Alpha Adrenoceptor Antagonists Beta Adrenoceptor Antagonists Ganglion-Blocking Drugs 2

Cardioselective β Blockers (β1-selective antagonists)

Metoprolol

- High lipid solubility.
- Less likely to worsen asthma.
- used to treat **angina** and **hypertension** & also used to treat or prevent Myocardial Infarction (AMI) without bradycardia.

Atenolol

- low lipid solubility. Longer duration action. One dose/ day.
- Side effects related to CNS are less prominent
- Most commonly used in Hypertension & angina .

Nebivolol

The **most highly selective ß 1** blocker.

↑ endothelial NO release (vasodilating effect)

Antioxidant ,can protect the vascular wall from free radicals that damage blood vessels and thereby contribute to the progression of cardiovascular disease.

Bisoprolol

low lipid solubility. Longer duration of action. One dose/ day

used to treat hypertension, coronary heart disease, arrhythmias.

Esmolol

- Ultra-short–acting β 1-selective blocker.
- Contains an ester linkage; esterases in red blood cells rapidly metabolize it.
- Has a short half-life (about 10 minutes).
- Given by continuous IV infusions
- Esmolol may be **safer** in critically ill patients who require a β -adrenoceptor antagonist.
- Esmolol is useful in controlling **supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis, perioperative hypertension, and myocardial ischemia in acutely ill patients**.

ß Blockers with **partial ß-agonist activity.**

Effective in hypertension and angina & less likely to cause **bronchoconstriction, bradycardia and abnormalities in plasma lipids** than other ß blockers.

Pindolol is a non-selective beta- adrenoceptor/5-HT1A antagonist accelerates the antidepressant effect of selective serotonin reuptake inhibitors.

Celiprolol is a ß 1-selective antagonist with a **partial ß2 -agonist activity** & may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation.

Acebutolol a ß 1-selective antagonist.

Drugs that block both alpha and beta receptors

Labetalol

- Causes Hypotension with less tachycardia than occurs with α blockers.
- it is a **partial agonist** at beta2- receptors

Carvedilol

- A nonselective beta blocker/alpha-1 blocker, calcium channel blocker.
- More potent at β than at α1 receptors
- Antioxidant property.
- Use: Hypertension, Angina, congestive heart failure

Clinical Uses of the Beta-Receptor-Blockers. Hypertension

- Used alone, but often used with either a diuretic or a vasodilator.
- In spite of the short half-life of many β antagonists, these drugs **may be administered once or twice daily** and still have an adequate therapeutic effect.
- May be less effective in the **elderly** and in black.

Ischemic Heart Disease

Clinical Uses cont..

- Reduce the frequency of anginal episodes and improve exercise tolerance in patients with angina.
- Decrease cardiac work & reduce oxygen demand.
- Slow heart rate may contribute to clinical benefits.
- The long-term use of **timolol, propranolol,** or **metoprolol** in patients who have had a myocardial infarction prolongs survival
- ß blockers are strongly indicated in the acute phase of a myocardial infarction.
- Contraindications include bradycardia, hypotension, moderate or severe left ventricular failure, shock, heart block, and active airways disease.

Cardiac Arrhythmias

- Class II antiarrhythmic drugs.
- By increasing the **AV nodal refractory** period,

  ß antagonists slow ventricular response rates in atrial **flutter and fibrillation**.
- They **reduce ventricular ectopic** beats, particularly if caused by catecholamines.

- **Sotalol** has a **marked class III antiarrhythmic** effects, due to **potassium channel blockade** (treats both ventricular & supraventricular arrhythmias).

Heart Failure

cont..

- Clinical trials have demonstrated that at least three ß antagonists, **metoprolol, bisoprolol,** and **carvedilol** are effective in reducing mortality in selected patients with chronic heart failure.
- Although administration of these drugs may worsen acute congestive heart failure, cautious long-term use with gradual dose increments in patients who tolerate them may prolong life.
- They have a beneficial effects on **myocardial remodeling** and decrease the risk of sudden death.

Glaucoma

- Systemic administration of ß -blocking drugs for other indications, reduced intraocular pressure in patients with glaucoma. Topical administration also reduces intraocular pressure.
- The mechanism involves reduced production of aqueous humor by the ciliary body.
- **Timolol** and related ß antagonists are suitable for local use in the eye because they lack local anesthetic properties.
- Beta antagonists have an efficacy comparable to that of **epinephrine** or **pilocarpine** in open-angle glaucoma and are far better tolerated.
- Sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart and airways in susceptible individuals.

Hyperthyroidism

- Excessive CA action is important in the pathophysiology of hyperthyroidism, especially in relation to the heart
- The ß antagonists are beneficial in this condition due to **blockade of adrenoceptors & in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.**
- Propranolol has been used extensively in patients with **thyroid storm** (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.

Neurologic Diseases

Clinical Uses cont..

