PCO 353 (REVISED EDITION)

ADRENOCEPTOR ANTAGONISTS OR BLOCKERS

Adrenoceptor antagonists or blockers antagonize the effects of adrenergic agonists by preventing the interaction of adrenergic agonists with their receptors (adrenoceptors).

Classification of adrenoceptor antagonists

Base on site and mechanism of action they can be classified as **α-**adrenoceptor antagonists or blockers and **β**- adrenoceptor antagonists or blockers.

α- Adrenoceptor antagonists

They inhibit the actions of adrenergic agonists such as epinephrine and norepinephrine at **α-** adrenoceptors.

Classification of α- adrenoceptor antagonists

a. Non selective **α-** adrenoceptor antagonists
- Haloalkylamine e.g. phenoxybenzamine
- Imidazoline e.g. phentolamine

b. **α_1-** selective adrenoceptor antagonists e.g. prazosin, doxazosin

c. **α_2-** selective adrenoceptor antagonists e.g. yohimbine, idazoxin

d. Mixed **α** and **β** adrenoceptor antagonists e.g. labetalol, carvedilol

e. Ergotamine derivatives e.g. ergotamine, dihydroergotamine

α_1- Selective adrenoceptor antagonists

They inhibit the activities of adrenergic agonists at **α_1-**adrenoceptor. They decrease blood pressure without producing reflex tachycardia due to the non-stimulation of norepinephrine (adrenaline) release from sympathetic nerve terminals.

α_2- Selective adrenoceptor antagonists

They are highly selective for **α_2**-adrenoceptor. They block the activities of adrenergic agonists at **α_2**-adrenoceptor. The blockade of **α_2**-adrenoceptor especially in blood vessels causes vasodilation and decreases blood pressure. The sparing of **α_1**-adrenoceptor may stimulate norepinephrine release causing tachycardia.

Mixed α and β- adrenoceptor antagonists

The drugs in this class block the activities of adrenergic agonists at both **α** and **β**-adrenoceptors.

Therapeutic uses of α-adrenoceptor antagonists

Hypertension: **α_1-** selective adrenoceptor antagonists e.g. prazosin, doxazosin and terazosin are used for the treatment of hypertension. They may cause postural or orthostatic hypotension on standing.

Pheochromocytoma: Phentolamine is used for the diagnosis of Pheochromocytoma. It is removed with the aid of surgery, but **α** and **β** adrenoceptors are usually blocked with phenoxybenzamine and atenolol or mixed **α** and **β**-adrenoceptor antagonists (labetalol and carvedilol).

Raynaud's syndrome: **α_1-** selective adrenoceptor antagonists e.g. doxazosin and prazosin are used to counteract the effect of norepinephrine, which constricts blood vessels.

Adverse effects of α- adrenoceptor antagonists

Tachycardia, cardiac arrhythmia, postural hypotension, ejaculation failure, sedation, dizziness, diarrhea, nausea and vomiting.

β- Adrenoceptor antagonists or blockers.

β-Adrenoceptor antagonists or blockers (BAAs) antagonize the effects of catecholamine (adrenergic agonists) at **β-**adrenoceptors. Most clinically used BAAs are pure antagonists. They occupy without activating adrenoceptors. Some are partial agonists, they occupy and partially activate adrenoceptors.

Classification of β- adrenoceptor antagonists

BAAs are classified based on their degree of selectivity for **β**-adrenoceptors

Classification of β- adrenoceptor antagonists

a. Non selective **β-**adrenoceptor antagonists e.g. propranolol, nadolol, pindolol
b. **β_1-**selective adrenoceptor antagonists e.g. atenolol, esmolol, betaxolol, acebutalol.
c. **β_2-** selective adrenoceptor antagonists e.g. butoxamine

Pharmacokinetics of β - adrenoceptor antagonists

BAAs are well absorbed after oral administration with peak plasma concentration occurring between 1-3hrs. The bioavailability of BAAs depend on their first pass effects. Propranolol has a low bioavailability due to extensive hepatic metabolism. BAAs have large volume of distribution. Propranolol and penbutolol are lipophilic hence cross the blood brain barrier. Most BAAs have half-lives of 3-10 hrs. Nadolol has the longest half-life and is excreted unchanged. Most BAAs are metabolized by the liver.

