

Beta-Adrenergic Blocker Poisoning

John Gualtieri, PharmD

Clinical Assistant Professor

Dept. of Experimental and Clinical Pharmacology

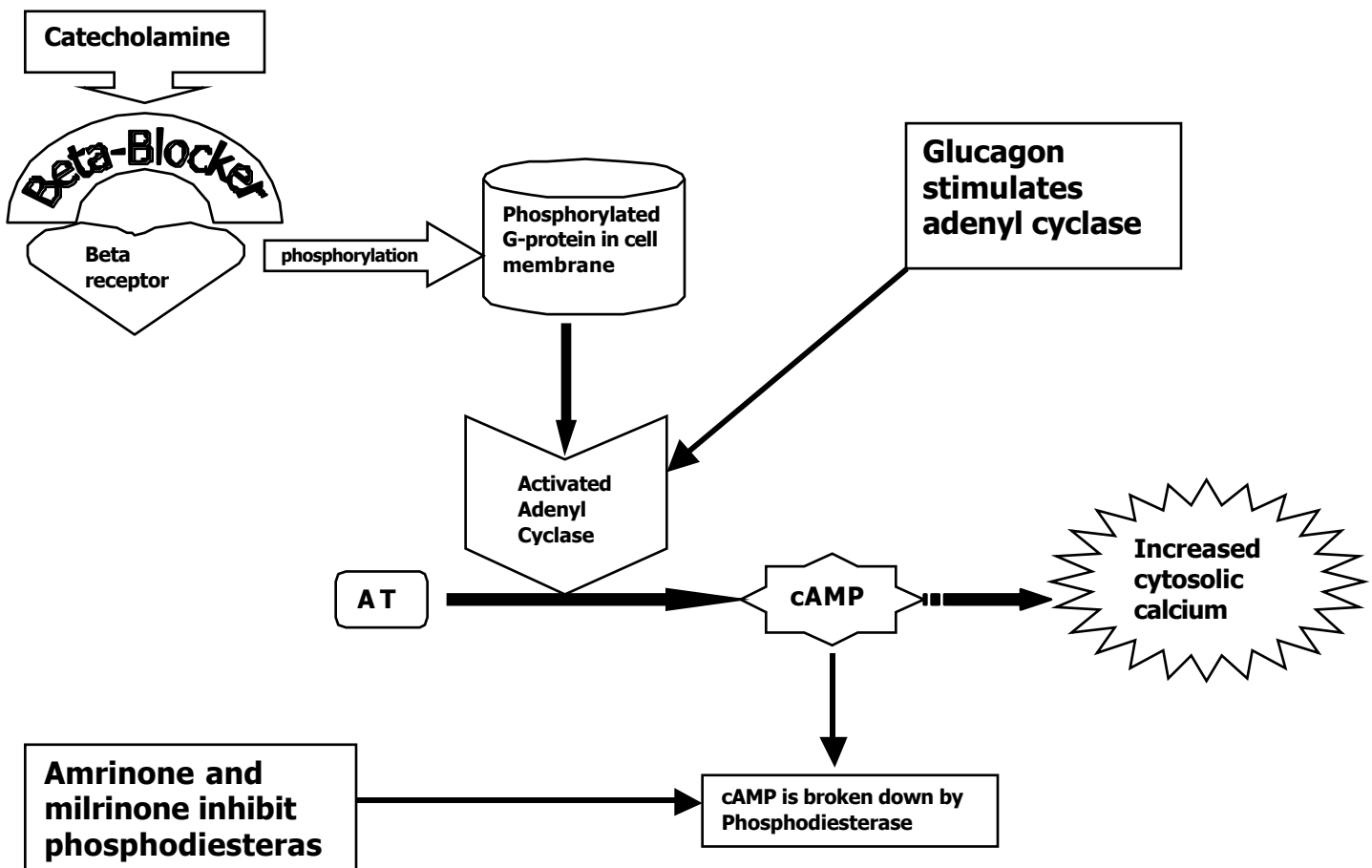
College of Pharmacy, Univ of Minnesota

I. Objectives

- 1.) Describe the classic clinical manifestations of Beta-blocker poisoning.
- 2.) Describe the mechanisms by which Beta-blockers exert their toxic effects in the setting of drug overdose.
- 3.) Be able to discuss patient disposition for cases of Beta-blocker overdose (i.e. when and where should these patients be admitted, how long should they be observed).
- 4.) Provide appropriate GI decontamination guidelines for the management of Beta-blocker overdose patients.
- 5.) Describe the pharmacological interventions available for the treatment of Beta-blocker poisoning, and be able to list them in order of importance or priority.
- 6.) Understand the mechanisms by which the treatments listed in objective 5 may potentially reverse the toxic effects produced by beta-blocker poisoning.
- 7.) Describe the appropriate dosing guidelines for the administration of glucagon in the treatment of Beta-blocker poisoning.
- 8.) Be familiar with how to appropriately monitor a Beta-blocker poisoned patient.

II. Pharmacology/Toxicology

The pharmacology of beta-adrenergic blocking drugs is probably best understood by describing the action of the beta-adrenergic receptors. Stimulation of beta-receptors by catecholamines ultimately results in increased intracellular calcium, which then causes the excitation-contraction coupling of the cell. The following schematic is a very simplified overview of intramembranous beta-adrenergic receptor activity, which may be blocked by drugs such as propranolol resulting in decreased intracellular cAMP with a resultant blunting of the effects of endogenous and exogenous catecholamines.



Drugs such as glucagon and amrinone which, in addition to exogenous catecholamines, may be used in the treatment of beta-adrenergic blocker poisoning are also shown in the above schematic to ultimately increase intracellular cAMP.

- The clinical expression of Beta-adrenergic stimulation is dependent on the type of receptor involved (Beta-1 or Beta-2) and the location of the receptor. The table below summarizes these effects.

Beta Receptor Type	Location	Pharmacological Effect of Stimulation
