Clinical Toxicology

Beta-blockers toxicity
ACE inhibitors toxcity

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Beta-blockers toxicity

- **Epidemiology**

- Common medications used in the treatment of various cardiovascular, neurologic, endocrine, ophthalmologic, and psychiatric disorders
- Accidental and intentional 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

Table 188-1 Location and Activity of β-Adrenergic Receptors			
β-Receptor Type	**Location**	**Agonism**	**Antagonism**
β_1	Myocardium	Increases inotropy	Decreases inotropy
		Increases chronotropy	Decreases chronotropy
	Kidney	Stimulates renin release	Inhibits renin release
	Eye	Stimulates aqueous humor production	Inhibits aqueous humor production
β_2	Bronchial smooth muscle	Causes bronchodilation	Causes bronchospasm
	Visceral smooth muscle	Relaxes uterus	–
		Causes ileus	
	Skeletal muscle	Increases force of contraction	–
		Stimulates glycogenolysis	
	Liver	Stimulates glycogenolysis and gluconeogenesis	Inhibits glycogenolysis and gluconeogenesis
	Vascular	Vasodilation	Vasoconstriction
β_3	Adipose tissue	Stimulates lipolysis	Inhibits lipolysis
	Skeletal muscle	Stimulates thermogenesis	Inhibits thermogenesis

Beta-blockers toxicity

- **Action**

- Beta -blockers antagonist competitively antagonize the effects of catecholamines at beta-adrenergic receptors and blunt the chronotropic and inotropic response to catecholamines.
- Slowing the rate of SA node discharge.
- Inhibit ectopic pacemakers & slow conduction through atrial & AV nodal tissue.
- Excessive beta -blockade may lead to profound pump failure, with bradycardia, decreased contractility, and hypotension.

Beta-blockers toxicity

- **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.
- Coingestants that alter gut function, such as opioids and anticholinergics, may affect absorption of beta -blockers and subsequent onset of symptoms.

Beta-blockers toxicity

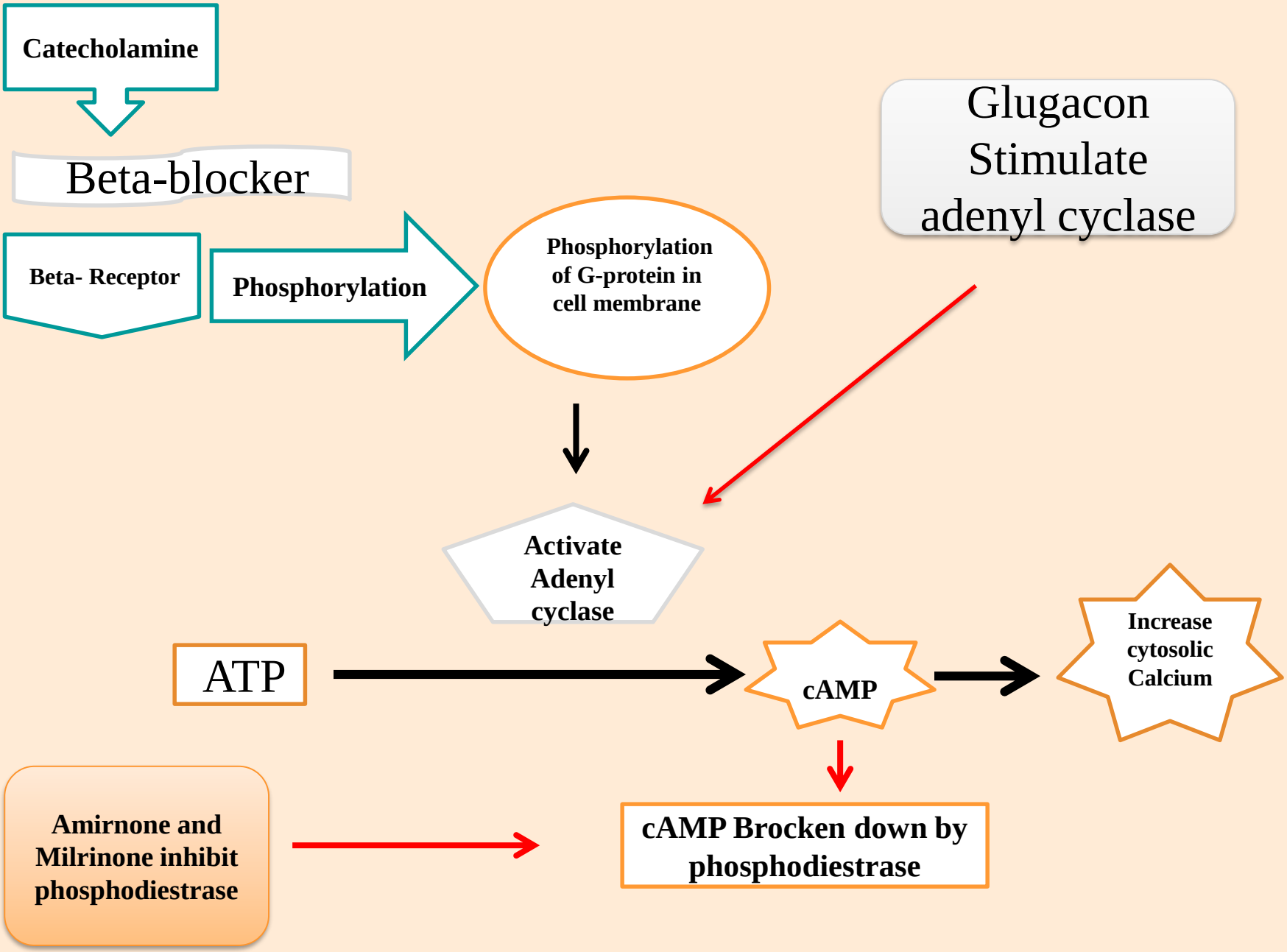
- **Distribution, Metabolism and Elimination**

