Drugs acting on the sympathetic nervous system

Dr.A.A. Nekooeian
Full Professor
Department of Pharmacology
Medical School
Shiraz University of Medical Sciences
Email: nekooian@yahoo.com

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Learning objectives:

- Explain mechanism of action of sympathomimetic drugs and adrenergic antagonists.
- Describe organ system effects of sympathomimetic drugs and adrenergic antagonists.
- Name clinical indications of sympathomimetic drugs and adrenergic antagonists.
- Describe adverse effects of sympathomimetic drugs and adrenergic antagonists.

Drugs that mimic the actions of epinephrine or norepinephrine have traditionally been termed

sympathomimetic drugs. The sympathomimetics can be grouped by mode of action, and by the spectrum of receptors that they activate. Some of these drugs are *direct* agonists; that is, they directly interact with and activate adrenoceptors. Others are *indirect* agonists, and may have either of two different mechanisms: (1) they may displace stored catecholamines from the adrenergic nerve ending, or they may decrease the clearance of released norepinephrine either by (2a) inhibiting reuptake of catecholamines already released, or (2b) preventing the enzymatic metabolism of norepinephrine. Some drugs have both direct and indirect actions.

Organ system effects of sympathomimetic drugs

Cardiovascular system In the heart sympathomimetic drugs increase heart rate and contractility, and atrioventricular conduction. These effects are mainly mediated by beta1 receptor; however, beta 2 receptors are also involved to a little extent. These drugs cause both constriction and dilation of blood vessels. The constriction is mediated mainly by alpha1 receptors, but alpha2 receptors are also involved to some extent. The dilation of vessels is mediated by beta2 receptors. Moreover, these drugs do cause vasodilation and decreased blood pressure by stimulation of alpha2 receptors in the central nervous system.

Eye- In the eye, the pupillary dilator (radial) muscle of the iris contains α1 receptors; activation by sympathmimetic drugs causes the muscle contraction and mydriasis. Alpha2 agonists increase the outflow of aqueous humor from the eye and can be used clinically to reduce intraocular pressure.

Respiratory system sympathomimetic drugs relax bronchial smooth muscle via activation of bronchial smooth muscle beta2 receptors. They also constrict upper respiratory vessels by activating alpha1 receptors.

Gastrointestinal drugs In the GI sympathomimetic drugs relax wall smooth muscle. The relaxation is the result of stimulation of alpha2 receptors, which both directly and by inhibiting the release of acetylcholine.

Uterine smooth muscle Sympathomimetic drugs cause both contraction and relaxation of uterine smooth muscle by activation alpha1 and beta2 receptors, respectively.

Urinary tract Sympathomimetic drugs cause relaxation of bladder wall, and contraction of bladder sphincter and prostate smooth muscle. These effects are respectively accomplished by activating beta2 and alpha1 receptors.

Metabolic effects Sympathomimetic drugs have important effects on intermediary metabolism. Activation of β adrenoceptors in fat cells leads to increased lipolysis with enhanced release of free fatty acids and glycerol into the blood. Human fat cells also contain α2 receptors that inhibit lipolysis by decreasing intracellular cAMP. Sympathomimetic drugs enhance glycogenolysis and gluconeogenesis in the liver, which leads to increased glucose release into the circulation. In the human liver, the effects of catecholamines are probably mediated mainly by β receptors, though α1 receptors may also play a role.

Endocrine glands Sympathomimetic drugs increase insulin secretion by stimulating β2 receptors on pancreatic cells. However, they also decrease insulin secretion by inhibiting α2 receptors on such cells. Similarly, sympathomimetics increase renin secretion stimulating β1 on juxtaglumerular cell. They also inhibit rennin secretion by inhibiting α2 receptors.

Apocrine (stress) sweat glands The apocrine sweat glands, located on the palms of the hands and a few other areas, are nonthermoregulatory glands that respond to psychological stress and adrenoceptor stimulation with increased sweat production. This effect is mediated by Alpha1 receptors.

