Al-Mustaqbal University

Pharmacology I

3rd stage

Adrenergic Antagonists (92- 105)

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Adrenergic Antagonists

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor mediated intracellular effects.

Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system.

α -Adrenergic Blocking Agents

α-Adrenergic blocking agents antagonize α -adrenergic receptors (α_1 or α_2). Blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This lowered blood pressure induces reflex tachycardia.

I- Phenoxybenzamine is a nonselective, noncompetitive (irreversible) blocker of α_1 and α_2 -adrenergic receptors.

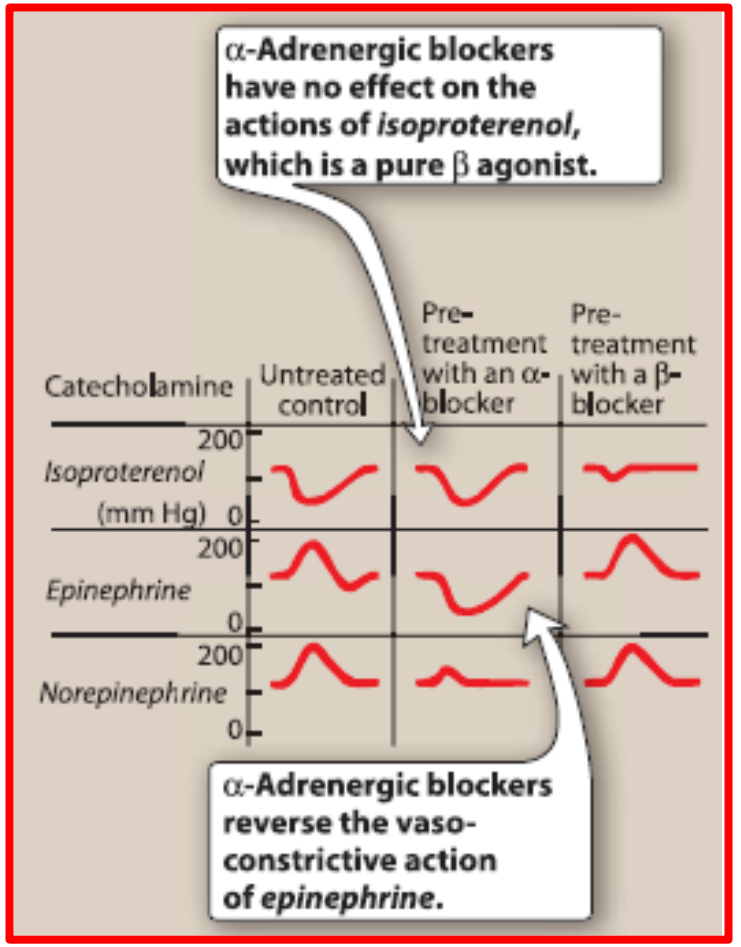
1. Actions (last 24 hours until new receptors synthesis) why?

a- Cardiovascular effects: The drug decreases peripheral resistance and resultant reflex tachycardia.

Blocking presynaptic α_2 (causes an increase in the release of norepinephrine, which in turn increases heart rate and cardiac output (mediated by β_1 receptors). This may lead to cardiac arrhythmias and anginal pain. Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.

b- Epinephrine reversal: The vasoconstrictive action of epinephrine is interrupted by α -adrenergic blockers, but vasodilation of other vascular beds caused by stimulation of β_2 receptors is not blocked.

[Note: The actions of norepinephrine are not reversed but are diminished because norepinephrine lacks significant β agonist action on the vasculature.] Phenoxybenzamine has no effect on the actions of isoproterenol, which is a pure β agonist



Therapeutic uses: 1- Treatment of sweating and hypertension associated with pheochromocytoma. 2- Treating Raynaud disease and frostbite.

Adverse effects: postural hypotension, nasal stuffiness, nausea, and vomiting. Inhibit ejaculation, reflex tachycardia.

II- Phentolamine produces a competitive block of α_1 and α_2 receptors. Effects last for 4 hours after a single injection.
Pharmacological effects of phentolamine are very similar to those of phenoxybenzamine.

