Sympathoplegic Agents & Adrenoceptor Antagonist

"Beta-Blockers"

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Drugs That Alter Sympathetic Nervous System Function

We don't paralyze, we reduce the activity of symp. System!!

Include the following:

1. **Centrally acting sympathoplegic drugs.**
2. **Ganglion-blocking agents.** ← Toxic and not used!
3. **Adrenergic neuron-blocking agents.**
4. **Adrenoceptor antagonists.**

Drugs That Alter Sympathetic Nervous System Function

- All of these agents can elicit compensatory effects through adrenergic nerve-independent mechanisms: Retention of sodium by the kidney expansion of blood volume.
- Thus, they are most effective when used concomitantly with a diuretic.

Centrally Acting Sympathoplegic Agents

- Reduce sympathetic outflow from vasomotor centers in the CNS, but allow these centers to retain or increase their sensitivity to baroreceptor control, and thus, are less likely to produce postural hypotension.

Methyldopa

Not active, Has to be metabolized first!

Mechanism of Action:

- It is converted in the CNS → α-methyldopamine → α-methylnorepinephrine, which is stored in adrenergic nerve vesicles, replaces norepinephrine, and is released by nerve stimulation.

Methyldopa

- **However, α-methylnorepinephrine released is an effective agonist at the α-adrenoceptors and can not explain the antihypertensive effect.**
- **It stimulates central α_2-adrenoceptors that mediate the negative feedback on catecholamine release.**

- *At first it elevates blood pressure because it stimulates α1 adrenoceptor which causes vasoconstriction, then it will lower blood pressure "α2 effect" due to inhibition of release of catecholamines.*

Methyldopa

- **This reduces sympathetic outflow from CNS, decreases catecholamine release, reduces peripheral vascular resistance and cardiac output, and thus blood pressure.**
- **Used primarily for hypertension of pregnancy.** ***Because it's very safe!!!***

Methyldopa

Adverse Effects: *Different frequency and severity*

1. Little postural hypotension, but may occur in volume-depleted patients. *Due to pooling of blood in the lower limb veins*
2. Sedation – most frequent at onset of treatment.
3. Impairs mental concentration. (so methyldopa is very bad for people who must be mentally active during the day!)
4. Nightmares, mental depression, vertigo.
5. Lactation: due to inhibition of dopaminergic transmission which stimulates prolactin.

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*All these adverse effects are Type A "predictable because it's exaggeration of the pharmalogical effect, A from augmented"

Methyldopa

6. Hepatitis and drug fever.

Immune mediated reaction, Type B adverse effect "B means Bizarre"

6. **Positive Coomb's test in 10-20% of patients taking the drug for > 12 months:**

   a. **Makes cross-matching of blood difficult.**

   b. **Rarely associated with hemolytic anemia.**

Coomb's test is a test for hemolytic anemia!

Clonidine

- Clonidine is a 2-imidazoline derivative.
- It is a direct agonist at central α_2-adrenoceptors, decreases circulating catecholamine levels, and reduces blood pressure.
- It may sensitize brainstem vasomotor centers to inhibition by baroreflexes.

Clonidine

- **After intravenous injection, it produces a brief rise in blood pressure followed by more prolonged hypotension.**
- **The pressor (increasing pressure)response is due to direct stimulation of α-adrenoceptors in arterioles.**

Vasoconstriction
In arterioles

Clonidine

- **The drug is classified as a partial agonist at α-receptors because it also inhibits pressor effects of other α agonists.**
- **It reduces sympathetic and increases parasympathetic tone, resulting in blood pressure lowering and bradycardia.**

Important!

Clonidine

- Clonidine also binds to a the imidazoline receptor, which may also mediate antihypertensive effects.
- Methyldopa and clonidine produce slightly different hemodynamic effects: clonidine lowers heart rate and cardiac output more than does methyldopa.