Salivary glands Sympathomimetic drugs with alpha2 agonist activity produce symptoms of dry mouth likely through a CNS effect.

Central nervous system The CNS effects of sympathomimetics have been described as ranging from "nervousness" to "an adrenaline rush" or "a feeling of impending disaster. In contrast, noncatecholamines with indirect actions, such as amphetamines, which readily enter the CNS from the circulation, produce qualitatively very different effects on the nervous system. These actions vary from mild alerting, with improved attention to boring tasks; through elevation of mood, insomnia, euphoria, and anorexia; to full-blown psychotic behavior. These effects are not readily assigned to either α- or β-mediated actions and may represent enhancement of dopamine-mediated processes or other effects of these drugs in the CNS.

Specific sympathomimetics

Epinephrine (adrenaline) is an agonist at both α (α1 and α2) and β (β1 and β2) receptors.

Norepinephrine (noradrenaline) is an agonist at both α1, α2, and B1 receptors.

Dopamine is agonist at D1, B1 and α1 receptors.

Phenylephrine is α1 agonist.

Midodrine is a prodrug that is enzymatically hydrolyzed to desglymidodrine, a selective α1-receptor agonist.

Clonidine, methyldopa, and tizanidine are alpha2-selective agonists

Oxymetazoline is a agonist of α2A receptors

Isoproterenol (isoprenaline) is an agonist of β (β1 and β2) receptors

Dobutamine is β1-selective agonist, and a α1 agonist and antagonist

Ephedrine is an α1 agonist and a releaser

Amphetamine and methamphetamine are releasers

Fenoldopam is a D1-receptor agonist

Clinical uses of sympathomimetics

Treatment of acute hypotension: Acute hypotension may occur in a variety of settings such as severe hemorrhage, decreased blood volume, cardiac arrhythmias, neurologic disease or accidents, adverse reactions or overdose of medications such as antihypertensive drugs, and infection. If cerebral, renal, and cardiac perfusion is maintained, hypotension itself does not usually require vigorous direct treatment. Rather, placing the patient in the recumbent position and ensuring adequate fluid volume while the primary problem is determined and treated is usually the correct course of action. The use of sympathomimetic drugs merely to elevate a blood pressure that is not an immediate threat to the patient may increase morbidity. On the other hand, sympathomimetics may be required in cases of sustained hypotension with evidence of tissue hypoperfusion.

Shock Norpeinephrine and phenylephrine are used

Chronic Orthostatic Hypotension: On standing, gravitational forces induce venous pooling, resulting in decreased venous return. Normally, a decrease in blood pressure is prevented by reflex sympathetic activation with increased heart rate, and peripheral arterial and venous vasoconstriction. Impairment of autonomic reflexes that regulate blood pressure can lead to chronic orthostatic hypotension. This is more often due to medications that can interfere with autonomic function (eg, imipiramine and other tricyclic antidepressants, a blockers for the treatment of urinary retention, and diuretics), diabetes, and other diseases causing peripheral autonomic neuropathies, and less commonly, primary degenerative disorders of the autonomic

nervous system. Increasing peripheral resistance is one of the strategies to treat chronic orthostatic hypotension, and drugs activating α receptors can be used for this purpose. Midodrine, an orally active α1 agonist, is frequently used for this indication.

Cardiac applications: Epinephrine is used during resuscitation from cardiac arrest. Current evidence indicates that it improves the chance of returning to spontaneous circulation, but it is less clear that it improves survival or long-term neurologic outcomes.

Dobutamine is used as a pharmacologic cardiac stress test. Dobutamine augments myocardial contractility and promotes coronary and systemic vasodilation. These actions lead to increased heart rate and increased myocardial work and can reveal areas of ischemia in the myocardium that are detected by echocardiogram or nuclear medicine techniques.

Inducing local vasoconstriction: Combining α agonists with some local anesthetics greatly prolongs the duration of infiltration nerve block; the total dose of local anesthetic can therefore be reduced. Epinephrine, 1:200,000, is the favored agent for this application.