Pharmacodynamics of β- adrenoceptor antagonists

BAAs produce effects due to occupancy or blockade of **β-**adrenoceptors.

Pharmacological effects of β- adrenoceptor antagonists

Cardiovascular system: BAAs decrease blood pressure due to effects on the heart, blood vessels and the suppression of renin-angiotensin system.

Heart: BAAs cause negative inotropic and chronotropic effects.

Respiratory system: BAAs can block β_2-adrenoceptors in bronchial smooth muscles thereby increasing airway resistance (bronchoconstriction). They are contraindicated in asthma.

Eye: BAAs reduce intraocular pressure especially in glaucoma. They are used to decrease aqueous humor production.

Metabolic and endocrine effects: BAAs inhibit sympathetic nervous system. Chronic use of BAAs can increase the serum levels of very low density lipoprotein and decrease high density lipoprotein which are benefactors of cardiovascular disorder.

Other effects of BAAs: BAAs have local anesthetic effects (membrane stabilizing effect) due to blockade of sodium channels.

Uses of β- adrenoceptor antagonists

a. Hypertension: BAAs are used for the treatment of hypertension e.g. atenolol, propranolol.
b. Ischemic heart disease: BAAs reduce the frequency of angina attack and improve exercise tolerance in patient with angina.

c. Cardiac arrhythmia: BAAs are effective in supraventricular and ventricular arrhythmia.
d. Glaucoma: BAAs are used to reduce intraocular pressure in patients with glaucoma.
e. Hyperthyroidism: BAAs are used to reduce catecholamine activities in hyperthyroidism. BAAs inhibit the conversion of thyroxine to triidothyronine. Propranolol is used in severe hyperthyroidism.
f. Neurological disease: BAAs reduce the frequency and intensity of migraine headache. E.g. propranolol is used for migraine headache.

Adrenergic neuron blockers

Adrenergic neuron blockers (ANBs) block or inhibit the release of noradrenaline from sympathetic nerve endings. ANBs selectively block sympathetic tone by preventing the release or depletion of noradrenaline store in adrenergic nerve endings. E.g. guanethidine, bretylium, debrisoguine, guanoxan and bethanidine

Pharmacodynamics of adrenergic neuron blockers

ANBs are selectively accumulated by nerve terminals. Guanethidine is stored by synaptic vesicles (displacing noradrenaline) and is released by nerve stimulation as a false transmitter. ANBs have local anesthetic effect and impair impulse conduction in adrenergic nerve terminals.

Pharmacokinetics of adrenergic neuron blockers (Guanethidine)

Guanethidine is well absorbed when given orally. Its pharmacological effects develop shortly and reach maximum within 2-3 weeks. It is excreted by the kidney unchanged. Therapy can start with an initial dose of 10mg/day which can be increased at weekly interval until the desired response is achieved.

Pharmacological effects of guanethidine

Hypotension: It causes postural hypotension. Fall in blood pressure is intensive when a patient is in an upright position.

Tolerance: It develops early with the use of guanethidine hence dose should be increased slowly.

Other effects of guanathidine: It increases gastrointestinal tract motility. Large doses can cause diarrhea. It delays or prevents ejaculation. It causes serve decrease in intraocular pressure.

Therapeutic uses of adrenergic neuron blockers

a. Ventricular arrhythmia: Bretylium is used for ventricular arrhythmia resistance to other drugs.
b. Severe hypertension: Guanethidine is used for the treatment of severe hypertension.

Adverse effects of adrenergic neuron blockers

Postural hypotension, nasal congestion, diarrhea and ejaculation failure.