Beta-1	Myocardium, kidneys, and eye	<ul style="list-style-type: none"> • Increased inotropy and chronotropy • Increased renin secretion in the kidneys • Increase aqueous humor production in the anterior chamber of the eye.
Beta-2	Smooth and skeletal muscle tissue, adipose tissue, pancreas, liver	<ul style="list-style-type: none"> • Relaxes smooth muscle in blood vessels, bronchial tree, intestinal tract, and uterus. • Stimulates lipolysis, glycogenolysis, and insulin release.

- Several beta-adrenergic blockers (atenolol, metoprolol, acebutolol) demonstrate selectivity for beta-1 adrenergic receptors with therapeutic dosing. This selectivity is essentially lost in the setting of acute overdose.
- Several beta-adrenergic blocking drugs also possess membrane stabilizing (aka Type 1a antiarrhythmic; quinidine-like) properties which may contribute to toxicity in an overdose setting. The membrane stabilization is believed to occur by the impedance of sodium entry via myocardial fast inward sodium channels, thus slowing phase zero depolarization resulting in myocardial conduction delays. This results in prolonged QRS intervals on EKGs and potentially ventricular arrhythmias. This is the same potentially deadly mechanism of toxicity for other notoriously dangerous drugs such as cyclic antidepressants and cocaine.
- Acebutolol, propranolol, pindolol, and oxprenolol are known to have some membrane stabilizing ability.
- Sotalol also has Type III antiarrhythmic activity which may result in prolonged QT intervals and may cause Torsades de Pointes and ventricular fibrillation.

III. Pharmacokinetics

- There are more than 20 beta-adrenergic blockers available, each which differ slightly in pharmacokinetic properties.

Absorption:

- All the beta-blockers display rapid GI absorption with the immediate release products with a typical onset of action of 1 to 3 hours.
- Sustained release formulations are available such that overdoses of these products may cause a delayed onset of toxicity with a much longer duration of toxicity.

Distribution, Metabolism and Elimination

- Agents with high lipid solubility, such as propranolol, may display greater CNS toxicity due to better penetration of the blood-brain-barrier.
- Those beta-blockers which have a Vd greater than 1.0 L/kg, are highly protein bound, and have high lipid solubility are not ideal agents for removal by hemodialysis.

