Poisoning by Beta-Adrenergic blockers

Beta-adrenergic–blocking agents are widely used for the treatment of hypertension, arrhythmias, angina pectoris, heart failure, migraine headaches, and glaucoma. Many patients with beta-blocker overdose will have underlying cardiovascular diseases or will be taking other cardioactive medications, both of which may aggravate beta-blocker overdose. Of particular concern are combined ingestions with calcium blockers or tricyclic antidepressants. A variety of beta blockers are available, with various pharmacologic effects and clinical uses.

Etiology of poisoning

- Accidental and intentional (suicidal) toxicity is common.
- Compared with the other β-adrenergic antagonists, propranolol accounts for a unequal 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, and migraine who may be more disposed to suicide attempts. Propranolol is also more lethal because of its lipophilic and membrane stabilizing properties.
- Combined ingestions with calcium blockers or tricyclic antidepressants or neuroleptic drugs.

Mechanism of toxicity

Excessive beta-adrenergic blockade is common to overdose with all drugs in this category. Although beta receptor specificity is seen at low doses, it is lost in overdose.

A. Propranolol, acebutolol, and other agents with membrane-depressant (quinidine-like) effects further depress myocardial contractility and conduction and may be associated with ventricular tachyarrhythmias. Propranolol is also lipid-soluble, which enhances brain penetration and can cause seizures and coma.

B. **Pindolol, acebutolol, and penbutolol**, agents with partial beta agonist activity, may cause tachycardia and hypertension.

C. **Sotalol,** which also has type III antiarrhythmic activity, prolongs the QT interval in a dose-dependent manner and may cause torsade de pointes and ventricular fibrillation.

D. **Labetalol and carvedilol** have combined nonselective beta- and alphaadrenergic– blocking actions, and nebivolol is a selective beta1 antagonist with vasodilating properties not mediated

by alpha blockade. With these drugs, direct vasodilation can contribute to hypotension in overdose.

Pharmacokinetics

- Peak absorption occurs within 1–4 hours but may be much longer with sustained-release preparations.
- Volumes of distribution are generally large.
- Elimination of most agents is by hepatic metabolism, although nadolol, atenolol, and carteolol are excreted unchanged in the urine
- Esmolol is rapidly inactivated by red blood cell esterases

Toxic dose.

The response to beta blocker overdose is highly variable, depending on underlying medical disease or other medications. Susceptible patients may have severe or even fatal reactions to therapeutic doses. There are no clear guidelines, but ingestion of only 2–3 times the therapeutic dose should be considered potentially life-threatening in all patients.

Clinical presentation.

The pharmacokinetics of beta blockers varies considerably, and duration of poisoning may range from minutes to days.

A. Cardiac disturbances, including first-degree heart block, hypotension, and bradycardia, are the most common manifestations of poisoning. High-degree atrioventricular block, intraventricular conduction disturbances, cardiogenic shock, and asystole may occur with severe overdose, especially with membrane depressant drugs such as propranolol. The ECG usually shows a normal QRS duration with increased PR intervals; QRS widening occurs with massive intoxication. QT prolongation and torsade de pointes can occur with sotalol.

B. Central nervous system toxicity, including convulsions, coma, and respiratory arrest, is commonly seen with propranolol and other membrane-depressant and lipid-soluble drugs.

C. Bronchospasm is most common in patients with preexisting asthma or chronic bronchospastic disease.

D. Hypoglycemia and hyperkalemia may occur.

E. Renal, oliguria and acute renal failure secondary to vascular hypoperfusion/shock.

(Oliguria: is defined as a urine output that is less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h in children, and less than 400 mL daily in adults.)

Diagnosis:

- ✓ From history of ingestion.
- ✓ Presence of bradycardia and hypotension.
- ✓ Exposure to other drugs that may cause a similar presentation after overdose include sympatholytic and antihypertensive drugs, digitalis, and calcium channel.
- ✓ Other useful laboratory studies include electrolytes, glucose, BUN, creatinine, arterial blood gases, and 12-lead ECG and ECG monitoring.