- 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. Such type of beta-blockers required hepatic biotransformation before they can be eliminated & tend to accumulate in patients with liver failure.
- While the water-soluble beta-blockers tend to be slowly absorbed, poorly protein bound, & eliminated by kidney. They tend to accumulate in patients with renal failure.

Beta-blockers toxicity

- **Pathophysiology**

- The primary organ system affected by beta-blocker toxicity is the cardiovascular system, and the hallmark of severe toxicity is bradycardia and shock.
- The beta -blockers with sodium channel antagonism [propranolol] can cause a wide-complex bradycardia, and may contribute to development of seizures (especially when the QRS interval is >100 milliseconds).
- Neurologic manifestations include depressed mental status, coma, and seizures may occur with Beta-blockers toxicity.
- More lipophilic beta-blockers, such as propranolol, cause greater neurologic toxicity than the less lipophilic agents (???).
- Seizures can occur but are generally brief, and status epilepticus is rare.


Catecholamine
Beta-blocker
Beta- Receptor
Phosphorylation
Phosphorylation of G-protein in cell membrane
Glugacon Stimulate adenyl cyclase
Activate Adenyl cyclase
ATP
cAMP
Increase cytosolic Calcium
Amirnone and Milrinone inhibit phosphodiestrase
cAMP Brocken down by phosphodiestrase

Beta-blockers toxicity

- 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.

➢ Sotalol is unique among beta-blockers in its ability to block potassium channels

➢ Sotalol is class III antiarrhythmic drugs.

➢ Sotalol is more often associated with ventricular dysrhythmias, include:

❖ premature ventricular contractions

❖ ventricular tachycardia

❖ ventricular fibrillation

❖ torsades de pointes (sotalol)

Beta-blockers toxicity

- **Clinical manifestations**
- Symptoms of toxicity generally occur within 2 hours after immediate release β-adrenergic antagonist overdose
- **Cardiovascular**
- 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.
- Congestive heart failure often complicates β-adrenergic antagonist overdose.

Asystole is the most serious form of cardiac arrest and is usually irreversible

Beta-blockers toxicity

- **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.

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. It is one of the clinical hallmarks of renal failure and has been used as a criterion for diagnosing and staging acute kidney injury (AKI), previously referred to as acute renal failure.

Beta-blockers toxicity

- **Diagnosis**

- Including patient history, physical examination findings, and results of basic diagnostic testing.
- Exposures to other drugs and toxins can present with bradycardia and hypotension.
- ECG & continuous cardiac monitoring performed.
- Serum glucose conc. should be measured because Beta-blockers may cause hypoglycemia.
- Chest radiograph when the patient experiencing symptoms of CHF.

Beta-blockers toxicity

Treatment

1-General Management

- Should be evaluated in a critical-care area with appropriate monitoring
- Protect air way
- The airway and ventilation should be maintained with endotracheal intubation if necessary.

