DRUGS THAT ACT IN THE ANS

β-Adrenergic Antagonists

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β-ADRENERGIC BLOCKING AGENTS

All of the clinically available β-blockers are **competitive antagonists**.

Nonselective β-blockers act at both β1 and β2 receptors, whereas **cardioselective β antagonists** primarily block β1 receptors.

These drugs also differ in intrinsic sympathomimetic activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics.

Although all β-blockers lower blood pressure, they **do not induce postural hypotension**. Therefore, normal sympathetic control of the vasculature is maintained.

β-ADRENERGIC BLOCKING AGENTS

β-Blockers are effective in treating hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma.

They are also used for the prophylaxis of **migraine** headaches.

[Note: The names of all β-blockers end in "-**olol**" except for **labetalol and carvedilol**.]

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol:

A nonselective β antagonist

Propranolol is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors with equal affinity.

Sustained release preparations for once-a-day dosing are available.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol:

1. Actions:

a. Cardiovascular: Propranolol diminishes cardiac output, having both **negative inotropic and chronotropic** effects.

It directly depresses **sinoatrial and atrioventricular** nodal activity. 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.

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

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol:

1. Actions:

b. Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β2-mediated vasodilation in skeletal muscles, **increasing peripheral vascular resistance**.

The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery.

In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of propranolol.

There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol:

1. Actions:

c. Bronchoconstriction: Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle.

This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (**COPD**) or **asthma**.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol:

1. Actions:

d. Disturbances in glucose metabolism: β blockade leads to **decreased glycogenolysis** and **decreased glucagon** secretion.

β-blockers also attenuate the normal physiologic response to hypoglycemia.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol:

1. Actions:

e. Blocked action of isoproterenol: Nonselective β-blockers, including propranolol, have the ability to block the actions of **isoproterenol (β1, β2 agonist)** on the cardiovascular system.

Thus, in the presence of a β-blocker, isoproterenol does not produce cardiac stimulation (β1 mediated) or reductions in mean arterial pressure and diastolic pressure (β2 mediated).

The actions of norepinephrine on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.]

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 2. Therapeutic uses:

a. Hypertension: Propranolol does not reduce blood pressure in people with normal blood pressure.

Propranolol lowers blood pressure in hypertension by several different mechanisms of action.

Decreased cardiac output is the primary mechanism, but **inhibition of renin release** from the kidney, decrease in total **peripheral resistance** with long-term use, and decreased **sympathetic** outflow from the CNS also contribute to the antihypertensive effects.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 2. Therapeutic uses:

b. Angina pectoris: Propranolol decreases the **oxygen requirement** of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina.

Propranolol is, thus, useful in the chronic management of stable angina.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 2. Therapeutic uses:

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

Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β-blockers.

In addition, administration of a β-blocker immediately following a myocardial infarction reduces infarct size and hastens recovery.

The mechanism for these effects may be a **blocking of the actions of circulating catecholamines**, which would increase the oxygen demand in an already ischemic heart muscle.

Propranolol also reduces the incidence of sudden arrhythmic death after myocardial infarction.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 2. Therapeutic uses:

d. Migraine: Propranolol is effective in reducing migraine episodes when used **prophylactically**.

It is one of the more useful β-blockers for this indication, due to its **lipophilic** nature that allows it to penetrate the CNS.

[Note: For the acute management of migraine, serotonin agonists such as sumatriptan are used, as well as other drugs.]

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 2. Therapeutic uses:

e. Hyperthyroidism: Propranolol and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 3. Pharmacokinetics:

After **oral** administration, propranolol is almost completely absorbed.

It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation.

The volume of distribution of propranolol is quite large (4 L/kg), and the drug readily crosses the **blood–brain barrier** due to its high **lipophilicity**.

Propranolol is extensively metabolized, and most metabolites are excreted in the urine.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 4. Adverse effects:

a. Bronchoconstriction: Propranolol has the potential to cause significant bronchoconstriction due to blockade of β2 receptors.

Therefore, propranolol is contraindicated in patients with COPD or asthma.

b. Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 4. Adverse effects:

c. Sexual impairment: Because ejaculation in the male is mediated through α-adrenergic activation, **β-blockers do not affect ejaculation** or internal bladder sphincter function.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 4. Adverse effects:

d. Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting **hypoglycemia** may occur.