Mucous membrane decongestants are α agonists that reduce the discomfort of allergic rhinitis and, to a lesser extent, the common cold by decreasing the volume of the nasal mucosa. These effects are probably mediated by α1 receptors. Phenylephrine and or the longer-acting oxymetazoline are often used in over-the-counter nasal decongestants.

Pulmonary applications; Beta2-selective drugs (albuterol, terbutaline) are used for asthma and COPD.

Anaphylactic shock is treated with epinephrine.

Ophthalmic applications; Phenylephrine is an effective mydriatic agent. Phenylephrine is used as decongestant. Apraclonidine and brimonidine are α2-selective agonists and used for glaucoma.

Premature labor: β2-selective agents Ritodrine and terbutaline are used

Narcolepsy and attention deficit hyperactivity disorder: methylphenidate is used.

Hypertension: methyldopa is used.

Diarrhea in diabetic patients with autonomic neuropathy; clonidine is used perhaps because of its ability to enhance salt and water absorption from the intestine.

Narcotics and alcohol rehabilitation; clonidine has efficacy in diminishing craving for these substances and reduce opioid requirements

Muscle relaxant; tizanidine is an α2 agonist that is used as muscle relaxant.

Adrenergic antagonists

Adrenergic antagonists are divided into two groups including alpha receptor antagonists and beta receptor antagonists

Alpha receptor antagonists

Mechanism of Action: Alpha-receptor antagonists reversible or irreversibly inhibit α1 and/or α2 receptors.

Pharmacologic effects

Cardiovascular Effects: α-receptor antagonist cause dilation of arteries and vein, and lowering of peripheral vascular resistance and blood pressure.

Other effects: Blockade of α receptors in other tissues elicits miosis and nasal stuffiness. Alpha antagonists also relax base of the bladder and the prostate smooth muscle, and decrease resistance to the flow of urine. They increase concentrations of high-density lipoproteins (HDL), the mechanism of which is not known.

Specific agents

Phenoxybenzamine binds covalently to α receptors, causing irreversible blockade. It is somewhat selective for α1 receptors but less so than prazosin. The drug also inhibits reuptake of released norepinephrine by presynaptic adrenergic nerve terminals. Phenoxybenzamine blocks histamine (H1), muscarinic, and serotonin receptors.

Phentolamine is a potent competitive antagonist at both α1and α2 receptors. Phentolamine reduces peripheral resistance through blockade of α1 receptors and possibly α2 receptors on vascular smooth muscle. Phentolamine also has minor inhibitory effects at serotonin receptors and agonist effects at muscarinic and H1 and H2 histamine receptors.

Prazosin is a competitive antagonist effective in the management of hypertension. It is highly selective for α1 receptors and typically 1000-fold less potent at α2 receptors. This may partially explain the relative absence of tachycardia seen with prazosin compared with that of phentolamine and phenoxybenzamine.

Terazosin is another reversible α1-selective antagonist (like prazosin).

Doxazosin differs from prazosin and terazosin in having a longer half-life (22 hours). Doxazosin has active metabolites, although their contribution to the drug's effects is probably small.

Tamsulosin has higher affinity for α1A and α1D receptors than for the α1B subtype. Evidence suggests that tamsulosin has relatively greater potency in inhibiting contraction in *prostate* smooth muscle versus *vascular* smooth muscle compared with other α1-selective antagonists.

Clinical uses of α antagonists

The clinical uses of α antagonists include hypertension, benign prostatic hyperplasia, pheochromocytoma, and hypertensive emergencies. They are not usually recommended as monotherapy for hypertension. Labetalol has been used for hypertensive emergencies. In theory, α-adrenoceptor antagonists are most useful when increased blood pressure reflects excess circulating concentrations of α agonists, eg, in pheochromocytoma, overdosage of sympathomimetic drugs, or clonidine withdrawal. However, other drugs are generally preferable, since considerable experience is necessary to use α-adrenoceptor antagonist drugs safely in these settings.