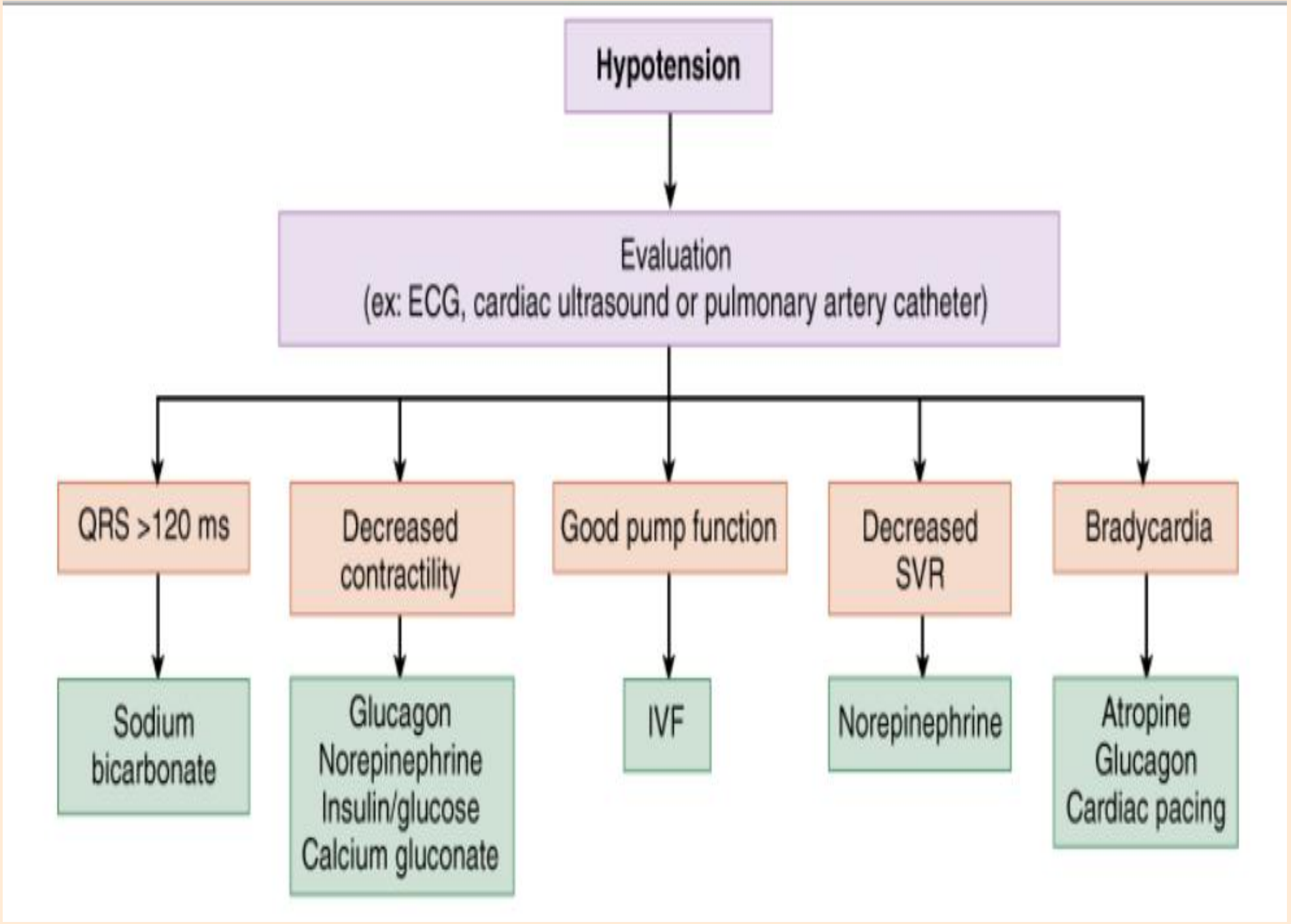
Beta-blockers toxicity

2-GI Decontamination

- 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 used.

Beta-blockers toxicity

- 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 after ingestion of a sustained-release product, If whole-bowel irrigation is used, adequate airway protection and normal GI function are important.


Hypotension
Evaluation
(ex: ECG, cardiac ultrasound or pulmonary artery catheter)
QRS >120 ms
Decreased contractility
Good pump function
Decreased SVR
Bradycardia
Sodium bicarbonate
Glucagon
Norepinephrine
Insulin/glucose
Calcium gluconate
IVF
Norepinephrine
Atropine
Glucagon
Cardiac pacing

Beta-blockers toxicity

3-Glucagon

- Glucagon is a first-line agent in the treatment of acute beta –blocker induced bradycardia and hypotension.
- Effects from an IV bolus of glucagon are seen within 1 to 2 minutes, reach a peak in 5 to 7 minutes duration of action of 10 to 15 minutes.
- Due to the short duration of effect, a continuous infusion is often necessary after bolus administration.

