Alpha Adrenoceptor Antagonists
Beta Adrenoceptor Antagonists
Ganglion-Blocking Drugs

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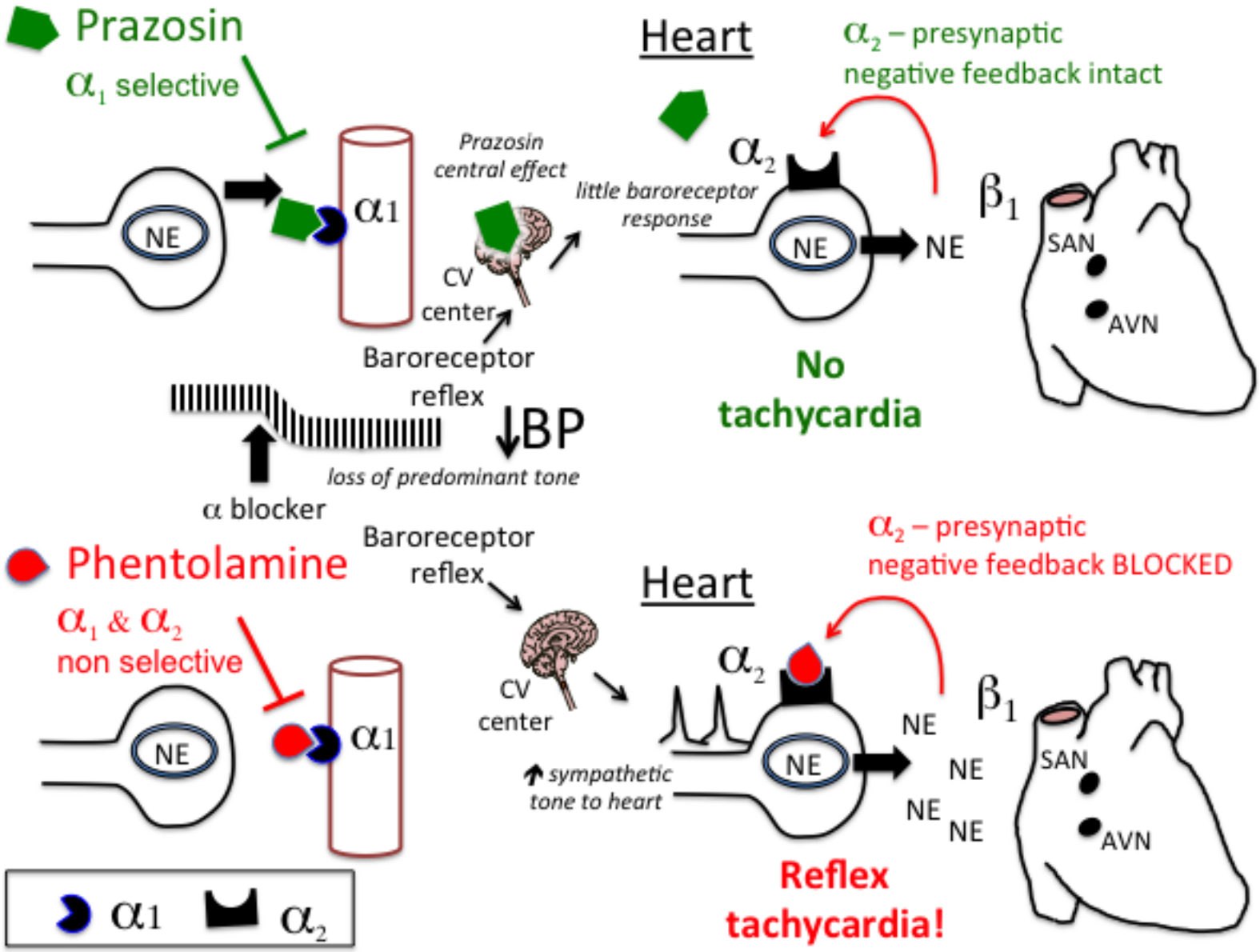
Alpha-Receptor Antagonist Drugs

Pharmacologic Effects

Cardiovascular Effects

- ↓ peripheral vascular resistance and blood pressure.
- Prevent the pressor effects of α agonists
- often cause orthostatic hypotension and reflex tachycardia; nonselective (α 1 = α 2,) blockers cause tachycardia if blood pressure is lowered below normal.

Effects of selective & Non selective alpha blockers on HR



Other Effects

- **miosis** and nasal stuffiness.

- **Alpha1** receptors are expressed in the base of the bladder and the prostate, and their blockade decreases resistance to the flow of urine and reduce urinary urgency.
- Alpha blockers are used for the treatment of urinary retention due to prostatic hyperplasia .