Clonidine

- This difference suggests that these two drugs do not have identical sites of action.
- They may act primarily on different populations of neurons in the vasomotor centers of the brainstem.

Clonidine

- **Reduction in arterial blood pressure by clonidine and methyldopa is accompanied by decreased renal vascular resistance and maintenance of renal blood flow.**

Kidney is very sensitive to ischemia!

Clonidine

Adverse effects: *Similar to methyldopa*

1. **Dry mouth and sedation are common. Both effects are centrally mediated and dose-dependent and coincide temporally with the drug's antihypertensive effect.**

Clonidine

2. Clonidine should not be given to patients who are at risk for mental depression and should be withdrawn if depression occurs during therapy.

3. Concomitant treatment with tricyclic antidepressants may block the antihypertensive effect of clonidine, due to α-adrenoceptor-blocking actions of the tricyclics.

Clonidine

4. Withdrawal of clonidine after prolonged use (and at high dosages), can result in life-threatening hypertensive crisis mediated by increased sympathetic nervous activity.

Clonidine

If the patient forgot a dose there will be what's called rebound hypertension which is higher than the original hypertension before the treatment and the reason for that Is the sensitization "up regulation" of the adrenoceptors

- **The withdrawal syndrome is manifested by nervousness, tachycardia, headache, and sweating after omitting one or two doses of the drug.**
- **All patients who take clonidine should be warned of this possibility.**

Clonidine

- When the drug must be stopped, it should be done gradually while other antihypertensive agents are being substituted.
- Treatment of the hypertensive crisis consists of reinstitution of clonidine therapy(IV Clonidine) or administration of both α- and β-adrenoceptor-blocking agents.

If we want to give the α & β blockers we should give the α blocker first because the β blocker causes vasoconstriction in the skeletal muscle blood vessels and increase the blood pressure.

Adrenoceptor Antagonists "Blockers"

- **The pharmacology of α- and β-adrenoceptor blockers was presented in the autonomic nervous system pharmacology lectures in second year.**

Previously we said that diuretics are first choice drug for hypertension, but actually there 4 groups that can be considered as first choice drugs for treating hypertension:

1. Diuretics
2. Adrenoceptors Antagonists "β-blockers in particular"
3. ACEI (Angiotensin-converting enzyme inhibitors) & ARBs (Angiotensin receptor blockers)
4. Calcium channel blockers

β-Adrenoceptor Antagonists

- **Propranolol (non-selective, blocks β_1- and β_2-adrenoceptors) was the first β blocker shown to be effective in hypertension and ischemic heart disease.**

- Propanolol is the prototypeالممثل الشرعي whom we compare other beta-blockers with,
- It is lipid soluble

- **It has now been replaced by cardioselective β_1-blockers such as bisoprolol, metoprolol and atenolol.**

- Water soluble

β-Adrenoceptor Antagonists

- All β-adrenoceptor blockers are useful for lowering blood pressure in mild-to-moderate hypertension.
- In severe hypertension, they are especially useful in preventing the reflex tachycardia that results from treatment with direct vasodilators.

β-Adrenoceptor Antagonists

- They reduce mortality after a myocardial infarction, and some also reduce mortality in patients with heart failure. *Although sometimes heart failure is an adverse effect of beta-blockers*
- They are indicated for treating hypertension in these conditions.
- Reduce blood pressure without prominent postural hypotension.