Alpha antagonists' adverse effects

Alpha antagonists' adverse effects include tachycardia, arrhythmias, myocardial ischemia, orthostatic hypotension, nasal stuffiness, inhibition of ejaculation. Tamsulosin causes intraoperative floppy iris syndrome (IFIS) in patients undergoing cataract surgery. This is characterized by the billowing of a flaccid iris, propensity for iris prolapse, and progressive intraoperative pupillary constriction.

Beta receptor antagonists

Mechanism of action: Beta-receptor antagonists competitively block β1, or β1 and β2 adrenergic receptors, and antagonize the effects of endogenous catecholamines at β adrenoceptors. Most β-blocking drugs in clinical use are pure antagonists. However, some are partial agonists; that is, they cause partial activation of the receptor, albeit less than that caused

by the full agonists epinephrine and isoproterenol. Partial agonists inhibit the activation of β receptors in the presence of high catecholamine concentrations but moderately activate the receptors in the absence of endogenous agonists. Finally, evidence suggests that some β blockers such as metoprolol are *inverse agonists*—drugs that reduce constitutive activity of β receptors—in some tissues.

Effects beta antagonists

Effects on the cardiovascular system: Beta-blocking drugs decrease heart rate and contractility, and AV conduction. They also decrease release of renin from the kidneys. In the vascular system, β-receptor blockade opposes β2-mediated vasodilation. Overall, although the acute effects of these drugs may include a rise in peripheral resistance, chronic drug administration leads to a fall in peripheral resistance in patients with hypertension.

Effects on the respiratory tract: Blockade of the β2 receptors in bronchial smooth muscle may lead to an increase in airway resistance, particularly in patients with asthma. Beta1-receptor antagonists such as metoprolol and atenolol may have some advantage over nonselective β antagonists when blockade of β1 receptors in the heart is desired and β2-receptor blockade is undesirable. However, no currently available β1-selective antagonist is sufficiently specific to *completely* avoid interactions with β2 adrenoceptors. Consequently, these drugs should generally be avoided in patients with asthma. On the other hand, some patients with chronic obstructive pulmonary disease (COPD) may tolerate β1-selective blockers and the benefits, for example in patients with concomitant ischemic heart disease, may outweigh the risks.

Effects on the eye: Beta-blocking agents reduce intraocular pressure, especially in glaucoma. The mechanism usually reported is decreased aqueous humor production.

Metabolic and Endocrine Effects: Beta-receptor antagonists such as propranolol inhibit sympathetic nervous system stimulation of lipolysis. Also, glycogenolysis in the human liver is at least partially inhibited after β2-receptor blockade. It is unclear to what extent β antagonists impair recovery from hypoglycemia, but they should be used with caution in insulin-dependent diabetic patients. Beta-receptor antagonists are much safer in those type 2 diabetic patients who do not have hypoglycemic episodes.

The chronic use of β-adrenoceptor antagonists has been associated with increased plasma concentrations of very-low-density lipoproteins (VLDL) and decreased concentrations of HDL cholesterol. Although low-density lipoprotein (LDL) concentrations generally do not change, there is a variable decline in the HDL cholesterol/LDL cholesterol ratio. These changes tend to occur with both selective and nonselective β blockers. The mechanisms by which β-receptor antagonists cause these changes are not understood.

Specific beta antagonists

Metoprolol and atenolol are β1-selective antagonists.

Timolol is nonselective β antagonist

Labetalol is a reversible alpha1 and beta unselective antagonist.

Carvedilol is a reversible alpha1 and beta unselective antagonist. It antagonizes the actions of catecholamines more potently at β receptors than at α1 receptors. Carvedilol also appears to attenuate oxygen free radical–initiated lipid peroxidation and to inhibit vascular smooth muscle mitogenesis independently of adrenoceptor blockade. These effects may contribute to the clinical benefits of the drug in chronic heart failure.

Esmolol is an ultra-short–acting β1-selective adrenoceptor antagonist. It is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis, perioperative hypertension, and myocardial ischemia in acutely ill patients.