Treatment

A. Emergency and supportive measures.

1. Maintain an open airway and assist ventilation if necessary.

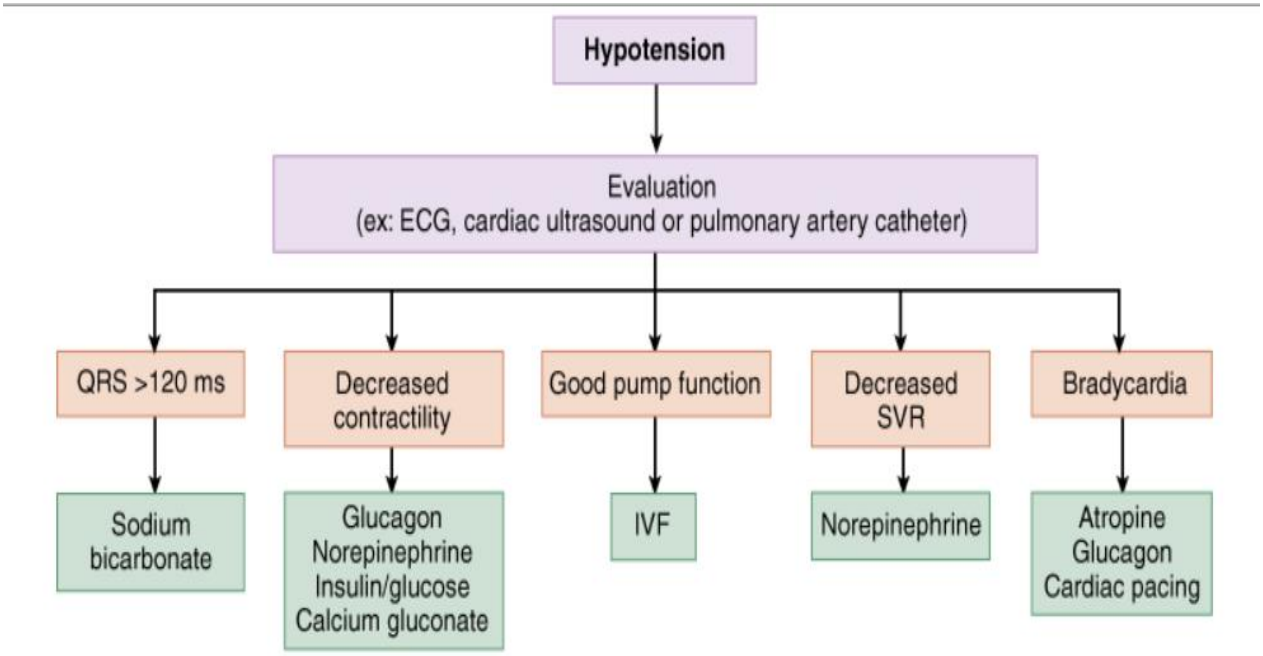
2. Treat coma (Coma cocktil), seizures (Diazepam), hypotension (See below), hyperkalemia (calcium salt, salbutamol, insulin and loop diurtics), and hypoglycemia (Dextrose IV) if they occur.

3. Treat bradycardia with glucagon, as discussed below, and if necessary with atropine, 0.01–0.03 mg/kg IV; isoproterenol (start with 4 mcg/min and increase infusion as needed); or cardiac pacing.

4. Treat bronchospasm with nebulized bronchodilators (Salbutamol).

5. Continuously monitor the vital signs and ECG for at least 6 hours after ingestion.

6. Treatment of hypotension according to the following guideline:



B. GI Decontamination

- In case of ingestion of a significant quantity of beta –blockers, decontamination should be considered. Activated charcoal may be of benefit if it can be given within 1 to 2 hours after ingestion. Multiple dose of activated charcoal therapy following ingestion of sustained-release –blockers may be used.
- Use of ipecac syrup is not recommended
- Gastric lavage is not routinely used, but may be considered for life-threatening ingestions when the airway is adequately protected from objective.
- Whole-bowel irrigation may be beneficial (with adequate airway protection) after ingestion of a sustained-release product.

C. Enhanced elimination (Note effective, explain why?)

Most beta blockers, especially the more toxic drugs such as propranolol, are highly lipophilic and have a large volume of distribution. For those with a relatively small volume of distribution coupled with a long half-life or low intrinsic clearance (eg, acebutolol, atenolol, nadolol, and sotalol), hemoperfusion, hemodialysis, or repeat-dose charcoal may be effective.

Specific drugs and antidotes

1- Glucagon

Bradycardia and hypotension resistant to the measures listed above should be treated with glucagon, 5- to 10-mg IV bolus, repeated as needed and followed by an infusion of 1–10 mg/h.

The positive inotropic and chronotropic effects of glucagon may not be maintained for a prolonged period due to possible tachyphylaxis.

Side effects: of high-dose glucagon therapy: Nausea , vomiting and esophageal sphincter relaxation.

2- Hyperinsulinemia-Euglycemia Therapy

Insulin facilitates myocardial utilization of glucose, the desired substrate during stress. This is in contrast to glucagon, epinephrine, and calcium, which promote free fatty acid utilization. The initial dose is regular insulin 1 unit/kg IV bolus followed by 0.5 to 1.0 unit/kg/h continuous infusion. Adverse effects from hyperinsulinemia-euglycemia therapy are hypoglycemia and hypokalemia.

3- Adrenergic Receptor Agonists

The beta -adrenergic receptor agonists, such as norepinephrine, dopamine, epinephrine, and isoproterenol. The most effective adrenergic receptor agonist may be norepinephrine due to its ability to increase heart rate and blood pressure.

4-Phosphodiesterase Inhibitors

Such as inamrinone (formerly known as amrinone), milrinone, and enoximone. These agents inhibit the breakdown of cAMP thereby maintaining intracellular calcium levels. In animal models, phosphodiesterase inhibitors produce positive inotropic effects without increasing myocardial oxygen demand, but have no appreciable effect on heart rate.

5- Magnesium sulfate

Torsade de pointes polymorphous ventricular tachycardia associated with QT prolongation resulting from sotalol poisoning can be treated with isoproterenol infusion, magnesium, or overdrive pacing . Correction of hypokalemia may also be useful.

6- Sodium bicarbonate injection

Wide-QRS-complex conduction defects and associated hypotension caused by membrane-depressant poisoning may respond to sodium bicarbonate, 1–2 mEq/kg, as given for tricyclic antidepressant overdose.

7- IV lipid emulsion therapy

IV lipid emulsion therapy was reported helpful for propranolol, atenolol, and nebivolol overdoses.