Beta-blockers toxicity

3-Glucagon

- The bolus dose of glucagon is

  0.05 to 0.15 milligram/kg (3 to 10 milligrams for the average 70-kg) and can be repeated as needed.

- If a beneficial effect is seen from bolus, a continuous infusion

  1 to 10 milligrams/h

Beta-blockers toxicity

3-Glucagon

- 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 and vomiting

esophageal sphincter relaxation

Beta-blockers toxicity

4-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.

Beta-blockers toxicity

4-Hyperinsulinemia-Euglycemia Therapy

- Adverse effects from hyperinsulinemia-euglycemia therapy are hypoglycemia and hypokalemia
- 0.5 gram/kg bolus of glucose should accompany the initial insulin bolus in a patient whose serum glucose level is <400 milligrams/dL.
- Serum glucose levels should be monitored regularly: every 20 to 30 minutes until stable euglycemia is achieved, and then every 1 to 2 hours thereafter.

Beta-blockers toxicity

5-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.

Beta-blockers toxicity

6-Atropine

- Muscarinic blocker, is unlikely to be effective in the management of beta blocker–induced bradycardia and hypotension.
- Although its use is unlikely to cause harm.

Beta-blockers toxicity

7-Calcium

- Calcium administration is not routinely recommended in beta -blocker overdose, it may be worth considering in patients with refractory shock unresponsive to other therapies.
- Calcium for IV administration is available in two forms, gluconate and chloride, both in a 10% solution. Calcium chloride solution contains three times more elemental calcium than calcium gluconate solution.

Beta-blockers toxicity

8-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.

Beta-blockers toxicity

- 9-Magnesium sulfate:
- used for treatment of Torsades de pointes (Sotalol)
- Magnesium sulfate 10 mmol (0.05 mmol/kg in children) IV over 15 minutes.
- Correct hypoxia, hypokalaemia and hypocalcaemia
- If heart rate is <100 beats/minute commence an isoprenaline infusion IV at 1-10 microgram/min (0.05-2.0 microgram/kg/min in children) or overdrive pacing to maintain heart rate at 100-120 beats/minute.

Homework

What are new treatment for beta blockers poisoning with their mechanism of action??

ACE Inhibitors

- An angiotensin-converting-enzyme inhibitor (ACE inhibitor) is a pharmaceutical drug used primarily for the treatment of hypertension (elevated blood pressure) and congestive heart failure.
- This group of drugs cause relaxation of blood vessels, as well as a decreased blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart.
- They inhibit the angiotensin-converting enzyme, an important component of the renin-angiotensin-aldosterone system.

ACE Inhibitors

- ACE inhibitors were initially approved for the treatment of hypertension, and can be used alone or in combination with other antihypertensive medications. Later, they were found useful in other cardiovascular and kidney diseases including:
- Acute myocardial infarction (heart attack)
- Cardiac failure (left ventricular systolic dysfunction)
- Kidney complications of diabetes mellitus (diabetic nephropathy)