In addition, β-blockers can prevent the counterregulatory effects of catecholamines during hypoglycemia.

Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β-blockers.

Lipases in fat cells are activated mainly by β2 and β3 receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 4. Adverse effects:

e. CNS effects: Propranolol has numerous CNS-mediated effects, including **depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression.**

Fewer CNS effects may be seen with more hydrophilic β-blockers (for example, atenolol), since they do not cross the blood–brain barrier as readily.

β-ADRENERGIC BLOCKING AGENTS/ A. Propranolol/ 4. Adverse effects:

f. Drug interactions: Drugs that interfere with, or inhibit, the metabolism of propranolol, such as cimetidine, fluoxetine, paroxetine, and ritonavir, may potentiate its antihypertensive effects.

Conversely, those that stimulate or induce its metabolism, such as barbiturates, phenytoin, and rifampin, can decrease its effects.

β-ADRENERGIC BLOCKING AGENTS/ B. Nadolol and timolol

Nonselective β antagonists

Nadolol and timolol also block β1- and β2-adrenoceptors and are **more potent than propranolol.**

Nadolol has a very long duration of action.

Timolol reduces the production of aqueous humor in the eye.

It is used topically in the treatment of chronic open-angle **glaucoma** and, occasionally, for systemic treatment of **hypertension**.

β-ADRENERGIC BLOCKING AGENTS/ B. Nadolol and timolol

1. Treatment of glaucoma: β-blockers, such as topically applied timolol, betaxolol, or carteolol, are effective in diminishing intraocular pressure in glaucoma.

This occurs 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.**

The β-blockers are only used for chronic management of glaucoma.

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).

β-ADRENERGIC BLOCKING AGENTS/ C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol:

Selective β1 antagonists

Drugs that preferentially block the β1 receptors **minimize the unwanted bronchoconstriction** (β2 effect) seen with propranolol use in asthma patients.

This cardioselectivity is most pronounced at low doses and is lost at high doses.

[Note: Since β1 selectivity of these agents is lost at high doses, they may antagonize β2 receptors.]

β-ADRENERGIC BLOCKING AGENTS/ C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol:

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

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.

In addition to its cardioselective β blockade, nebivolol releases nitric oxide from endothelial cells and causes vasodilation.

β-ADRENERGIC BLOCKING AGENTS/ C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol:

2. Therapeutic uses: The cardioselective β-blockers are useful in **hypertensive** patients with impaired pulmonary function.

These agents are also first-line therapy for **chronic stable angina**.

Because these drugs have less effect on peripheral vascular β2 receptors, coldness of extremities (Raynaud phenomenon), a common side effect of β-blockers, is less frequent.

β-ADRENERGIC BLOCKING AGENTS/ Labetalol and carvedilol:

Antagonists of both α and β adrenoceptors

1. Actions: Labetalol and carvedilol are nonselective β-blockers with concurrent α1-blocking actions that produce **peripheral vasodilation**, thereby reducing blood pressure.

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

β-ADRENERGIC BLOCKING AGENTS/ Labetalol and carvedilol:

2. Therapeutic use in hypertension and heart failure: Labetalol is employed as an alternative to methyldopa in the treatment of **pregnancy-induced hypertension**.

Intravenous labetalol is also used to treat **hypertensive emergencies**, because it can rapidly lower blood pressure.

β-blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition.

However, carvedilol as well as metoprolol and bisoprolol are beneficial in patients with stable chronic heart failure.

β-ADRENERGIC BLOCKING AGENTS/ Labetalol and carvedilol:

3. Adverse effects: Orthostatic hypotension and dizziness are associated with α1 blockade.

β-ADRENERGIC BLOCKING AGENTS/ Labetalol and carvedilol:

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
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension

DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the neurotransmitter into the adrenergic neuron.

However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically.

Reserpine is one of the remaining agents in this category.

Reserpine, a plant alkaloid, blocks the Mg2+/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**.

DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

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.

It has been used for the management of hypertension but has largely been replaced with newer agents with better side effect profiles and fewer drug interactions.