Additional Slide

Mortality rate for beta-blocker using patients with MI is lower than the mortality rate for MI patients using other drugs. (An Advantage of Beta-Blockers)

β-Adrenoceptor Antagonists

Mode of action:

1. **Reduction of cardiac output (β_1).**
2. **Inhibition of Renin secretion (β_1) depression of renin-angiotensin-aldosterone system.**
3. **Block presynaptic β-adrenoceptors to reduce sympathetic Vasoconstrictor nerve activity.**

Due to reduction of contractility

After beta-blockers start to work, Diastolic pressure increases due to vasoconstriction in the skeletal muscles blood vessels,
Yet after a while this effect disappear due to the inhibition of angiotensin system which causes general vasodilation

Aldosterone causes water sodium retention, inhibition of aldosterone causes lower blood volume ->less venous return -> lower cardiac output -> less systolic pressure

Additional slide

- **Renin-angiotensin-aldosterone system inhibition works on both systolic and diastolic pressures, *lowering them both!***
- **While β blockers works only on the systolic, *lowers systolic only!***

- Clonidine and Methyldopa reduce central sympathetic stimulation by stimulating presynaptic alpha2 receptors.
- While beta blockers reduce central sympathetic stimulation by blocking presynaptic beta receptors
- Only lipid soluble beta-blockers “propranolol” can cause this CNS effect, because it can cross BBB!

- Alpha2 stimulation reduce sympathetic activity
- Beta stimulation increase sympathetic activity

β-Adrenoceptor Antagonists

Major adverse effects:

1. **Bradycardia (β_1-block)**
2. **Cardiac block (β_1-block)**
3. **Increased peripheral vascular resistance (β_2-block)**
4. **Bronchoconstriction (β_2-block)**
5. **Masking signs and symptoms of hypoglycemia.**

hypoglycemia induces Sympathetic stimulation, which causes tachycardia, nausea, sweating (fight or flight)!
Beta-blockers mask these symptoms by the adverse effects mentioned above

***catecholamines are insulin antagonists, they induce* gluconeogenesis and glycogenlysis to compensate for the hypoglycemia**

β-Adrenoceptor Antagonists

6.Withdrawal syndrome (nervousness, tachycardia, increased intensity of angina, increase of blood pressure, and myocardial infarction).

β- blockers <u>should not be discontinued abruptly</u>. The withdrawal syndrome may involve upregulation or supersensitivity of β-adrenoceptors.

Tolerance!

you should stop beta-blockers gradually and by replacement with other drug to control the patient blood pressure.

α-Adrenoceptor Antagonists

- **Prazosin, terazosin, and doxazosin are selective α_1-receptors blockers in arterioles and venules ⇨ dilation.**
- **These agents produce less reflex tachycardia when lowering blood pressure than do nonselective a antagonists such as phentolamine.**

Postural Hypotension!

α-Adrenoceptor Antagonists

- **α_1-Receptors selectivity allows norepinephrine to exert unopposed negative feedback (mediated by presynaptic α_2-receptors) on its own release.**

Alpha1 receptors are bound to the drug -> more free catecholamines -> more binding of catecholamines to alpha2 receptors -> central inhibition of catecholamines release!!

α-Adrenoceptor Antagonists

- **In contrast, phentolamine blocks both presynaptic and postsynaptic α-receptors.**
- **Block of α_2-receptors results in reflex activation of sympathetic neurons and greater release of norepinephrine and *greater cardio-acceleration.*** *Reflex tachycardia!*

α-Adrenoceptor Antagonists

- **α-Receptor blockers reduce arterial pressure by dilating both resistance and capacitance vessels.** *Arteries and veins!*
- **Blood pressure is reduced more in the upright than in the supine position (postural hypotension).**

α-Adrenoceptor Antagonists

Due to vasodilation!

- **Retention of salt and water** is a recognized adverse effect.
- The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone.

α-Adrenoceptor Antagonists

- They relax prostatic smooth muscle.
- They are used primarily in men with concurrent hypertension and benign prostatic hyperplasia and bladder neck obstruction.

α-Adrenoceptor Antagonists

Adverse effects of α-Adrenoceptor Antagonists:

1. **Venular dilators -> postural hypotension**
2. **Reflex sympathetic stimulation "baroreceptor"**
3. **Sodium water retention**

these 3 develop tolerance rapidly, so you should never give them alone, they are always given with beta-blockers and diuretics (in combination) ***for severe not mild hypertension!***