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Pharmacology

Doctor 2018 | Medicine | JU

◉Sheet ○Slides

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❖ Adrenergic receptors (β1-selective antagonists):

- **Nebivolol:** The most highly selective β 1 blocker.
- Increases endothelial **NO release (vasodilating effect) antioxidant**, can protect the vascular wall from **free radicals** that damage blood vessels and thereby contribute to the progression of cardiovascular disease.
- Surprisingly β3-adrenergic receptors are found in cardiovascular tissues, and nebivolol can activate these receptors (partial agonist effect), these receptors resemble targets for therapeutic intervention **(protective mechanism against heart failure and myocardial ischemia).**
- **Bisoprolol:**
- A β-blocker with low lipid solubility.
- It has longer duration of action, one dose/day is enough to achieve the desired therapeutic effect
- Used to treat **hypertension, coronary heart disease, arrhythmias**.
- **Esmolol:**
- Ultra-short acting β1-selective blocker, this drug is given to hospitalized patients to achieve rapid onsets.
- Has a short half-life (about 10 minutes), because it contains an ester linkage that get hydrolyzed by a non-specific esterase in red blood cells which can rapidly metabolize this linkage.
- Given by continuous IV infusions.
- Esmolol may be **safer** in critically ill patients who require a β -adrenoceptor antagonist.
- Esmolol is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis (excess of thyroid hormone) and myocardial ischemia in acutely ill patients.

Some explanations:

supraventricular arrhythmias = irregular beats in the atria that can either be bradycardia or tachycardia.

-Why atrial arrythmias matter?

If the atria contract irregularly or fail to contract, blood will accumulate and pools in the atria, when blood has the opportunity to pool, it also has the opportunity to clot, if a blood clot forms in atria it can be pumped out of the heart to the brain causing a stroke. Also these irregularities might reach the ventricles and cause a more severe and fatal arrythmias (ventricular arrythmia), that is why it is so important to control these arrythmias.

❖ β Blockers with partial β-agonist activity:

- This partial activity is beneficial because it reduces the most common SE of β-blockers (bradycardia, bronchoconstriction in non-selective β-blockers, and abnormalities in plasma lipids).
- **Pindolol:**
- A non-selective **beta- adrenoceptor/ 5-HT1A** (serotonin//n autoreceptor) that modulate the release of serotonin, once activated it inhibits the release of serotonin by a negative feedback mechanism, if this receptor is blocked more serotonin would be released.
- If a depressed patient suffers from hypertension and takes pindolol it accelerates the antidepressant effect of selective serotonin reuptake inhibitors that are used to treat depression (synergistic effects).

- **Celiprolol:**
- A **β1-selective antagonist** with a **partial β2 -agonist activity** & may have less adverse bronchoconstrictor effect in asthma and may even **promote bronchodilation** (remember β2 blockers are troublemakers, β1-selective blockers are usually preferred to treat CVS issues).
- **Acebutolol** is a β1-selective antagonist.

❖ Drugs that block both alpha and beta receptors (non-selective adrenergic blockers):

- **Labetalol** Causes Hypotension with less tachycardia than occurs with α blockers.
- Very effective vasodilator that can decrease blood pressure by decreasing peripheral resistance with no effect on the heart rate (baroreceptor reflex cannot increase heart rate to restore BP through blocked β1receptors).
- It is a **partial agonist at beta2- receptors** (beneficial because it does not induce bronchoconstriction).
- **Carvedilol:**
- A nonselective **beta blocker/alpha-1 blocker**, calcium channel blocker (promotes vasodilation without observed baroreceptor reflex).
- More potent at β than at α1 receptors
- Antioxidant property (protects blood vessels from free radicals).
- Used to treat: Hypertension, Angina, congestive heart failure.

❖ Clinical Uses of the Beta-Receptor–Blockers:

- **Hypertension:**
- Could be used alone, but often used with either a **diuretic** or a **vasodilator (If the blocker is not effective by its own)**.
  Why?

Vasodilators:	**Diuretic:**
Dilate blood vessels preventing smooth muscles of these BV from tightening and narrowing. As a result, blood flows more easily through vessels. Heart does not have to pump as hard, reducing blood pressure.	Most of drugs that treat hypertension decrease cardiac output. As a result, less blood will reach the kidneys and urination is decreased in these patients, this will cause accumulation of fluids that would elevate BP by increasing blood volume. Prescribing diuretics would solve this problem by removing excess salt and water from the body.

- In spite of the **short half-life** of many β antagonists, these drugs **may be administered once or twice daily and still have an adequate therapeutic effect.**
- May be less effective in the **elderly** and in individuals of **African ancestry.**
- **Ischemic Heart Disease (IHD):**
- Adequacy of coronary blood flow is relative to the heart's O2 demands at any given moment. In the normal heart, coronary blood flow increases correspondingly as O2 demands rise. With coronary artery disease or (IHD), coronary blood flow may not be able to keep pace with rising O2 needs.
- β-blockers decrease heart rate and the force of contraction in the heart, as a result they reduce the demand of the heart muscle for oxygen, that is why they are useful in treating IHD when oxygen demand exceeds the supply (during exercise).

