THE UNIVERSITY OF JORDAN
FACULTY OF DENTISTRY
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Pharmacology

■ SUMMARY

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LECTURE # :18,19,20

ANTIHYPERTENSIVE DRUGS SUMMARY#1

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The drug	The use of the drug	Side effect	Mechanism of action	Alternatives	Notes
Diuretics : are drugs that enhance urine execration(diuresis) ➔if we increase execration of sodium in the kidney, water will follow the sodium so more sodium in the urine and more water and less blood plasma volume so we decrease the blood pressure.					**Needs some weeks to work." 3-4 weeks "**
Loop\high ceiling diuretics : Furozamide "Lasix"	-decrease Blood pressure	-affect serum lipid -affect insulin sensitivity	-act on Na\K\Cl symporter .	-Torsamide: free of metabolic side effects. - Potassium sparing diuretics	-Not used for type 2 diabetic patients . -not used for whom ,we don't want to lower their K concentration. -NOT USED FOR high cholesterol level ,gout and acute MI
Thiazide family : -hydrochlorothiazide **" first discovered ,** -chlorothalidone	-decrease blood volume and CO➔ decrease BP.	Early effect ➔increase PVR AFTER 3-4 weeks: Chronic effect➔dec. PVR	**Inhibit or blocking of the symporter,** so secretion of Na+ and Cl in the urine and more water secretion, increase urine volume decrease bloodvolume		Symporter responsible for reabsorbing of Cl- and K and Na+ in the distal tubules in the kidney and pump them back to the blood stream .
Potassium sparing diuretics	Treat hypertension and Preserve K in the body .			If no problem with furosemide we can give the patient K supplements , high K diet	
This is all in sheet 18 related to diuretics					

The drug	The use of the drug	Side effect	Mechanism of action	Alternatives	Notes
Vasodilators VD ➔ reflex tachycardia " major side effect "					
Hydralazine	-decrease B.P. -**heart failure** in combination with **isosorbide dinitrate**	-Drug induce Lupus syndrome Allergic reaction -tachyphylaxis➔tachycardia ➔baroreflex activation…	Not known but the effect of it is predicted to be on K-channels lead to hyperpolarization OR it release NO .	We replace them with CCB's	-First vasodilators used -Positive control **Isosorbide** = VD for angina Dinitrate= release NO
Diazoxide thiazide family*		-it causes **excessive hypotension**, so it used for emergency as IV bolus -working very fast 30sec	-work on K-channels ➔ hyperpolarization for **S.M**		-not a diuretic but VD
Sodium nitroprusside	Emergency – heart failure – suicide-surgery	-on respiratory process -**No** excessive reflex increase in cardiac output	-releases NO directly ,and affect walls of artery and veins		-Dangerous ,contains **cyanide** , - toxic metabolites thiocyanate
minoxidil	Retractable H.T	-hypertrichosis " increase the hair growth" **It's a therapeutic effect but becomes side effect when we use it as anti-HTD .** **-it might cause pericarditis**	Hyperpolarization, K-channels , potassium efflux	In intractable H.T used in combination with diuretic or beta blocker	(means the tension that is very hard to treat, so it is not responding to other vasodilators),

Fenildopam		-given in hospitals in small amounts it lead to fast hypotension,	Activation of dopamine receptors ,dilation of renal vasculature, decrease Blood pressure		-dopamine agonist -rapidly metabolized -
CCB calcium channel blockers	-effective in elderly - they are beneficial in inhibiting the heart failure when you want to inhibit the muscle contraction of the heart	- It does not have a lot of metabolic disturbances	-They block Ca-channels which influx Ca to the cell to activate the enzyme which needed to phosphorylate the myosin to intercalate actin so contraction . -it affect the PVR	- used in combination with diuretics	-The enzyme called "myosin light chain kinase "
nifidipine		**" compensating "** activate baro-reflex so increase H.R and C.O	-decrease PVR. very powerful		Very powerful
Dilitiazem +verapamil	Both are beneficial in inhibiting the heart failure when you want to inhibit the muscle contraction of the heart	Decrease PVR	-work on the heart calcium channel receptors by blocking them		
ACEI angiotensin II converting enzymes inhibitors The family name		-**cough** (dry cough); -**angioedema** (swallowing of the throat, an allergic reaction) -**Angioedema.** -**K+ retention**, especially in the presence of: 1.renal dysfunction or 2. when combined with K+ sparing diuretics or ARBs.	-inhibit ACE "less VC" -inhibit breakup bradykinin "more VASODILATION "		- we are elevating the bradykinin, which is an inflammatory mediator, so it causes some kind of an **allergic response**, so it causes cough. -angioedema can be lethal if it blocks the respiratory system
Aliskiren		They still studying the side effects	It inhibit one step of angiotensin II formation		Renin enzyme inhibitor

