Drugs Affecting the Autonomic Nervous System-5 Adrenoceptor Blockers

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Adrenoceptor Antagonists

Alpha Blockers

- Alpha2-selective (yohimbine)
- Alpha1-selective (prazosin)
- Nonselective
  - Reversible (phentolamine)
  - Irreversible (phenoxybenzamine)

Beta Blockers

- Beta2-selective (butoxamine)
- Beta1-selective (atenolol)
- Nonselective (propranolol)

Alpha-blocking Drugs
Pharmacokinetics

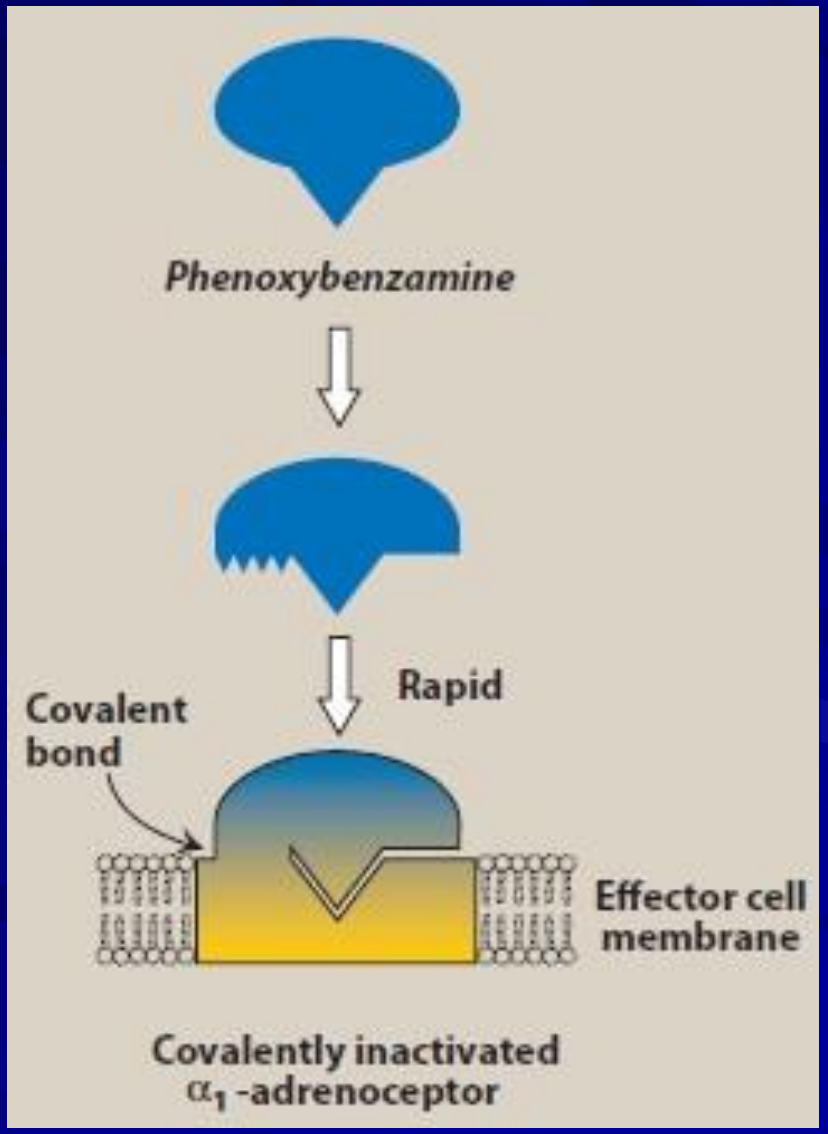
- Oral & parenteral route, phentolamine is rarely given orally.
- Phenoxybenzamine has a short elimination half-life but a long duration of action out 48 h-because it binds covalently to its receptor.
- Phentolamine has a duration of action of 2-4 h when used orally and 20-40 min when given parenterally.
- Prazosin and the other α1-selective blockers act for 8–24 h.