- Decrease cardiac work & reduce oxygen demand.
- Slow heart rate may contribute to clinical benefits (lower oxygen demand).

- The long-term use of timolol, propranolol, or metoprolol in patients who have had a myocardial infarction prolongs survival.
- β-blockers are strongly indicated in the acute phase of a myocardial infarction.
- Contraindications include bradycardia, hypotension, moderate or severe left ventricular failure, shock (sudden drop in blood flow through the body), heart block, and active airways disease.
- **Cardiac Arrhythmias:**

Antiarrhythmic drugs:
Class Ⅰ Na^+ channel blockers.
Class Ⅱ β-blockers
Class Ⅲ K^+ channel blockers.
Class Ⅳ Ca^{+2} channel blockers.
Class V Unknown mechanism

- **Class II antiarrhythmic drugs.**
- By **increasing the AV nodal refractory period**, β antagonists slow ventricular response rates in atrial **flutter** and **fibrillation**.

Atrial flutter: rapid but regular sequence of atrial depolarization but at high rates.
Atrial fibrillation: rapid but irregular uncoordinated depolarization of the atria (chaotic and asynchronized).

- They reduce ventricular ectopic beats (beats that arise from fibers outside the SA node, appear like an extra or missed beat), particularly if caused by catecholamines.
- Sotalol has a marked class III antiarrhythmic effects, due to potassium channel blockade (treats both ventricular & supraventricular arrhythmias).
- **Heart Failure (protective mechanism at low doses):**
- Clinical trials have demonstrated that at least three β antagonists, metoprolol, bisoprolol, 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.
- They have a beneficial effect on **myocardial remodeling** (heart muscle is thickened which makes it harder for the heart to pump blood), and decrease the risk of sudden death.

Heart Failure is characterized by β-adrenergic receptor (βAR) dysregulation that is primarily due to the upregulation of G protein–coupled receptor kinases that leads to **overdesensitization** of β1 and β2ARs, and this clinically manifests as a loss of **inotropic reserve**. The β3AR, found in the heart, lacks G protein– coupled receptor kinases recognition sites, and is not subject to desensitization.

• β3ARs can activate different signaling pathways that can protect the heart. The effects of β-blockers which are well known for their **cardioprotective effects**, are mediated, at least in part, by enhancement of β3AR activity.

Explanation:

When heart failure occurs, compensatory changes occur in the heart to preserve cardiac output, some of these changes are mediated by increased sympathetic activity, increased catecholamines outflow induces elevated activation of β-adrenergic receptors, this causes desensitization of β1 and β2 adrenergic receptors. Fortunately, β3 receptors are not subject to desensitization, some β-blockers have partial agonist effect on these receptors producing protective effects on the heart.

❖ Glaucoma:

- Systemic administration of β -blocking drugs can be for other indications, such as **reduced intraocular pressure in patients with glaucoma**. Topical administration also reduces intraocular pressure.
- The mechanism involves reduced production of aqueous humor by the ciliary body.
- Timolol and related β antagonists are suitable for local use in the eye because they lack local anesthetic properties.
- Sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart (bradycardia) and airways (bronchoconstriction) in susceptible individuals (patients with HF or Asthma respectively).

- Beta antagonists have an efficacy comparable to that of epinephrine or pilocarpine-(pilocarpine has more SE like pinpoint pupils and blurred vision)- in open-angle glaucoma and are far better tolerated.

❖ Hyperthyroidism (excessive production of thyroid hormone by the thyroid hormone):

- Hyperthyroidism is characterized by increased sympathetic tone because thyroid hormones increase the body sensitivity to catecholamines (CA).
- The β antagonists are beneficial in this condition due to blockade of adrenoceptors (to prevent the excess CA from binding) and in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine (the active form of the thyroid hormone).
- **Propranolol** has been used extensively in patients with **thyroid storm** (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.

❖ Neurologic Diseases:

- Propranolol reduces the frequency and intensity of **migraine headache**.
- Other β -receptor antagonists with preventive efficacy include **metoprolol, atenolol, timolol, and nadolol** but the mechanism is not known.
- β antagonists reduce certain tremors (essential tremors, tremors with unknown cause (idiopathic)).
- The somatic manifestations of **anxiety** may respond dramatically to low doses of propranolol, particularly when taken prophylactically.
- Benefit has been found in musicians with performance anxiety (**"stage fright" and public-speaking fears**), some musicians take β-blockers to control stage fright that causes the adrenal gland to pump epinephrine the classic fight or flight hormone, by blocking adrenergic receptors symptoms like trembling hands are reduced.
- Propranolol may be used in symptomatic treatment of alcohol withdrawal in some patients.

• Clinical Toxicity of the Beta-Receptor Antagonist Drugs:

- **Bradycardia is the most common adverse effect**, as well as coolness of hands and feet in winter due to blockade of β2 receptors in arterioles of skeletal muscles leading to their constriction and reduced circulation to hands and feet.