Non selective alpha blockers

Phenoxybenzamine

Binds covalently to α receptors, causing irreversible blockade of long duration (14–48 h).

Blocks α1& to less extent α2 receptors.

Also inhibits reuptake of NE and blocks histamine (H1), ACh, and serotonin receptors.

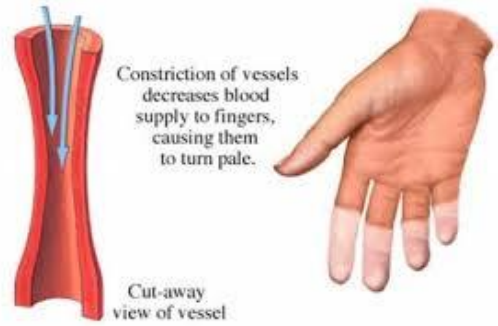
Causes little fall in BP in normal supine individuals, it reduces BP when sympathetic tone is high, e.g., as a result of upright posture.

Absorbed poorly but usually given orally.

Uses: treatment of **pheochromocytoma,** Peripheral vascular diseases, e.g. **Raynaud's phenomenon** (excessive reversible vasospasm in the peripheral circulation). **Prazosin** or **phenoxybenzamine** are used but **calcium channel blockers** are preferable for most patients

Adverse effects

Orthostatic hypotension, tachycardia, Nasal stuffiness and inhibition of ejaculation.



Phentolamine

- Rapidly acting α blocker with short duration t½ 19 min.
- Competitive α1 and α2 antagonist.
- Reduces peripheral resistance (α1) and causes cardiac stimulation (α 2 receptors blockade enhances release of NE) .
- minor inhibitory effects at 5HT receptors and agonist effects at muscarinic (salivary, sweat, lacrimal) and H1 and H2 receptors (Increase acid secretion).
- Uses: Diagnostic of pheochromocytoma, control of hypertension due to clonidine withdrawal, Cheese reaction.
- To counteract vasoconstriction due to alpha agonists..
- **Adverse effects:** severe tachycardia, arrhythmias, and myocardial ischemia.

Selective α 1 blockers
Prazosin

- Highly selective α1 blocker & less potent at α 2 receptors.
- Relaxes **both arterial and venous vascular** sm muscle

& smooth muscle in the **prostate**, due to blockade of α 1 receptors with **no or little tachycardia**

- Extensively metabolized, only 50% is available after oral administration. The half-life is **3** hours.
- Favorable effect on plasma lipids: increase HDL/LDL ratio.
- **Uses** Antihypertensive ,Benign prostatic hyperplasia (BPH) Blocks α1 in bladder trigone & prostate & decreases tone & Improves urine flow .
- **Adverse effects**: First dose phenomenon i.e. postural hypotension with initial doses.

Terazosin

High bioavailability. The half-life is 9–12 hours.

Doxazosin

Has a longer half-life of about 22 hours.

Tamsulosin

Uroselective α1A blocker. α 1A are predominant in bladder base & prostate. No effect on BP and heart rate.

High bioavailability and a half-life of 9–15 hours.

Side Effects: Dizziness & retrograde ejaculation.

Prazosin, doxazosin, and terazosin are all effective.

Tamsulosin is preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists.

Yohimbine

- An indole alkaloid, is **α 2-selective antagonist**. Blocks other receptors also – 5HT, DA
- Increases ADH release
- Enhances sexual activity – aphrodisiac
- Sometimes used in the treatment of **orthostatic hypotension** because it promotes NE release through blockade of presynaptic α 2 receptors.
- Was widely used to improve male **erectile dysfunction** but has been superseded by phosphodiesterase-5 inhibitors like **sildenafil (viagra).**

β- Adrenoceptor Antagonists

First generation: non selective (β1 and β 2) .

Second generation: Cardioselective (β1)

Third generation: Vasodilator β blockers.

The **selectivity is dose-related; it tends to diminish at higher drug concentrations.**

Other major differences relate to their **lipid solubility** and **local anesthetic (membrane-stabilizing)** effects. However, the concentration in plasma is **too low** for the anesthetic effects.

Most drugs are well absorbed after oral administration; peak concentrations **1–3** hours after ingestion.

- Lipophilic β blockers
  - **propranolol, metoprolol, oxprenolol, carevdilol**
  - readily absorbed from GI, metabolized in liver
  - large volume of distribution, and penetrate BBB well
  - hepatic failure prolongs their t1/2.