Mechanism of Action

- Phenoxybenzamine binds covalently to the α receptor, thereby producing an irreversible NON competitive (insurmountable) blockade.
- The other agents are competitive antagonists, and their effects can be surmounted by increased concentrations of agonist.

Note: This difference may be important in the treatment of pheochromocytoma because a massive release of catecholamines from the tumor may overcome a reversible blockade.

Covalent inactivation of α_1 adrenoceptor by phenoxybenzamine.



Actions:

Cardiovascular Effects:

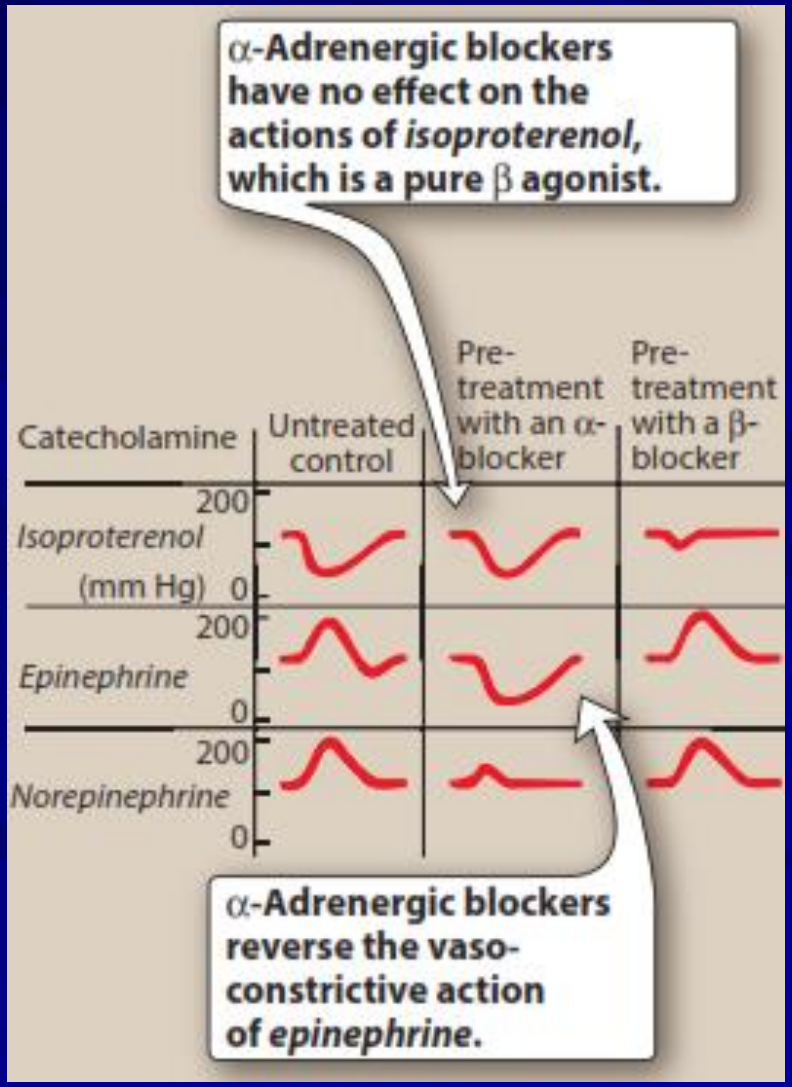
- Blocking α receptors, phenoxybenzamine Prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines.
- The decreased peripheral resistance provokes a reflex tachycardia.
- Increased cardiac output, due to The ability to block presynaptic inhibitory α2 receptors in the heart (results in more norepinephrine release)
- (No longer used in hypertension)

Epinephrine Reversal:

In the presence of agonists with both α & β2 recepter effects (epinephrine), blockade of α1 receptor selectivly may convert the pressor to a depressor response)

- All α-adrenergic blockers reverse the α agonist actions of epinephrine (the vasoconstrictive action) but vasodilation caused by stimulation of β2 receptors is not blocked.
- In the presence of phenoxybenzamine, the systemic blood pressure decreases in response to epinephrine

Summary of effects of adrenergic blockers on the changes in blood pressure induced by isoproterenol, epinephrine, and norepinephrine.