IV. Range of Toxicity

- The dose-response assessment in the setting of a beta-blocker overdose is highly variable and dependent on the drug involved, underlying medical conditions of the patient, and age. There are no clear guidelines for estimating toxicity but beta-blocker doses in excess of 2-3 times the therapeutic dose should be considered potentially life-threatening.

V. Clinical Manifestations of Toxicity

Systems	Clinical Effects
Cardiovascular	<ul style="list-style-type: none">• Hypotension and bradyarrhythmias are the most common initial clinical findings.• Atrioventricular block, intraventricular conduction disturbances, cardiogenic shock, and asystole may occur with severe overdose, especially with membrane depressant drugs, such as propranolol.
Respiratory	Bronchospasm may be seen usually in patients with pre-existing bronchospastic diseases such as asthma.
CNS	Overdoses of membrane depressant and lipophilic drugs such as propranolol may produce seizures and coma.
Renal	Oliguria and acute renal failure secondary to vascular hypoperfusion/shock

VI. GI Decontamination

- 1.) If the patient presents within 1 hour of ingestion, **orogastric lavage** until returns are clear. Ipecac is not recommended because of the risk of rapid loss of consciousness or abrupt hypotension and cardiac arrhythmias.
- 2.) **AC: Dose: 50-100 gm (1 gm/kg in kids).**
 - Sustained release products may warrant repeat doses of AC. For repeat doses give 1/2 the original dose (**0.5gm/kg or 25gm**) **q4-6 hours x 2** then reassess to determine if additional doses are needed.
- 3.) Use of whole-bowel irrigation (WBI) for ingestions of sustained-released CCB preparations has been strongly advocated by some toxicologists but this intervention must not be considered conventional.
PEG Dose (polyethylene glycol solution): 1-2 L/h in adults (0.5 L/h in kids) via nasogastric tube until clear rectal effluent.

VII. Treatment

- A. Airway support, adequate ventilation and oxygenation, IV access, foley catheter.
- B. Hypotension
 - ❖ *The following interventions are listed in order of importance for the treatment of Beta-adrenergic blocker poisoning*
 1. **Intravenous Fluid Boluses (10 ml/kg)** may help restore blood pressure but the patient needs to be monitored closely for pulmonary edema.

2. **Glucagon: 2-5 mg IV push** (may give up to 10 mg IV push), then 2-5 mg/hour (may titrate up to 10 mg/hr as necessary) in normal saline and titrate as necessary. Do not use the phenol-containing diluent supplied by the manufacturer as it is intended for IM administration.
 - Positive inotrope and chronotrope agent that is unaffected by adrenergic depletion or blockade.
 - Glucagon circumvents Beta-receptors, and independently stimulates adenylyl cyclase, thereby increasing intracellular cAMP which promotes calcium ion influx via calcium channels. (see diagram on page 1)
3. **Catecholamines** (*Very high doses of the following are frequently required*)
 - ❖ Continuous intraarterial and pulmonary artery pressure monitoring are required during prolonged treatment with the following agents.
 - a. Isoproterenol (direct Beta-1 and Beta-2 agonist)
 - 0.1 mcg/kg/min and titrate rapidly to effect.
 - Fantastically high infusion rates as high as 800 mcg/min have been reported in cases of severe beta-blocker poisoning.
 - Beta-2 mediated peripheral vasodilation may potentially exacerbate hypotension.
 - b. Dobutamine (direct Beta-1 agonist; theoretically useful but clinical experience is limited)
 - 2.5 mcg/kg/min and titrate rapidly to effect
 - c. Epinephrine (direct Beta-1 Agonist, Beta-2 Agonist, Alpha-1 agonist)
 - 1 mcg/kg/min and titrate rapidly to effect.
 - As much as 6 mg has been administered over one hour for the treatment of beta-blocker poisoning.
4. **Amrinone or Milrinone:** Inotropes which increases intracellular cAMP activity by inhibiting the enzyme phosphodiesterase III. As seen for glucagon, increased cardiocyte cAMP activity increases intracellular calcium, which improves inotropy. However, increase intracellular cAMP activity in vascular smooth muscle produces relaxation, peripheral vasodilation, and reduced systemic vascular resistance, thus potentially exacerbating hypotension. They must not be considered a first-line agent, and should be used in combination with another vasopressor/inotrope such as epinephrine.