Clinical uses of β-adrenoceptor–blocking drugs

Hypertension The β-adrenoceptor–blocking drugs have proved to be effective and well-tolerated in hypertension. Although many hypertensive patients respond to a β blocker used alone, the drug is often used with either a diuretic or a vasodilator.

Ischemic heart disease Beta-adrenoceptor blockers reduce the frequency of anginal episodes, and improve exercise tolerance in many patients with angina. These actions are due to blockade of cardiac β receptors, resulting in decreased cardiac work and reduction in oxygen demand. In addition, β-adrenoceptor antagonists are strongly indicated in the acute phase of a myocardial infarction.

Cardiac arrhythmias Beta antagonists are often effective in the treatment of supraventricular and ventricular arrhythmias. By increasing the atrioventricular nodal refractory period, β antagonists slow ventricular response rates in atrial flutter and fibrillation. These drugs can also reduce ventricular ectopic beats, particularly if the ectopic activity has been precipitated by catecholamines.

Heart failure Clinical trials have demonstrated that metoprolol and carvedilol are effective in reducing mortality in selected patients with chronic heart failure. Although administration of these drugs may worsen acute congestive heart failure, cautious long-term use with gradual dose increments in patients who tolerate them may prolong life.

Glaucoma The mechanism appears to involve reduced production of aqueous humor by the ciliary body, which is physiologically activated by cAMP.

Hyperthyroidism Sympathetic activity increases in excessive hyperthyroidism, especially in relation to the heart. Beta blockers reduce the effects of hypertyroidism on the heart. The effects presumably relate to blockade of adrenoceptors and perhaps in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine. Propranolol has been used extensively in patients with severe hyperthyroidism to control supraventricular tachycardias.

Performance anxiety ("stage fright") propranolol is used for this.

Neurologic Diseases Propranolol reduces the frequency and intensity of migraine headache. The mechanism is not known. Since sympathetic activity may enhance skeletal muscle tremor, it is not surprising that β antagonists have been found to reduce certain **tremors**.

Cirrohsis Beta-receptor antagonists have been found to diminish portal vein pressure in patients with cirrhosis. There is evidence that both propranolol and nadolol decrease the incidence of the first episode of bleeding from esophageal varices and decrease the mortality rate associated with bleeding in patients with cirrhosis.

Beta blockers adverse effects

Bradycardia is the most common adverse cardiac effect of β-blocking drugs. CNS effects include mild sedation, vivid dreams, and rarely, depression. Discontinuing the use of β blockers in any patient who develops psychiatric depression should be seriously considered if clinically feasible.

Beta2 receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting asthma and other forms of airway obstruction without having these consequences in normal individuals. While β1-selective drugs may have less effect on airways than nonselective β antagonists, they must be used very cautiously in patients with reactive

airway disease. Beta1-selective antagonists are generally well tolerated in patients with mild to moderate peripheral vascular disease, but caution is required in patients with severe peripheral vascular disease or vasospastic disorders. Beta-receptor blockade depresses myocardial contractility and excitability. In patients with abnormal myocardial function, cardiac output may be dependent on sympathetic drive. If this stimulus is removed by β blockade, cardiac decompensation may ensue. Sudden discontinuation of beta blockers can cause increased heart rate and angina in patients with ischemic heart disease. Also, it can cause rebound hypertension in patients with renovascular hypertension. The mechanism of this effect might involve up-regulation of the number of β receptors. Gradual tapering of beta antagonists use is recommended. Beta2 receptor antagonism prolongs hypoglycemic episodes in diabetics. Beta1-selective antagonists offer some advantage in these patients

Drug interaction

Beta blockers may interact with the calcium antagonist verapamil; severe hypotension, bradycardia, heart failure, and cardiac conduction abnormalities have all been described.

Contraindications

Contraindications to beta antagonists include bradycardia, hypotension, moderate or severe left ventricular failure, shock, heart block, and active airways disease.

Which of the following drugs can be used for glaucoma?

A) An alpha agonist

B) A Beta agonist

C) An alpha antagonist

D) A beta antagonist

E) A and D