Therapeutic Uses of Phenoxybenzamine

- Pheochromocytoma (tumor of the adrenal medulla)
  - Preopretive management of the tumor
  - Chronic management of inoperable tumors (metastatic Pheochromocytoma)
- Raynaud disease.

Adverse Effects of Phenoxybenzamine

1. Postural hypotension
2. Nasal stuffiness
3. Nausea, and vomiting.
4. Inhibition of ejaculation.
5. Reflex tachycardia, which is mediated by the baroreceptor reflex.
6. Phenoxybenzamine should be used with caution in patients with cardiovascular disease.

Phentolamine

- Competitive block of α_1 and α_2 receptors
- Short lasting 4 hours after a single injection(reversible)

Uses of Phentolamine

- Pheochromocytoma (for short-term management)
- Prevent dermal necrosis following extravasation of norepinephrine (used locally)
- Hypertensive crisis (due to abrupt withdrawal of clonidine and from ingesting tyramine-containing foods in patients taking monoamine oxidase inhibitors

Adverse Effects of Phentolamine

- Postural hypotension and causes epinephrine reversal.
- Reflex tachycardia are mediated by the baroreceptor reflex and by blocking the α2 receptors of the cardiac sympathetic nerves.
- Arrhythmias and anginal pain & myocardial ischemia

Note: Phentolamine is contraindicated inpatients with coronary artery disease

Selective Competitive α1 Receptor Blockers Prazosin, Terazosin, Doxazosin, Tamsulosin and Alfuzosin

Mechanism of Action:

- Decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle.
- These drugs, unlike phenoxybenzamine and phentolamine, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.
- Tamsulosin has the least effect on blood pressure because it is less selective for α1B receptors found in the blood vessels and more selective for α1A receptors in the prostate and bladder. Blockade of the α1A receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow

Pharmacokinetic of Selective Competitive α_1 Receptor

- Prazosin have short half life,
- Terazosin have intermedaite half life
- Doxazosin is the longest acting.
- Metabolisd to inactive products that are excreted in urine
- Doxazosin, appear in feces.

Uses of Selective Competitive α1 Receptor Blockers

- Hypertension

  Prazosin ,terazosin ,and doxazosin are useful in the treatment of hypertension.

  (not used as monotherapy)

- Benign prostatic hyperplasia

  Tamsulosin (higher affinity for a α1 A, mediating prostate smooth muscle contraction, so this drug cause inhibiting contraction of prostate smooth muscle) , alfuzosin also used .

Note: The first dose of these drugs may produce an exaggerated orthostatic hypotensive response that can result in syncope (fainting). This termed a “first-dose” effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime

Adverse Effects of Selective Competitive α1 Receptor Blockers

α1-Blockers Such as Prazosin and Doxazosin

1. Headache , dizziness, drowsiness
2. Nasal congestion
3. Orthostatic hypotension (lesser degree than with phenoxybenzamine and phentolamine).
4. Additive antihypertensive effect occurs when given with vasodilators such as nitrates or sildenafil
5. Inhibition of ejaculation by blocking α receptors in the ejaculatory ducts and impairing smooth muscle contraction.

Selective Competitive α2-blocker

Yohimbine

- Selective competitive α2-blocker
- Limitted benefit for sexual stimulant and in the treatment of male erectile dysfunction.
- It works at the level of the CNS to increase sympathetic outflow to the periphery.

Note: It is contraindicated in cardiovascular disease, psychiatric conditions, and renal dysfunction

β -antagonists

- Drugs in this group are usually classified into subgroups on the basis of β1 selectivity, partial agonist activity, local anesthetic action& lipid-solubility
- All of the β blockers used clinically are competitive pharmacologic antagonists.
- Propranolol is the prototype.

Receptor Selectivity

- (β1 block > β2 block) is a property of acebutolol, atenolol, esmolol, metoprolol), this property may be an advantage when treating patients with asthma.
- Nadolol, propranolol,and timolol are typical nonselective β blockers.
- Labetalol and carvedilol (α- and β-blocking actions).
- Nebivolol has vasodilating action +β1-selective antagonism.