- Drugs that penetrate blood-brain barrier have CNS effects including mild sedation, vivid dreams, and rarely, depression.
- **Nonselective agents** commonly cause worsening of preexisting **asthma** (by blocking β2 receptors).
- Caution is required in patients with severe **peripheral vascular disease** (lowered arterial BP could potentially adversely affect limbs with impaired blood flow) and in patients with compensated heart failure even though long-term use may prolong life.
- A very small dose of a β antagonist may provoke severe cardiac failure in a susceptible individual.
- Beta blockers may interact with the calcium antagonist verapamil causing bradycardia (negative chronotropic, inotropic, and dromotropic effects), heart failure, and cardiac conduction abnormalities.
- These adverse effects may even arise in susceptible patients taking a topical β blocker (topical Timolol eye drops to reduce IOP) and oral verapamil.
- Patients with ischemic heart disease or hypertension may be at increased risk if β blockade is suddenly interrupted.

❖ WHY?

When tissues are exposed to β-blockers for a long period of time their response is to increase the density of β receptors (up-regulation), if these blockers are suddenly stopped, a similar pattern to excessive activity of thyroid hormones and sympathetic factors can occur due to the increased sensitivity toward normal CA concentrations by the additional receptors.

- It is inadvisable to use β antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions (low blood sugar reaction). Beta1-selective antagonists are safer in these patients because if β2 receptors are blocked the response to hypoglycemia is reduced since glycogenlysis is inhibited by this blockade.
- An additional risk of β-blockers is the masking of hypoglycemia symptoms like tachycardia which serves as a warning sign of the patient blood glucose levels being below normal.

- **Ganglion-Blocking Drugs:**

- **Tetraethylammonium (TEA)** first ganglion blocker with a very short duration of action.
- **Hexamethonium ("C6")** the first drug effective for hypertension, but tolerance rapidly develops after using this drug because up-regulation of M1 receptors in the ganglia counteracts the blockade.
- **Decamethonium ("C10")** analog of hexamethonium, is a depolarizing neuromuscular blocker.
- **Mecamylamine** A secondary amine that has central actions, developed to improve absorption from the GIT because the quaternary amines were poorly absorbed after oral administration.
- **Trimethaphan** A short-acting ganglion blocker. It is inactive orally & is given by intravenous infusion.

❖ Mechanism of Action:

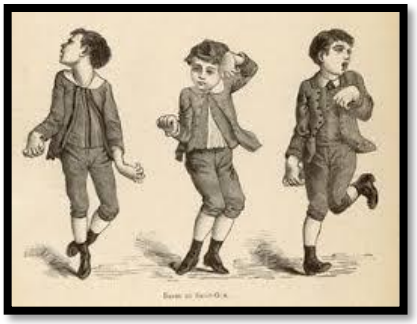
- Ganglionic nicotinic receptors are subject to both depolarizing and nondepolarizing blockade.
- Nicotine and acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block, that's why it does not make sense to use these drugs to treat any condition.
- Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists.
- Competitive inhibition can be reversed by increasing the concentration of agonist, e.g., acetylcholine.
- This is not the same case with depolarizing blockade, increasing the concentration of ACh would worsen the condition.

❖Organ System Effects:

Because these drugs block sympathetic and parasympathetic actions, their effects are related to which autonomic division provides the dominant baseline (dominant tone) for a given organ.

• Central Nervous System:

- **Mecamylamine** enters the CNS causing sedation, tremor, choreiform movements, and mental abnormalities.



- **Eye**:
- Cycloplegia with loss of accommodation and moderate dilation of the pupil because parasympathetic tone usually dominates this tissue.

❖ Cardiovascular System:

- Marked decrease in arteriolar and venomotor tone.
- BP may fall because both peripheral vascular resistance and venous return are decreased
- Orthostatic or postural hypotension, diminished contractility and a moderate tachycardia.

❖ GIT (PANS dominates):

- Secretion and Motility are profoundly inhibited, and constipation can be marked. But these effects can be reversed if the SANS dominates at any moment, severe constipation might be reversed to severe diarrhea as a result of sympathetic antagonism.

❖ Other Systems:

- May precipitate urinary retention in men with prostatic hyperplasia.
- Sexual function is impaired in that both erection (parasympathetic) and ejaculation (sympathetic).
- Sweating is reduced by the ganglion-blocking drugs.

❖ Clinical Applications and Toxicity:

- Ganglion blockers are used infrequently because more selective agents are available.
- **Mecamylamine:**
- Blocks central nicotinic receptors and has been advocated as a possible adjunct with the transdermal nicotine patch to reduce nicotine craving in patients attempting to quit smoking (not used because better drugs are available).
- **Trimethaphan:**
- Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery and plastic surgery to reduce bleeding in the operative field.
- The toxicity of the ganglion-blocking drugs is limited to the autonomic effects.
- These effects are intolerable except for acute use.

GOOD LUCK ♥