Doctor 021

PHARMACOLOGY

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β Blockers with partial β-agonist activity

These are B blockers with partial B agonist activity:
block Epi & NE from binding to their receptors + partially stimulate the receptors with useful effects:

- **effective in hypertension and angina.**
- **less likely to cause bronchoconstriction in asthma patients, bradycardia, and abnormalities in plasma lipids than other β blockers**, because β2 can still be stimulated.
- remember that β2 receptor blockade causes changing the plasma lipids metabolism and Increase the concentration of low-density lipoproteins (LDL) which is a Bad cholesterol

Drugs of this class:

Pindolol

1) **is a non-selective beta- adrenoceptor antagonist**
2) **5-HT1A antagonist** (5HT = 5 hydroxytryptamine receptors or serotoninreceptors)
3) **accelerates the antidepressant effect of selective serotonin reuptake inhibitors**. (How?)
   →5HTR are auto receptors (pre-synaptic receptors), that inhibit the release of serotonin. so when these receptors are blocked by pindolol—preventing the feedback inhibition effect and increase serotonin release.

Celiprolol

1) **is a β1-selective antagonist with a partial β2-agonist activity**
2) **safe to give people with bronchial asthma: has less adverse bronchoconstriction effect and may even promote bronchodilation.**
3) Very good for asthmatic patients who need beta-1 blockers for their heart conditions or blood pressure.

Acebutolol

a β1-selective antagonist with partial agonistic effects.

Drugs that block both alpha and beta receptors

• blocking Alpha receptors causes vasodilation, decreases peripheral resistance, and decreases blood pressure which evokes baroreflex pathway and leads to tachycardia in order to maintain homeostasis. but blocking Beta receptors prevents tachycardia stimulation without changing the decrease in blood pressure.

Drug Examples

Labetalol

- **Treats emergency hypertension, causes Hypotension with less tachycardia that occurs with other α-blockers.**
- **it is a partial agonist at beta2- receptors** (causes vasodilation in blood vessels that supply skeletal muscles—activation of **β2** receptors)

Carvedilol

• **A nonselective beta blocker +alpha-1 blocke**r, and **calcium channel blocker** all at the same time.
→beta blocking prevents cardiac stimulation due to baroreflex, while alpha-1 and calcium channel blocking cause vasodilation
→calcium channel blocker is a class of drugs that is used to treat hypertension and other cardiovascular diseases.
Ca^{2+} is needed to vasoconstrict the blood vessels, which explains why calcium blockers cause vasodilation.

• **More potent at β than at α1 receptors**, this characteristic protects the heart.
• **Antioxidant property (protective effect against free radicals that damage bloodvessels)**
• **Use: hypertension, angina, congestive heart failure**
Effective in reducing mortality in selected patients with chronic heart failure.

Congestive heart failure: heart fails in pumping the full amount of blood that retreats back to it.
therefore, blood accumulates in the heart after every contraction, which also causes blood accumulation in the veins and fluid escape out of the circulation leading to edema.

Clinical Toxicity of the Beta-Receptor Antagonist Drugs

• **Bradycardia is the most common adverse effect** (especially for nonselective betablockers) **patients suffer from coolness of hands and feet in winter** because the beta-2 receptors in the peripheral blood vessels are blocked causing vasoconstriction in peripheral skeletal muscles and lower the concentration of circulating blood, so beta-1 selective blockers are the preferred one in this condition.

• **CNS effects caused by all lipids soluble drugs by penetrating the blood brain barrier include mild sedation, vivid dreams (nightmares), and rarely depression.**

• **Nonselective agents commonly cause worsening of preexisting asthma** because of blockade of beta2 receptors.

•**Caution is required in patients with severe peripheral vascular disease** (Raynaud's phenomenon) **and in patients with compensated heart failure** (because their heart function is dependent on sympathetic activity) **even though long-term use may prolong life**.

• A very small dose of a β antagonist may provoke severe cardiac failure in susceptible individuals

• Beta blockers may interact with the calcium antagonist *verapamil* causing bradycardia, heart failure, and cardiac conduction abnormalities if these two drugs are combined. These adverse effects may even arise in susceptible patients (who have heartproblems) taking a topical β blocker and oral verapamil.

• ***verapamil:*** is a calcium antagonist—blocks Ca^{2+} channels, vasodilator, heart depressor, which causes low heart rate, decreased cardiac output and decreases AV conduction.

• Patients with ischemic heart disease or hypertension may be at increased risk if β blockade is suddenly interrupted.

• when taking beta blockers for a long time, the administration shouldn't be stopped suddenly but rather gradually.
Taking beta blockers for a long time causes up-regulation of β receptors (increased no. of receptors more than the normal number) because the receptors have been blocked for a long time, and sudden drug cutout leads to an dangerous exaggerated response.