Partial Agonist Activity

- (Intrinsic sympathomimetic activity) may be an advantage in treating patients with asthma because these drugs (eg, pindolol, acebutolol are less likely to cause bronchospasm,
- In contrast, full antagonists such as propranolol are more likely to cause severe bronchospasm in patients with airway disease.

Local Anesthetic

- (Membrane-stabilizing activity) is a disadvantage when β blockers are used topically in the eye because it decreases protective reflexes and increases the risk of corneal ulceration.
- Local anesthetic effects are absent from Timolol and several other β blockers that are useful in glaucoma.

Beta Adrenoceptor Antagonist

Drug	Selectivity	Partial Agonist Activity	Local Anesthetic Activity	Lipid Solubility	Elimination Half-Life
Acebutolol	β_1	Yes	Yes	Low	3–4 h
Atenolol	β_1	No	No	Low	6–9 h
Carvedilol[a]	None	No	No	Moderate	7–10 h
Esmolol	β_1	No	No	Low	10 min
Labetalol[a]	None	Yes[b]	Yes	Low	5 h
Metoprolol	β_1	No	Yes	Moderate	3–4 h
Nadolol	None	No	No	Low	14–24 h
Pindolol	None	Yes	Yes	Moderate	3–4 h
Propranolol	None	No	Yes	High	3.5–6 h
Timolol	None	No	No	Moderate	4–5 h

Pharmacokinetics

- Most of the systemic agents have been developed for chronic oral use,
- Esmolol is a short-acting ester β blocker that is used only parenterally.
- Nadolol is the longest-acting β blocker.
- Acebutolol, atenolol, and nadolol are less lipid-soluble than other β blockers ,enter (CNS) to a lesser extent.

Effects and Clinical Uses

Blockade of the β-receptor–mediated Effects of Sympathetic Discharge.

1. Hypertension
   (not cause postural hypotension)
2. Angina
   (decrease cardiac work& cause reduce in oxygen demand)

3. Arrhythmias (Sotalol)
4. Heart failure
   chronic (not acute), Labetalol, carvedilol & metoprolol reduce morbidity and mortality)
5. Pheochromocytoma
   Sometimes treated with combined α- and β-blocking agents (labetalol).
6. Open-angle glaucoma (Timolol)

Adverse Effect of Beta Adrenoceptor Antagonist

1. Bradycardia, atrioventricular blockade, heart failure duo to β adrenoceptor blockade
2. Cardiac arrhythmias (long term used lead to up regulation of β -receptors) so never be stoped quickly.
3. Bronchoconstriction, β 2 receptor blockade associated with non selective beta blockers (e.g.propranolol)
4. Hypoglycemia from insulin over dosage (tachycardia, tremor and anxiety) may be masked by β blockers
5. CNS :sedation, fatigue & sleep disturbance
6. Sexual dysfunction
7. Inter act with calcium antagonist

Drugs Used in Glaucoma

Group, Drugs	Mechanism	Method of Administration
Beta blockers		
Timolol, others	Decreased secretion of aqueous humor from the ciliary epithelium	Topical drops
Prostaglandins		
Latanoprost, others	Increased aqueous outflow	Topical drops
Cholinomimetics		
Pilocarpine, physostigmine	Ciliary muscle contraction, opening of trabecular meshwork, increased outflow	Topical drops or gel, plastic film slow-release insert
Alpha agonists		
Nonselective: epinephrine	Increased outflow via uveoscleral veins	Topical drops (obsolete)
Alpha$_2$-selective agonists		
Apraclonidine, brimonidine	Decreased aqueous secretion	Topical drops
Carbonic anhydrase inhibitors		
Acetazolamide, dorzolamide	Decreased aqueous secretion due to lack of HCO_3^-	Oral (acetazolamide) or topical (others)
Osmotic agents		
Mannitol	Removal of water from eye	IV (for acute closed-angle glaucoma)