Therapeutic uses:
1- for the diagnosis and short-term management of pheochromocytoma.
2- used locally to prevent dermal necrosis following extravasation of norepinephrine.
3- Phentolamine is useful to treat hypertensive crisis due to abrupt withdrawal of clonidine or ingestion of tyramine containing foods in patients taking monoamine oxidase inhibitors.

III- Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

Prazosin, terazosin , and doxazosin are selective competitive blockers of the α_1 receptor.

Tamsulosin and alfuzosin are examples of other selective α_1 antagonists indicated for the treatment of benign prostatic hyperplasia.

Metabolism: doxazosin is excreted in feces while others are excreated in urine. Doxazosin is the longest acting of these drugs.

1. Mechanism of action: These agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle (α_1 antagonists) .

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 α_{1B} receptors found in the blood vessels and more selective for α_{1A} receptors in the prostate and bladder. Blockade of the α_{1A} receptors a decrease tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

Therapeutic uses: Treatment of hypertension [but not used as monotherapy].

Adverse effects: dizziness, a lack of energy, nasal congestion, headache, drowsiness, sexual dysfunction, and floppy iris syndrome.

orthostatic hypotension: “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.

V- Yohimbine is a selective competitive α_2-blocker that works at the level of the CNS to increase sympathetic outflow to the periphery.

It is found as a component of the bark of the yohimbe tree and has been used as a sexual stimulant and in the treatment of erectile dysfunction.

Its use in the treatment of these disorders is not recommended due to lack of demonstrated efficacy.

β-Adrenergic Blocking Agents

All of the clinically available β-blockers are competitive antagonists. Although all β-blockers lower blood pressure, they do not induce postural hypotension.
The names of all β-blockers end in "-olol" except for labetalol and carvedilol.

I. Propranolol: is the prototype β -adrenergic antagonist and a nonselective β antagonist blocks both β_1 and β_2 receptors with equal affinity.

Nonselective β -blockers, including propranolol, can block the actions of isoproterenol (β_1 and β_2 agonist) on the cardiovascular system.

I. Propranolol: [proe-PRAN-oh-lole]

In the presence of a nonselective β-blocker, epinephrine no longer lowers diastolic blood pressure or stimulates the heart. But the actions of norepinephrine (α agonist) are mostly unaffected.

1. Actions

a. Cardiovascular: Propranolol diminishes cardiac output, having both negative inotropic (reduce cardiac output) and chronotropic (bradycardia) effects.

Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina.

It directly depresses sinoatrial and atrioventricular nodal activity.

The β-blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).

The resulting bradycardia usually limits the dose of the drug.

During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate.

Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina.

b. Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β_2 -mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance.
But the long use of propranolol lead to gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

c. Bronchoconstriction: Blocking β_2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle.
β-blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.

d. Disturbances in glucose metabolism: β-Blockade leads to decreased glycogenolysis and decreased glucagon secretion.
β-Blocker may cause pronounced hypoglycemia may occur after insulin injection. β-blockers also attenuate the normal physiologic response to hypoglycemia. So careful monitoring of blood glucose is essential

Therapeutic uses

a. Hypertension: Antihypertensive by different mechanisms of action.

- ❖ Decreased cardiac output is the primary mechanism.
- ❖ Inhibition of renin release from the kidney.
- ❖ Decrease in total peripheral resistance with long-term use, and
- ❖ decreased sympathetic outflow from the CNS.

b. Angina pectoris: Propranolol decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain

c. Myocardial infarction: Propranolol and other β-blockers have a protective effect on the myocardium against a second heart attack

d. Migraine: due to Propranolol lipophilic nature, it is effective in reducing migraine episodes when used prophylactically. (by blunting the widespread sympathetic stimulation).

e. Hyperthyroidism: In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

Pharmacokinetics:

- Good GIT absorption.
- It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation.
- The volume of distribution is quite large (4 L/kg).
- It readily crosses the blood-brain barrier due to its high lipophilicity.
- It is excreted in the urine.

Adverse effects

a. Bronchoconstriction, due to blockade of β_2 receptors. Therefore, propranolol is contraindicated in patients with COPD or asthma.

b. Arrhythmias: The β-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor.

c. Sexual impairment: (reasons for this are not clear).

d. CNS effects: depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, nightmares.
Fewer CNS effects may be seen with more hydrophilic β-blockers (for example, atenolol because they do not cross the blood-brain barrier as readily.

e. Metabolic disturbances:

β-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur.
In addition, β -blockers hidden symptoms of hypoglycemia such as tremor, tachycardia, and nervousness.