• It is inadvisable to use β antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions. Because the blockade of beta-2 receptors in the liver delays the recovery from hypoglycemia. Beta1- selective antagonists are safer in these patients

Ganglion-Blocking Drugs

Ganglion blocking drugs were first developed in the 50s, and are the first drugs to be used in treating hypertension

Ganglion blockers are used **infrequently** because more selective agents are available.

Competitive Ganglionic blockers:

Tetraethylammonium (TEA)

First ganglion blocker, very short duration of action soit's not used clinically, has a quaternary amine so low lipid solubility

Hexamethonium ("C6")

The first drug effective for hypertension longer duration of action that TEA, but with terrible side effects, has two quaternary amines (two positive charges) so low lipid solubility, tolerance for hexamethonium is developed quickly.

Decamethonium, "C10" analog of hexamethonium,is a depolarizing neuromuscular blocker **(not a ganglion blocker),** has two quaternary amine so low lipid solubility because of the two positive charges as well.

Mecamylamine

A secondary amine, developed to improve absorption from the GIT because the quaternary amines were poorly absorbed after oral administration due to their polarity. has Central side effects in the brain, as it blocks central nicotinic receptors. But has been advocated —only a suggestion as a possible adjunct with the transdermal nicotine patch to reduce nicotine craving in patients attempting to quit smoking.

Trimethaphan

A short-acting ganglion blocker, is inactive orally & is given by intravenous infusion. The only one that is used clinically nowadays.

Trimethaphan is occasionally used in:
•the treatment of hypertensive emergencies.
•producing hypotension in neurosurgery & 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.

Mechanism of Action

• Ganglionic nicotinic receptors are subject to both depolarizing and non-depolarizing blockade.

• Nicotine & acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block →irreversible block

• Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists. (drugs mentioned in the previous page)

• Blockade can be reversed by increasing the concentration of an agonist, e.g., acetylcholine.

Organ System Effects

These drugs act on the **active** autonomic ganglia:
if the sympathetic stimulation is the active one, the drug will act on the sympathetic ganglia, and the same concept applies to the parasympathetic ganglia, if it is active the drug will act on the parasympathetic ganglia and block it.

1) Central Nervous System

Mecamylamine enters the CNS causing Sedation, tremor, choreiform movements (involuntary movements), and mental abnormalities (that's why Mecamylamine is not used clinically nowadays) .

2) Eye

• The dominant (active) ganglia is parasympathetic so when its blocked the effect of the other sympathetic ganglia will appear.

• The ciliary muscle is only innervated by parasympathetic neuron so when it's blocked the ciliary muscle will be paralyzed this phenomenon is called **cycloplegia.**

• Cycloplegia with loss of accommodation & moderate dilation of the pupil because parasympathetic tone usually dominates this tissue (The neuron that supplies the iris muscle is also parasympathetic).

3) Cardiovascular System

• Blood vessels have only sympathetic ganglia, when blocked **marked decrease in arteriolar and venomotor tone** is observed—arteries and veins dilate.

• BP may fall because both peripheral vascular resistance and venous return are decreased.

• venous return: blood retreat to the heart by veins

➔ When veins are dilated less blood returns to the heart which decreases cardiac output and BP falls.

• Orthostatic or postural hypotension, diminished contractility and a moderate tachycardia

→actually the patients who use **Hexamethonium** are advised not to stand in a line for a long time, when they stand in a line they have to move the their legs in order to help the circulation & aid blood return + and wear tight dressing to compress their legs to prevent the pooling of blood.

4) GIT

• Is under the parasympathetic tone.

• Secretion & Motility are profoundly inhibited, dry mouth and constipation can be marked.

• But these effects can be reversed if the sympathetic ANS dominates at any moment, severe constipation might be reversed to severe diarrhea as a result of sympathetic antagonism

5) Other Systems

• may precipitate urinary retention in men with prostatic hyperplasia.

• Sexual function is impaired in that both erection and ejaculation.

• Sweating is reduced by the ganglion-blocking drugs

Clinical Applications & Toxicity

• Ganglion blockers are used infrequently because more selective agents are available. Trimethaphan

• Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery to reduce bleeding in the operative field.

• The toxicity of the ganglion-blocking drugs is limited to the autonomic effects.

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• remember that β2 receptor blockade causes changing the plasma lipids metabolism and decrease (increase) the concentration of low-density lipoproteins (LDL) which is a good (Bad) cholesterol

3) Very good for asthmatic patients who need beta-2 (beta-1) blockers for their heart conditions or blood pressure.