Amrinone: 1 mg/kg IV bolus over 2 minutes followed by 5 to 20 mcg/kg per minute.

Milrinone: 50 mcg/kg IV bolus over 2 minutes, then 0.25-1.0 mcg/kg/min.

5. Other Treatment Modalities to Consider for Refractory Hypotension

Calcium: case reports have demonstrated that calcium chloride may be effective in treating hypotension from isolated beta-blocker poisoning as well as combined calcium channel blocker and beta-blocker poisoning.

DOSE: Calcium Chloride 1-2 grams (10-20 ml 10% CaCl₂) IV bolus over 5 minutes, repeat every 10-20 minutes.

Hyperinsulinemic Euglycemia (Experimental but promising)

- Insulin has demonstrated positive inotropic effects when administered in conjunction with dextrose in experimental canine models of beta-blocker poisoning. This inotropic effect is believed to be due to better carbohydrate delivery and utilization by cardiac cells, as well as increases in intracellular calcium. High dose insulin has not been evaluated in human cases of beta-blocker poisoning.

6. **Non-pharmacologic Interventions**

- Intra-aortic balloon counterpulsation
- Cardiopulmonary bypass
- Extracorporeal membrane oxygenation

C. Arrhythmias

- Arrhythmias are usually bradyarrhythmias, making atropine the first-line intervention.
- It is not uncommon for beta-blocker induced bradyarrhythmias to be refractory to atropine therapy.
- **cardiac pacing** will generally follow atropine for the treatment of refractory bradyarrhythmia.

Atropine: 0.5 to 1.0 mg (0.02 mg/kg in kids) IV every 2 to 3 minutes to a maximum dose of 3 mg.

- ❖ Wide complex conduction defects caused by membrane depressant effects of certain beta-blockers may respond to **hypertonic sodium bicarbonate 1-2 meq/kg IV bolus** as given for cyclic antidepressant overdose.

D. Bronchospasms

- Aerosolized or nebulized Beta-2 agonist such as albuterol

E. Seizures

- Diazepam and, if necessary, phenobarbital.

VIII. Monitoring/Goals of Therapy

Patient Disposition

- ❖ Patients who present without signs and symptoms, who have received gastrointestinal decontamination, and whose serial EKGs have remained unchanged after an 8 to 10 hour observation period may be safely discharged to psychiatric care following a suspected overdose of immediate release dosage forms.
- ❖ Patients ingesting sustained-release products must receive a minimum of 24-hours of ICU observation. Patients presenting with severe signs and symptoms of beta-blocker toxicity should be admitted to an ICU where they can be closely monitored and treated.

- ❖ The overall goal of therapy is to restore perfusion to critical organ systems by increasing cardiac output.

Monitor	Goals of therapy
Continuous telemetry with 12-lead EKG every 3 hours	Normal sinus rhythm or return to baseline EKG
Chem-7 and Magnesium q6-8h initially then q24hrs when the patient is stabilized.	Values within normal limits
Blood pressure	SBP > 90 mmHg
HR	> 60 beats/min
Urine output via foley catheter	1-2 ml/kg/hr
Mental status changes	A/O x3, Denotes adequate hemodynamic stability.
Respiratory function: ABG's, pulse oximeter	ABG's and oxygenation within normal limits

Best monitoring methods for patients with severe toxicity are:

1. Early insertion of an arterial catheter to accurately monitor changes in SBP with treatment.
2. Swan-Ganz catheter to monitor pulmonary capillary wedge pressure and cardiac output.

References

- 1.) Kerns W, Kline J, and Ford MD. Beta-blocker and calcium channel blocker toxicity. Emergency Medicine Clinics of North America 1994. 12(2): 365-390.