Subject | Pharmacology
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- Some of β blocker drugs can block the action of α1 adrenergic receptors such as → labetalol and carvedilol.
- Are the mechanisms of inhibiting α adrenergic receptors will help us in reduce the BP?

  *THE ANSWER: YES , because the inhibition of α receptors will cause vasodilation then→ lower PVR , BUT when the α receptors are stimulated through binding epinephrine and norepinephrine→that will cause vasoconstriction → increase PVR → increase BP

- Also , β blocker drugs can be used in pheochromocytoma (tumor that secreted high level of epinephrine) and emergencies, so to counteracting the action of epinephrine we can use these drugs to inhibit both α and β receptors
- We said that β blocker drugs → decrease CO →and this is how they reduce BP . another mechanism that they can block β receptor in the kidney→ leading to decrease the secretion of Renin → decrease the activity of Renin –angiotensin system → decrease angiotensin II (its activity causing constriction)→decrease total PVR→ leading to dilation → decrease BP
- Side effects:

1-Bronchial Constriction/spasm - They can act on smooth muscles of the bronchi and cause vasoconstriction; therefore, these drugs should be avoided in patients with asthma (espically propranolol cuz its non-selective β blocker

2- Induce glucose intolerance – We have to be careful in diabetic and obese patients.

3- mask hypoglycemia – decrease the glucose level happens in diabetic patients (whose taking drugs for diabetes) , BUT , why do β blockers cause hypoglycemia?

➔ ANSWER: in diabetic patients whose taking drugs for diabetes and β blocker ➔ they may have state of hypoglycemia that will be sense by the sympathetic system (at this state the patient need to eat something sweet to elevate the glucose level) ALL THAT IS DUE TO ➔ β blockers will inhibit the sympathetic system by inhibit β receptors in the liver (which these receptors are responsible for increasing glycogenesis) ➔ then decrease glycogenesis ➔ so that hypoglycemia state will be developed

- **Examples of β blockers :**
  1- Atenolol – It's a Beta 1 selective antagonist
  2-Metoprolol – It's a Beta 1 selective antagonist
  **** these two drugs are useful in asthma & COPD patients**

- **Indications:-**
  1- Treatment of mild-moderate hypertension
  2- Very useful for patients who are taking vasodilators ,why? to prevent reflex tachycardia (due to homeostasis through the regulation by minute – minute mechanism)
  3- Useful in controlling blood pressure in patients with underlying heart diseases. (CCB & β blockers)➔ isn't useful for patient with low functioning heart , BUT it is useful to treat certain stages of heart failure to affect the compensatory mechanism of the heart.

ACE Inhibitors (Angiotensin converting enzyme inhibitors)

History:

Workers in the banana plantations of Brazil were known to collapse (decrease in the BP) after being bitten by a specific viper A Brazilian biochemist Maricio Rocho e Silva purified the venom extracts and sent his post-doc with extracts to study their effects in the lab of Sir John Vane (London)By 1970, the lab of Sir John Vane found the effect was on ACE, ultimately leading to the development of ACE inhibitors

- **Mechanism of Renin-angiotensin system: -**
  -Upon certain stimuli, such as low blood flow to the kidney, the kidney will start to secrete renin (stimulated by sympathetic pathway) which will convert a peptide called angiotensinogen into angiotensin 1(doesn't have much activity in vascular) and this will be worked upon by an enzyme called Angiotensin converting enzyme (ACE) in different parts of the body, to be converted into angiotensin 2. Angiotensin 2 will bind either on AT1 or AT2 receptors.

- **So by using ACEI we will inhibit the formation of angiotensin 2 and the pathway downstream to inhibit the vasoconstriction and Na+ retention**

- **ACEI also can prevent the degradation of bradykinin to its inactive peptide. Bradykinin causes vasodilation which helps in the treatment of hypertension.**
  ***High level of bradykinin (type of cytokines)→ mean high level of immunologic responses (allergic reaction) → leading to vasodilation**

- **Side effects:**

1-Hypotension in hypovolemic patients9 because of inhiting angiotensin 2 to bind to AST2 then decrease PVR

2-Hyperkalemia – as we said, when we block the action of aldosterone, more sodium will be excreted, and more potassium will be reabsorbed.(so when we used the ACEI with sparing K+ diuretics → here we must be careful about the potassium level , we said that patients with heart failure and arrhythmias (that they are taking digoxin) → we must have normal level of potassium.

3- Angioedema- rapid swelling of throat, nose, mouth larynx or tongue. However, this is very rare. may relate to inhibitory effect bradykinin catalysis & has Greater risk in African Americans due to specific genetics

4- Cough- This is the most common side effect of ACE inhibitors, because of high level of bradykinin

5- Skin rash

6- Taste alterations(due to contain sulfur moiety)

- **Examples of ACEI :**
  -Most ACE inhibitors end with the suffix "Pril" such as Enalapril, Ramipril, Lisinopril, Captopril.

