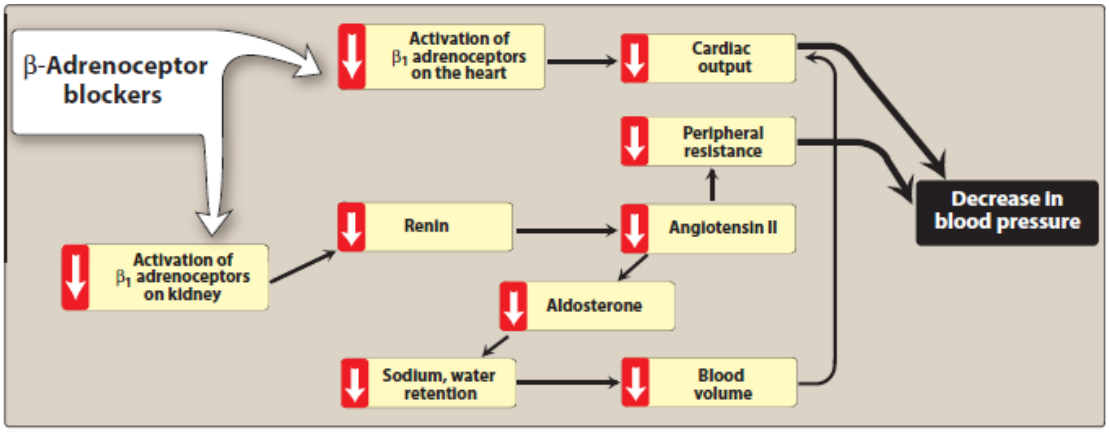
β-adrenergic antagonists:

A number of β-adrenergic antagonists are widely used for treatment of multitude of disease states, including hypertension, cardiac arrhythmias, angina pectoris, open angle glaucoma, & to protect against migraine headaches**.**

Mechanism of Action:

The β-blockers reduce blood pressure primarily by decreasing cardiac output. They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone. The prototype β-blocker is propranolol, which acts at both β1 and β2 receptors. Selective blockers of β1 receptors, such as metoprolol and atenolol, are among the most commonly prescribed β blockers. Nebivolol is a selective blocker of β1 receptors, which also increases the production of nitric oxide, leading to vasodilation. The selective β-blockers may be administered cautiously to hypertensive patients who also have asthma. The nonselective β-blockers, such as propranolol and nadolol, are contraindicated in patients with asthma due to their blockade of β2-mediated bronchodilation. β-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease. These drugs have significant pharmacologic & pharmacokinetic differences. The pharmacokinetic properties of importance include lipid solubility, route of metabolic elimination, plasma half-life, degree of protein binding, & volume of distribution. The β-adrenergic antagonists also differ in their β1-adrenergic selectivity, intrinsic sympathomimetic activity (ISA), membrane stabilizing activity & vasodilatory properties.



β1 selectivity (acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol)

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.

Membrane-stabilizing effect (acebutolol, betaxolol, carvedilol, oxprenolol, propranolol):

β-adrenergic antagonists that inhibit fast sodium channels are said to possess membrane stabilizing activity. Propranolol possesses the most membrane stabilizing activity of this class, & propranolol poisoning is characterized by coma, seizures, hypotension, bradycardia, impaired AV conduction, & prolonged QRS interval.

Intrinsic sympathomimetic activity (acebutolol, carteolol, oxprenolol, pindolol)

These antagonists act as partial agonists at β-adrenergic receptors & are said to have ISA. High doses of these drugs can cause tachycardia & hypertension as a result of their partial agonist effect.

Potassium channel blockade (acebutolol, sotalol):

Sotalol blocks the delayed rectifier potassium current responsible for repolarization, prolonging the action potential duration. This is manifested on the electrocardiogram (ECG) by a prolonged QT interval.

The prolonged QT interval predisposes to torsades de pointes, & ventricular dysrhythmias may complicate the therapeutic use of sotalol.

In patients taking sotalol therapeutically, torsades de pointes occurs more commonly in those who have renal failure, use other xenobiotics that prolong the QT interval, or have predisposing factors for QT prolongation such as hypokalemia, hypomagnesemia, bradycardia, or congenital QT prolongation. In addition to QT prolongation, sotalol overdose may also be complicated by hypotension, bradycardia, & asystole & fatalities are well documented.

Vasodilation (betaxolol, carvedilol, labetalol):

Labetalol & carvedilol are nonselective βadrenergic antagonists that also possess αadrenergic antagonist activity. Betaxolol & carvedilol also have calcium channel blocking properties that result in vasodilation. The vasodilatory properties of these antagonists would theoretically act in synergy with βadrenergic antagonism to increase toxicity.

PHARMACOKINETICS

The pharmacokinetic properties of the β-adrenergic antagonists depend in large part on their lipophilicity. Propranolol is the most lipid soluble, and atenolol is the most water soluble. The highly lipid soluble drugs cross lipid membranes rapidly and concentrate in adipose tissue. These properties allow rapid entry into CNS and typically result in large volumes of distribution. While, highly water-soluble drugs cross lipid membranes slowly, distribute in total body water, and tend to have less CNS toxicity. The highly lipid-soluble β-adrenergic antagonists are highly protein bound and are therefore poorly excreted by the kidneys.