- Hydrophilic β blockers
  - **acebutolol, atenolol, bisoprolol,, nadolol. sotalol**
  - less readily absorbed, not extensively metabolized
  - long plasma half-lives which are prolonged in renal failure.

Pharmacodynamics

Effects on the Cardiovascular System

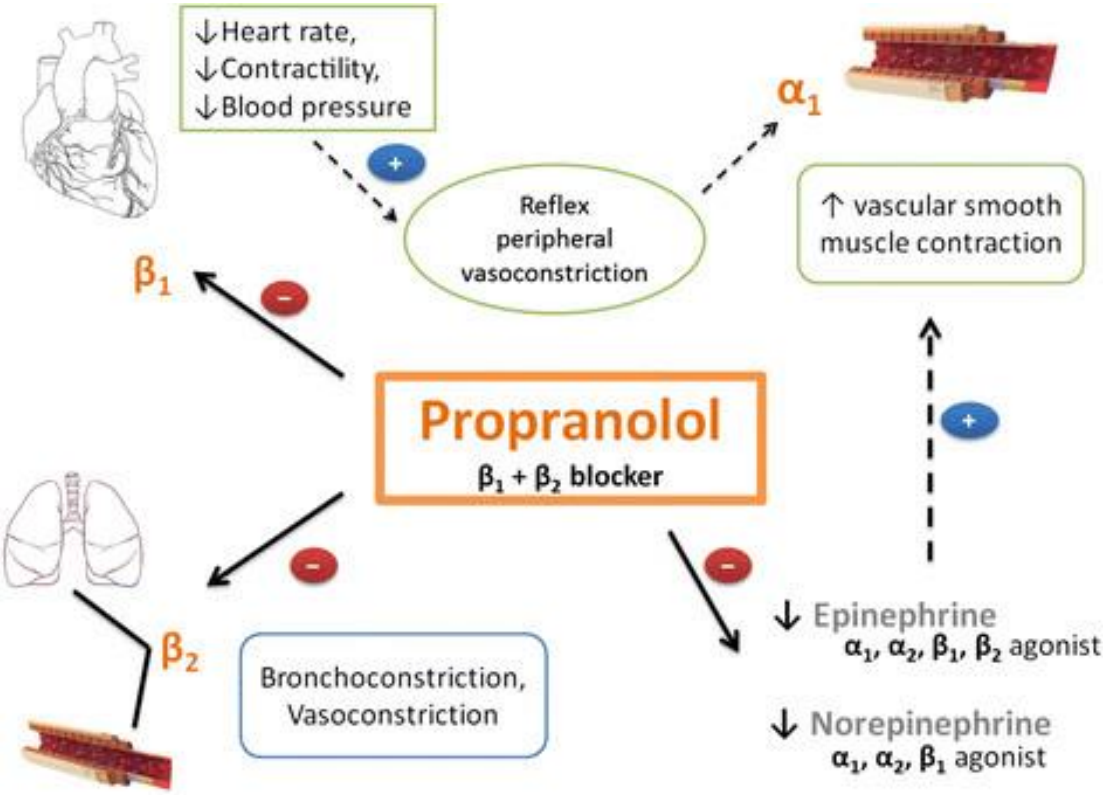
Very valuable in **hypertension, angina** and **chronic heart failure** and **following myocardial infarction (MI)**.

Heart:↓ HR, ↓SV, ↓COP. ↓ AV conduction. ↓cardiac work & O2 consumption.

Blood vessels:↓BP both diastolic and systolic after continuous treatment.

Do not cause hypotension in healthy individuals with normal BP.

Nonselective and β1-block – Also, an inverse agonist (↓ resting Heart Rate)



Effects on the Respiratory Tract

Increase in airway resistance, particularly in patients with asthma.

β1 blockers are safer than nonselective β blockers.

β 1-selective blocker are not sufficiently specific to *completely* avoid interactions with β 2 receptors.

Consequently, these drugs should generally be **avoided in patients with asthma**.

Many patients with chronic obstructive pulmonary disease may tolerate these drugs & the benefits e.g. in patients with concomitant **ischemic heart disease**, may outweigh the risks.

Effects on the Eye

Reduce intraocular pressure in **glaucoma** by decreasing aqueous humor production.

Glaucoma is treated by:

1- reduction of aqueous humor secretion.

2- enhancement of aqueous out-flow.

Drugs useful in reducing intraocular pressure:

Cholinomimetics, α agonists, β blockers

prostaglandin F2 analogs., diuretics

Prostaglandin analogs & β blockers are the most popular.

Metabolic and Endocrine Effects

- Beta-receptor antagonists increases LDL, triglycerides, ↓ HDL by inhibiting **lipolysis.**
- **Glycogenolysis** in the liver is inhibited after β 2-receptor blockade.
- β –blockers should be used with caution in **insulin-dependent diabetic patients**.