  ***These drugs have low affect in African Americans because they have already low Renin level**
  ***extra note: the level of Renin doesn't determine if the patient has hypertension or not.**

- **Contraindications:**
  - Pregnancy – They are contraindicated, because they will affect proliferation and cell growth, so if this is inhibited, it will affect the growth of the fetus.(during first trimesters)

Angiotensin Receptor Blockers (ARB's)

These drugs are Competitive antagonists of the AT1 receptor. They prevent binding of Angiotensin 2.
***once angiotensin2 binds to AT1 receptor → it will cause vasoconstriction , Na+ retention and aldosterone released**
***we name it AT1 because there is another receptor named AT2**
***what does AT2 in our bodies ? it will balance the amount of AT1 in the body → causing vasodilation and renal Na+ excretion**
***in hypotension patients → the have high level of angiotensin 2 → more prominent effect on AT1**
*** in our bodies blood vessels under many types of regulation but the dominant type is sympathetic system to have contraction then push the blood towards the tissues , there is a balance between AT1 and AT2**
***when we used ACEI we will inhibit the release of angiotensin and its good and bad effects , AT1→ increasing in the BP BUT , AT2→ lowering BP „ so we developed a drug that will inhibit only AT1 → ARB'S (example → Losatran)→that will cause vasodilation and increase growth and proliferation of cells very effective in hypertensive patients with heart failure.**
***we said that when had chronic hypertension → that will lead to change in the structure of the blood vessels → such as hypertrophy and stenosis. Some of these drugs are mediated by the cell growth and proliferation that happen when the angiotensin binds to AT1 and then get activated.**

Vasoconstriction
Cell Growth and Proliferation
Aldosterone release
Central Sympathetic activation

these effects when angiotensin2 binds to AT1

Sodium and water retention

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Vasodilation

Restrains cell growth and proliferation

Mediates NO(endogenous vasodilation) and PGI2 release in kidney

Renal sodium excretion

Dilates afferent renal arteriole

these effects when angitensin2 binds to AT2

Side Effects: -

1- Angioedema – This is not related to bradykinin, it is related to the vasodilatory effect of the blood vessels

2- Contraindicated in pregnancy - for the same reason as ACE inhibitors.(high growth and proliferation of the cells)

3- Dizziness

ACEI or ARB?

We use ACEI as the first choice unless the patient cannot handle the angioedema or cough, then we resort to using ARB's.

Peripheral Alpha 1 adrenergic receptor blockers

Prazosin is one of these drugs, it is a competitive inhibitor of the alpha 1adrenergic receptors.

Norepinephrine usually binds to the Alpha 1 receptor and causes Constriction of the vessels. So, Prazosin prevents the binding of norepinephrine and there will be less constriction and there will be dilation. They decrease PVR & BP.

These drugs aren't used a lot as anti-hypertensive because they have side effects, and other drugs have shown better efficacy.

Side effects: -

1- Postural dizziness

2- Headaches

3- Drowsiness

4-First dose phenomenon - when we give the patient this drug, he usually

experiences a syncopal reaction – orthostatic hypotension (upon standing). So,we advise the patient to take the drug at bed time so that he will not experience this side effect, the patient then develops tolerance to this reaction after the first dose.

Other drugs from this family include Doxazosin, Terazosin. They have different pharmacokinetics. Doxazosin and Terazosin have a Longer half-life than Prazosin. And these two drugs are mainly used to treat benign prostate hypertrophy. People with this condition have a problem in emptying their bladders as a result of the hypertrophy of the prostate. So alpha 1 adrenergic receptors are on the neck of the bladder and their function is constriction, when they are inhibited, the patient can empty their bladder with much more ease.

Recent recommendations on Alpha 1 Blockers

Alpha 1 blockers are less effective than diuretics in preventing cardiovascular events, mainly heart failure.

The National Institiute of health(NIH) recommends not to use Alpha 1 blockers as the first drug of choice in hypertension (not effective in preventing heart failure) We usually give it as an additional drug with other drugs if we do not see an improvement in reduction of blood pressure.

Adrenergic Neuron blocking agents/Sympatholytics

As we know, Sympathetic activation is involved in elevation of Blood pressure either by increasing the Cardiac output or increasing the Total peripheral resistance.

These drugs work by decreasing the production/secretion of norepinephrine from then nerve terminal entering the vesicles causing emptying the vesicles from norepinephrine either degradation or prevent the release , we will have less of the effect of NE and therefore will have less of the sympathetic stimulation.

However, NE is necessary for many functions in the body. We will therefore have a lot of side effects, this is why they aren't used as a first line of treatment.