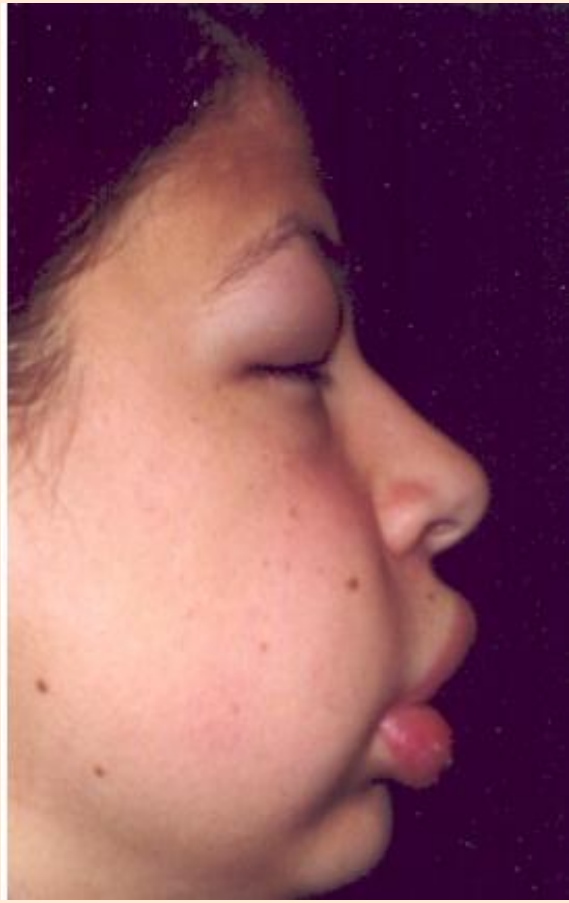
ACE Inhibitors

ACE adverse effects

- Common adverse drug reactions include: hypotension, cough, hyperkalemia, headache, dizziness, fatigue, nausea, and renal impairment. ACE inhibitors might increase inflammation-related pain, perhaps mediated by the buildup of bradykinin that accompanies ACE inhibition.
- The main adverse effects of ACE inhibition can be understood from their pharmacological action. The other reported adverse effects are hepatotoxicity and effect on the fetus.
- Renal impairment is a significant potential adverse effect of all ACE inhibitors, that directly follows from their mechanism of action. Patients starting on an ACE inhibitor usually have a modest reduction in glomerular filtration rate (GFR) that stabilizes after several days.

ACE Inhibitors

- **ACEI-Induced Angioedema**
- Now most common exogenous cause of angioedema seen in emergency rooms
- Angioedema is an inflammatory reaction in which there is increased capillary blood flow and permeability, resulting in an increase in interstitial fluid.
- Angioedema most commonly involves the periorbital, perioral, or oropharyngeal tissues.
- If this process is confined to the superficial dermis, urticaria develops; if the deeper layers of the dermis or subcutaneous tissue are involved, angioedema results.



ACE Inhibitors

- This swelling may progress rapidly over minutes and result in complete airway obstruction and death.
- The pathogenesis of acquired angioedema involves multiple vasoactive substances, including histamine, prostaglandin D2 , leukotrienes, and bradykinin.
- Because ACE also inactivates bradykinin and substance P, ACE inhibition results in elevations in bradykinin concentrations that appear to be the primary cause of both ACEI-induced angioedema and cough.
- There is no evidence that the ACEI-induced angioedema phenomenon is IgE mediated.

ACE Inhibitors

- Face and lips most commonly involved but laryngeal edema reported
- Can cause dramatic swelling of tongue, pharynx, or larynx may require intubation or tracheostomy acutely
- Risk factors include obesity, prior endotracheal intubation and face and neck surgery
- ACE inhibitors will trigger attacks in those with hereditary angioedema (HAE), so avoid in these patients.

ACE Inhibitors

- Angioedema develops in 0.1% to 0.5% of those receiving the drug
- Onset from 1st week of use to 2-3 years of use
- Symptoms resolve within 24-48 hours of cessation of drug
- Most commonly seen with captopril and enalopril, but described with all ACE inhibitors
- Genetic factors may be important
- Subjects with a history of angioedema from other causes are more susceptible to ACE-induced angioedema

ACE Inhibitors

Management

- **Emergency and supportive measures.** Monitor blood pressure and heart rate for 6 hours after ingestion. If symptomatic or significant hypotension develops, observe for at least 24 hours.
- **1.** If hypotension occurs, treat it with supine positioning and IV fluids (Normal saline). **in the most severe cases, hypotension may require pressor therapy (eg. Nor adrenaline).**
- **2.** Treat angioedema with usual measures (eg, Diphenhydramine, corticosteroids) and discontinue the ACE inhibitor. Switching to an Angiotensin receptor blockers (ARABs) may not be appropriate as angioedema has also been reported with these agents.

Treatment of ACE inhibitors

- **3. Treat hyperkalemia** if it occurs by administration of (Calcium chloride, Sodium bicarbonate, Glucose plus insulin, inhalation of Beta2 agonist (salbutamol) and hemodialysis which rapidly lower the potassium level.
- **4. Decontamination** Administer activated charcoal orally if conditions are appropriate
- 5. **Enhanced elimination**. Hemodialysis may effectively remove these drugs but is not likely to be indicated clinically.
- **Note:** ACE receptor antagonists are generally considered to be safe and there are few cases of poising has been reported.

Case study

A 6-year-old white male presents to the emergency department with his parents after accidently ingesting one nadolol tablet. One hour following the ingestion, the child became dizzy and vomited. Because the child appeared to be very sleepy, the parents brought him in ED for evaluation.

- PMH (past medical history): None.
- Physical Examination:
- T: 37°C HR: 100 bpm RR: 22 breaths per minute BP: 100/60 mm Hg
- General: Sleepy, but easily aroused.
- HEENT: Normocephalic, pupils equal and reactive to light.
- Pulmonary: Clear to auscultation.
- CV: Regular rate and rhythm.
- Neurologic: Unremarkable.


Thank You
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