  β blockers delay recovery from hypoglycemia due to insulin and oral anti diabetics and mask early symptoms of hypoglycemia (tremors, sweating & tachycardia).

Specific Agents

Propranolol

- Prototype of β -blocking drug. High lipid solubility.
- Has low and dose-dependent bioavailability (first-pass metabolism).
- First-pass effect varies among individuals,
- A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period.
- No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear.
- It has no partial agonist action at β receptors.

Propranolol has been used extensively in patients with **thyroid storm** (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.

The β antagonists are beneficial due to **blockade of adrenoceptors & in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.**

β antagonists reduce certain **tremors.**

Low doses of **propranolol**, particularly when taken prophylactically, is useful in musicians with **performance anxiety ("stage fright").**
Propranolol may be used in symptomatic treatment of alcohol withdrawal in some patients.
Propranolol reduces the frequency and intensity of **migraine** headache.

Metoprolol , **atenolol, timolol,** and **nadolol** are also effective, mechanism is not known

Other non-selective beta blockers

Nadolol

Has a **very long duration of action**.

Timolol

no local anesthetic activity used topically to treat glaucoma.

Sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart and airways in susceptible individuals.

Sotalol

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

Cardioselective β Blockers (**β1-selective** antagonists)

less effects on bronchioles, carbohydrate metabolism, lipids.

Lower incidences of Cold hands and feet.

Less liable to impair exercise tolerance

Safer in patients who experience bronchoconstriction in response to propranolol, but their β 1 selectivity is modest, so they should be used with great caution in patients with **asthma.**

β1-selective antagonists cont..

- However, the benefits may exceed the risks, e.g., in patients with myocardial infarction.
- Beta1-selective antagonists are preferred in patients with **diabetes or peripheral vascular disease** since β 2 receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).

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 β 1** blocker.

↑ endothelial NO release (vasodilating effect)

Antioxidant ,can protect the vascular wall from free radicals that damage blood vessels.

Bisoprolol

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

used to treat hypertension, coronary heart disease, arrhythmias.

Clinical trials have demonstrated that at least three β antagonists, **metoprolol, bisoprolol,** and **carvedilol** are effective in reducing mortality in selected patients with chronic heart failure.

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.

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 and myocardial ischemia in acutely ill patients**.

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

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

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

Celiprolol is a β 1-selective antagonist with a **partial β2 -agonist activity** & may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation.

Acebutolol a β 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

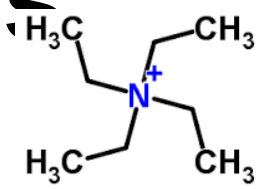
- A nonselective beta blocker/alpha-1 blocker, calcium channel blocker.
- More potent at β than at α1 receptors
- Antioxidant property.
- Use: Hypertension, Angina, congestive heart failure

Clinical 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.

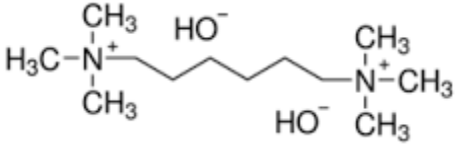
- Beta blockers may interact with the calcium antagonist **verapamil** causing bradycardia, heart failure, and cardiac conduction abnormalities. These adverse effects may even arise in susceptible patients taking a **topical** β blocker and oral verapamil.
- Patients with ischemic heart disease or hypertension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

Ganglion-Blocking Drugs



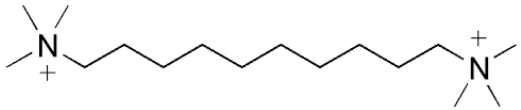
Tetraethylammonium (TEA)

First ganglion blocker, very short duration of action



Hexamethonium ("C6")

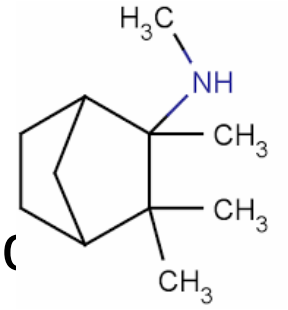
The first drug effective for hypertension.



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

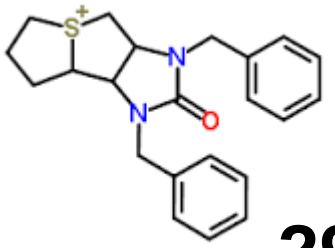
Mecamylamine

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



Trimethaphan

A short-acting ganglion blocker, is inactive oral & 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.

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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**.

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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.

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.