They require hepatic biotransformation before they can be eliminated and tend to accumulate in patients with liver failure .

While, the water-soluble β-adrenergic antagonists tend to be slowly absorbed, poorly protein bound, and renally eliminated. They tend to accumulate in patients with renal failure.

Characteristics of Poisoning

The major features of beta-adrenergic blocker toxicity are related to their antagonistic action on cardiac beta receptors. Patients who develop symptoms after ingesting regular release β-adrenergic antagonists do so within the first 6 hours. Extended-release formulations may result in delayed toxicity. β 1 -selective antagonists (atenolol) may avoid some of the adverse effects of the nonselective antagonists. Their β 1 -adrenergic selectivity, however, is incomplete, and adverse reactions secondary to β 2 -adrenergic antagonism may occur with therapeutic dosage as well as in overdose. In overdose, cardioselectivity is largely lost, and deaths attributable to the β 1 -adrenergic selective agents have been reported. β-adrenergic antagonists with membrane stabilizing effects which inhibit fast sodium channels have no significant membrane stabilization with therapeutic use of β-adrenergic antagonists, but this property contributes to toxicity in overdose. Propranolol possesses the most membrane-stabilizing activity of this class, and its poisoning is characterized by coma, seizures, hypotension, bradycardia, impaired AV conduction, and prolonged QRS interval.

β-adrenergic antagonists with intrinsic sympathomimetic activity (Acebutolol, Pindolol) act as partial agonists at β-adrenergic receptors. This property avoids the severe decrease in resting heart rate that occurs with β-adrenergic antagonism in susceptible patients.

β-adrenergic antagonists with ISA would theoretically make them safer than the other β-adrenergic antagonists .

In overdose, the more lipophilic β-adrenergic antagonists may cause delirium, coma, and seizures even in the absence of hypotension .

Atenolol, the least lipid soluble of the β-adrenergic antagonists, appears to be one of the safer β-adrenergic antagonists when taken in overdose.

DIAGNOSTIC TESTING

1- ECG and continuous cardiac monitoring performed.
2- Serum glucose conc. should be measured because β-adrenergic antagonists may cause hypoglycemia .
3- A chest radiograph should be obtained if the patient is at risk for or experiencing symptoms of congestive heart failure.

MANAGEMENT

Most patients respond to simple measures, and aggressive therapy is rarely required. The **airway and ventilation** should be maintained with endotracheal intubation if necessary. Because laryngoscopy may induce a vagal response, it is reasonable to give atropine before intubation of patients with bradycardia.

Since overdoses of beta-adrenergic blockers are likely to involve solid dosage forms, gastric decontamination after a large ingestion may be indicated. Gastric lavage is usually preferred over emesis because of the possibility of beta-blocker-induced seizures. Orogastric lavage is recommended for patients with significant symptoms such as seizures, hypotension, bradycardia or if the drug is still expected to be in the stomach. Orogastric lavage causes vagal stimulation and carries the risk of worsening bradycardia, so it is reasonable to pretreat patients with standard doses of atropine. Activated charcoal can be given repeatedly during the first 24 hours to minimize enterohepatic cycling. Activated charcoal alone for persons with minor symptoms after an overdose with one of the more water-soluble β-adrenergic antagonists who present later than 1 hour after ingestion .Whole-bowel irrigation with polyethylene

glycol should be considered in patients who have ingested sustained-release preparations. Seizures in a patient with relatively normal vital signs should be treated with benzodiazepines followed by propofol if benzodiazepines fail . The major emphasis in management of toxicity will be to minimize cardiovascular manifestations. In the treatment of bradycardia, if the patient is stable hemodynamically, no specific therapy is required. If the patient is compromised hemodynamically, atropine may be given. If vagal blockade is unsuccessful, isoproterenol, a specific beta-1 agonist, can be given cautiously. The hypotensive patient may respond to fluids in the absence of pulmonary edema. Pressor agents, such as dopamine, dobutamine, or norepinephrine, may be useful. However, beta blocker-induced hypotension generally does not respond well to these agents. The treatment of choice in the hemodynamically compromised person appears to be glucagon. Glucagon produces positive inotropic and chronotropic activity and improves AV conduction by binding to glucagon-specific receptors (not beta-one receptors) in the myocardium and activating the adenyl cyclase system. This results in increased intracellular cyclic AMP concentration. The action is similar to beta-receptor stimulation by catecholamines, except that beneficial activity continues despite the presence of beta-adrenergic blockers.

Insulin And Glucose: There is evidence that high-dose insulin combined with sufficient glucose to maintain euglycemia is beneficial in patients with β-adrenergic antagonist poisoning .Glucose should be monitored every half hour for the first 4 hours and titrated to maintain euglycemia.

Phosphodiesterase Inhibitors (Milrinone): They are theoretically beneficial in β-adrenergic antagonist overdose because they inhibit the breakdown of cAMP by phosphodiesterase and hence increase cAMP independently of β-adrenergic receptor stimulation. Given with glucagon, the two will theoretically act synergistically to elevate intracellular cyclic

AMP levels thereby causing sustained elevation of cardiac tone. Hemoperfusion or hemodialysis may be considered in cases involving nadolol or atenolol, especially if there are signs of renal failure. Due to their extensive protein binding and large volume of distribution, most other beta- adrenergic blockers are poor candidates for dialysis.