Non-selective β –blockers inhibit lipolysis of β_2 & β_3.
increased low density lipoprotein (“bad” cholesterol), increased triglycerides, and reduced high-density lipoprotein (“good” cholesterol).

II- Nadolol and timolol are nonselective β_1 and β_2- antagonists, and more potent than propranolol. Nadolol has a very long duration of action.

Chronic management of glaucoma : β-Blockers "timolol, carteolol and betaxolol are topically applied, effective in diminishing intraocular pressure in glaucoma by decreasing the secretion of aqueous humor by the ciliary body.

Unlike the cholinergic drugs, these agents neither affect the ability of the eye to focus for near vision nor change pupil size.

When administered intraocularly, the onset is about 30 minutes, and the effects last for 12 to 24 hours.
In an acute attack of glaucoma, pilocarpine is still the drug of choice for emergency lowering of intraocular pressure.

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, metipranolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide,* and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: selective β_1 antagonists' drugs that preferentially block the β_1 receptors minimize the unwanted bronchoconstriction (β_2 effect) seen with use of nonselective agents in asthma patients.

Cardioselective β-blockers, such as acebutolol, atenolol, and metoprolol antagonize β_1 receptors at doses 50- to 100-fold less than those required to block β_2 receptors.

This cardioselectivity is most pronounced at low doses and is lost at high doses. [Note: Because β_1 selectivity of these agents is lost at high doses, they may antagonize β_2 receptors.]

Actions: These drugs lower blood pressure in hypertension and increase exercise tolerance in angina.

Nebivolol releases nitric oxide from endothelial cells and causes vasodilation.

In contrast to propranolol, the cardioselective β-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism.

Nevertheless, asthma patients treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised.

Because these drugs have less effect on peripheral vascular β_2 receptors, coldness of extremities (Raynaud phenomenon), a common side effect of β-blockers, is less frequent.

Therapeutic uses:

1- hypertensive patients with impaired pulmonary function.

2- first-line therapy for chronic stable angina.

3- Bisoprolol and the extended-release formulation of metoprolol are indicated for the management of chronic heart failure.

4- Esmolol has a very short half-life and only available intravenously and is used to control blood pressure or heart rhythm in critically ill patients and those undergoing surgery or diagnostic procedures.

D. Acebutolol and pindolol: antagonists with partial agonist activity

1. Actions

a. Cardiovascular: Acebutolol (β_1 -selective antagonist) and pindolol (nonselective β-blocker) are not pure antagonists.

These drugs can also weakly stimulate both β_1 and β_2 receptors and are said to have intrinsic sympathomimetic activity (ISA).

These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous epinephrine and norepinephrine. The result of these opposing actions is a diminished effect on reduction of cardiac rate and cardiac output compared to that of β-blockers without ISA.

b. Decreased metabolic effects: β-Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other β-blockers. For example, these agents do not decrease plasma HDL levels.

Therapeutic use: β-Blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs.

[Note: β-blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect.]

E. Labetalol and carvedilol: antagonists of both α- and β-adrenoceptors

1. Actions: Labetalol and carvedilol
are nonselective β-blockers with concurrent α_1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure.

They contrast with the other β-blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable.

Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

Therapeutic use in (hypertension and heart failure):
Labetalol is used
- in the treatment of pregnancy-induced hypertension, as an alternative to methyldopa.
Intravenous labetalol is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure.
In general, β-Blockers should not be given to heart failure patients.
However, carvedilol as well as metoprolol and bisoprolol are beneficial in patients with stable chronic heart failure.
These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time.

Adverse effects: Orthostatic hypotension and dizziness are associated with α_1-blockade.

Drugs Affecting Neurotransmitter Release or Uptake

Reserpine a plant alkaloid, blocks the Mg^{2+} /adenosine triphosphate dependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues.

This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine.

Reserpine has a slow onset, a long duration of action, and effects that persist for many days after discontinuation.

Uses:

- Hypertension
- Agitated psychotic states such as schizophrenia to relieve symptoms.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction Atrial fibrillation
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension

References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.

Thank you