1- Guanethidine;(has long half life 5 days) it is a false Neurotransmitter. It will use the uptake mechanism of NE, it can take the place of NE and enter into the vesicle, and instead of NE being secreted from the vesicle, Guanethidine will be released, and it will have no effect on NE receptors. This drug is effective Orally. It does not cross the Blood brain barrier.(then NE will be catalyzed)

Important: - We only use it in cases of Moderate-Severe cases of hypertension→ patient who is not responded to another treatment

We save this drug for cases of refractory hypertension, in which hypertension is not being resolved by any other drugs.

2- Reserpine;(long half life, cost effective(cheap) Prevents the uptake of Dopamine inside the vesicle, dopamine is a precursor of NE, so less uptake of dopamine means less production of NE, the NE stores will be depleted. It can also affect the uptake of Serotonin, however this is related to some side effects, such as depression. Sympathetic tone will be decreased, so we will have decreased TPR & CO.

Side effects: -

1- Orthostatic hypotension(guanethidine)

2- Depression

3- Nasal congestion

4- Bradycardia

5- Incompetence (guanethidine)

6- Diarrhea (guanethidine)

7- Salt and water retention

Drug interactions: -

Amine pump is involved in the uptake of dopamine. There are drugs that can block this pump such as; Tricyclic antidepressants, monoamine oxidase inhibitors, ephedrine, amphetamines, phenothiazines. After chronic use of guanethidine, the above agents could cause hypertension due to development of receptor super sensitivity.--> then there will be decreased of the Guanethidine and Reserpine to lowering BP

It is RARELY INDICATED because of its adverse effects. It is often only used as a last resort in refractory hypertension.

Central Alpha 2 agonist

The alpha 2 receptors are found in presynaptic nerve terminals ,they inhibit the release of norepinephrine and epinephrine(a feedback mechanism when we have high sympathetic activity) When we have I epinephrine it binds to alpha 2 receptors and they reduce the release of epinephrine and norepinephrine .

These drugs are very good when we have activation to different receptors (alpha and beta) for example in hypotensive crisis because when I block the activation(outflow) of the sympathetic nervous system It will affect all receptors not only on one receptor.(literally)

1-Methyldopa and clonidine. Both work in the CNS through inhibiting sympathetic and increase the parasympathetic to the periphery so lowering Bp.

At higher concentration we loose selectivity and they start activating the alpha 1 rectopors causing vasoconstriction.(not seen in theraptic doses.

They lower the heart rate, cardiac output,TPR , plasma – renin activity and barorecptor function.

Remember:methyleopa is a prodrug(not active on its own) needs to be metabolized to methynorepinephrine.

Clonidine has a high plasma half life so it is used as a transdermal patch , the patch is switched every week.(used for patients who can't take oral medications.

Side effects:

Dry mouth ,drowsiness,

Diszzines(most drugs that cross bbb will cause this side effect because they loose their selectivity.

Drug interactions;

They can interact with the tricyclic antidepressants reducing the ability to reduce Bp.

A special and rare side effect for methyldopa it can cause hemolytic anemia in certain subset of populations.

Methyldopa is the first choice for hypertension during preganancy.

Vasodilators

1-Hydralizine: Mechanism of action is not known very well; we know that it causes vasodilation through causing hyper polarization of the cell through altering intraclleular Ca+2 may be by activating K+channels(not sure that this is the exact target) .

Because we decreased peripheral resistance we will have the reflex response of the sympathetic activity; Increased heart rate ,heart contractility,plasma renin.(counteracted by giving additional beta blockers.

They also increase in the retention of Na in the vessel wall so to counteract we give diruetics.

Side effects

- Reflex tachycardia
  - Can precipitate MI in elderly patients or patients with coronary artery disease
  - Reflex response can be blocked by addition of propranolol
- Sodium and water retention – can be prevented by addition of a diuretic
- Headache, Nausea, Dizziness

Lupus like syndrome

2- **MINOXIDIAL same as hydralizine but we are sure that it works on K+ channels through activating ATP senstive K+ channels causing smooth muscle cell relaxtion.**

An important side effect and got converted it its medical use is hypertrichosis (hair growth) so used to treat males with baldness

Used to treat severe resistant hypertension with diuretic and beta blockers.

Which drugs are used in hypertensive crisis?

We have a direct vasodilator such as

SNP

Which liberates No(a vasodilator works through increasing the action of guanine cyclase- increasing Cgmp -cascade of events -increasing K+ channels)

Snp is very light sensitive and unstable in aqueous solution.

Vert short half life when you stop infusion you stop the effect

Not used because it is metabolized to sodium thiocyanate which causes toxicity through lactic acidosis

Side effects;

Rebound hypertension and tolerance

Diazoxide:

A vasodilator was used but not used now

because side effects of tachycardia and angina