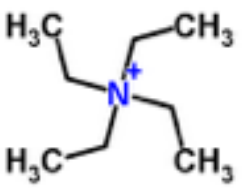
- Propranolol reduces the frequency and intensity of **migraine** headache.
- Other ß -receptor antagonists with preventive efficacy include **metoprolol** , **atenolol, timolol,** and **nadolol**.
- The mechanism is not known.
- ß antagonists reduce certain **tremors.**
- The **somatic manifestations of anxiety** may respond dramatically to low doses of **propranolol**, particularly when taken prophylactically.
- Benefit has been found in musicians with **performance anxiety ("stage fright").**
- Propranolol may be used in symptomatic treatment of alcohol withdrawal in some patients.

Clinical Toxicity of the Beta-Receptor Antagonist Drugs

- **Bradycardia** is the most common adverse effect. Coolness of hands and feet in winter.
- CNS effects include mild sedation, vivid dreams, and rarely, depression.
- Nonselective agents commonly causes worsening of preexisting **asthma.**
- Caution is required in patients with severe peripheral vascular disease and in patients with compensated heart failure even though long-term use may prolong life.
- A very small dose of a β antagonist may provoke severe cardiac failure in a susceptible individual.

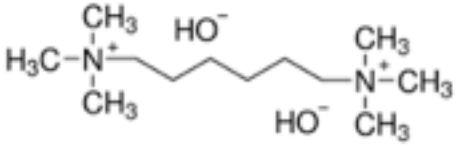
- Beta blockers may interact with the calcium antagonist **verapamil** causing bradycardia, heart failure, and cardiac conduction abnormalities. These adverse effects may even arise in susceptible patients taking a **topical** ß blocker and oral verapamil.
- Patients with ischemic heart disease or hypertension may be at increased risk if ß blockade is suddenly interrupted.
- This might involve **up-regulation** of **ß receptors**.
- It is inadvisable to use ß antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions. **Beta1-selective antagonists** are safer in these patients

Ganglion-Blocking Drugs



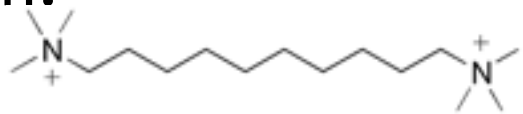
Tetraethylammonium (TEA)

First ganglion blocker, very short duration of action



Hexamethonium ("C6")

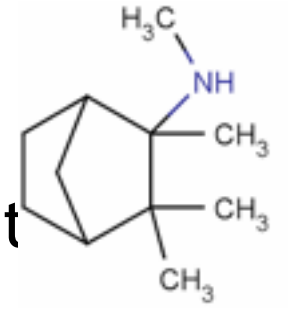
The first drug effective for hypertension.



Decamethonium, "C10" analog of hexamethonium, is a depolarizing neuromuscular blocker.

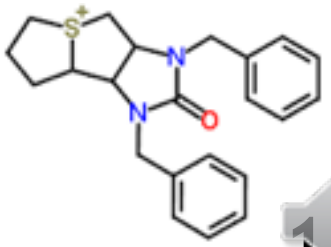
Mecamylamine

A secondary amine, developed to improve absorption from the GIT because the quaternary amine were poorly absorbed after oral administrat



Trimethaphan

A short-acting ganglion blocker, is inactive ora & is given by intravenous infusion.



Mechanism of Action

- Ganglionic nicotinic receptors are subject to both depolarizing and nondepolarizing blockade
- Nicotine & acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.
- Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists.
- Blockade can be reversed by increasing the concentration of an agonist, e.g., acetylcholine.

Organ System Effects

Central Nervous System

Mecamylamine enters the CNS causing Sedation, tremor, **choreiform** movements, and mental abnormalities.

Eye

- **Cycloplegia** with loss of accommodation & **moderate dilation of the pupil** because parasympathetic tone usually dominates this tissue.

Cardiovascular System

- Marked decrease in arteriolar and venomotor tone.
- **BP may fall** because both peripheral vascular resistance and venous return are decreased
- **Orthostatic or postural hypotension**, **diminished contractility** and a **moderate tachycardia**.

GIT

- Secretion & Motility are profoundly inhibited, and constipation can be marked.

Other Systems

- may precipitate urinary retention in men with prostatic hyperplasia.
- **Sexual function** is impaired in that both erection and ejaculation.
- **Sweating** is reduced by the ganglion-blocking drugs.

Clinical Applications & Toxicity

- Ganglion blockers are **used infrequently** because more selective agents are available.

Mecamylamine

- Blocks central nicotinic receptors and has been advocated as a possible adjunct with the transdermal nicotine patch to **reduce nicotine craving in patients attempting to quit smoking.**

Trimethaphan

- Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery to reduce bleeding in the operative field.

- The toxicity of the ganglion-blocking drugs is limited to the autonomic effects.
- These effects are intolerable except for acute use.