of severe hypoperfusion such as cardiogenic shock or coma
1. All of the above plus:
2. Increase glucagon infusion to 10 mg/h
3. Intra-arterial and pulmonary artery pressure monitoring and frequent reassessment
4. Catecholamine infusion: Very high doses of the following are typically required; invasive hemodynamic monitoring is recommended
(a) Isoproterenol (β1, β2 agonist caution for β2-mediated vasodilation)
(b) Epinephrine (α, β agonist caution for "unopposed a" effect)
(c) Dobutamine (β1 agonist theoretically useful but limited experience)
(d) Norepinephrine (α, β1 agonist caution for "unopposed a" effects)
5. Phosphodiesterase inhibitors:
(a) Milrinone
(b) Amrinone
6. Ventricular pacing: This intervention often increases heart rate without improving cardiac output
7. Intra-aortic balloon pump or extracorporeal circulation

NOTE: Induction of emesis is contraindicated because of the potential for catastrophic deterioration of mental status and vital signs, and because vomiting increases vagal stimulation and can worsen bradycardia.

Glucagon: Humans have cardiac glucagon receptors that, like β-adrenergic receptors, are coupled to Gs proteins. Glucagon binding increases adenylyl cyclase activity, independent of β-adrenergic receptor binding. Glucagon's inotropic effect is enhanced by its ability to inhibit phosphodiesterase and thereby prevent cAMP breakdown.