Spironolactone	When we **inhibit aldosterone** we will have **more sodium excretion** and more **absorption of** K.	**gynecomastia** (breast formation in the males), some people use another drug coz of this S.E		we use Spironolactone as a potassium sparing diuretic,	aldosterone inhibitor
Captopril	-diapitic neuropathy -diabetes. -protect from **progressive glomerulonephritis**.	-contraindicated **bilateral renal artery stenosis** -contraindicated in **pregnancy** -in the **2nd and 3rd** trimester because they cause malformation in the…	-they cause dilation of the afferent arterioles of the kidney -decreased proteinuria	-They can be combined with CCB	- **SH containing drug**, it is very **toxic**, so we don't use it that much, and it causes **proteinuria**
Enalapril	-ischemic H.D , heart failure ➔high renin hypertension	….kidneys development, - in **the 1st** trimester they are teratogenic. -These drugs are associated with First Dose Phenomena		-they don't work very well with beta-blockers .	-used a lot today -given **orally** as prodrug then metabolized to be **active "enalaprilat"** -given directly IV drug
Prazonsin	anti-hypertensive drug		-antagonist for alpha-1 receptor in the blood vessels - vasodilator		**First Dose Phenomena:** when you first give the drug to the patient he will go into hypotension so don't give him the drug when he is awake or standing, **it is better to give the first dose of the drug at bed time** until his body tolerates it (gets used to it) and then he will take it during the day.

ARB angiotensin II receptor blockers Losartan, Eprosartan, Valsartan, Candesartan. Irbesartan .					**Binding to: - ATR1➔vasoconstrction -ATR2➔vasodilation**
" sartan " **Telmisartan** peroxisome proliferator activator receptor PPAR	Hypertension + metabolic syndromes		It's an transcriptional factor and help in glucose metabolism - gamma agonist activity		
Sympatholyticsor Adrenergic Blockers					
Alpha Adrenergic Antagonist					
*Non selective Antagonists -phentolamine -phentoxibenzamine	**now Used only for pheochromocytcoma * Other that there are better drugs than them.**	- high NE in the circulation will lead to beta 2 receptors activation so reflex tachycardia	They inhibit both alpha 1 &2 receptors ,inhibit alpha 1 receptor will stop V.C Inhibit alpha 2 will stop the negative regulation of NE	All following drugs	**Tumor of adrenal gland** Used in operation of this tumor removal to counter the sudden change
*Alpha 1 -Selective Antagonists. -**Pra**zosin/ **Tera**zosin/ **Doxa**zosin.	Effective in moderate hypertension -and benign prostatic hypertrophy	- drowsiness, diarrhea, postural hypotension, tachycardia, fluid retention	-Same above but Selective for (α1 more than α2) -prostate hypertrophy lead to difficulty of urination ,so we inhibit alpha 1 receptors ➔ relax the muscles to able to urinate		**It follows First dose phenomena -free of metabolic effects -**
Beta Adrenergic Blockers -**Propran**olol: non selective -**Metapr**olol, **Bisopr**olol,Atenolol Betaxolol ,	-target both beta 1 and 2 -are more selective toward beta1	Bronchospasm, Impair lipid and glucose metabolism, hypoglycemia, heart failure in very sick hearts , CNS: fatigue, depression, impotence	1. Decrease HR, SV, and consequently C.O .2. Decrease Renin Release 3. Central Action 4. Inhibit NE release		**-non selective are not recommended when COPD i.e asthma -**

Adrenergic Neuron Blockers. Labetalol,carbedalol non selective	Lower blood pressure -phechromocytocoma	Decrease NE release or syn.			
Guanethidine			-replaces NE in the vesicles and kicks NE out - if NE displaced so it will be broken down .		**No NE release**
Reserpine		it blocks 5-HT receptors for serotonin , coz dopamine and NE participate in many other synthesis pathways.	-stops the uptake of dopamine into the vesicle ,so no NE synthesis.		**-No NE synthesis** **-Slow not for emergency** **-Cheap but not used now**
Ganglionic Blockers					
-Trimethaphan -Pentolinium -MecamylamineBlock	**-intraoperativel** -emergency	**Many side effects.** Coz the suppression will be for everything controlled by the blocked ganglia .	-If we block sympathetic ganglia ➔vasoconstriction - block parasympathetic ganglia ➔vasodilation		**-Not commonly used daily** , -Blocking the effect cause the opposite -

Centrally Acting Antihypertensive Drugs

Affect on: 1.Nucleus Tractus Solitarius ,2. Nucleus Ambiguus,3. Rostral Ventral Medulla

Propranolol Reserpine. Clonidine ➔read about it from the slides	1.Lipid soluble 2.Can cross BBB 3.Reduce the preganglionic sympathetic activation	No orthostatic hypotension but we still have side effects	➔Activation alpha receptors will decrease BP **(Act,alpha.dec.BP)للحفظ** Inhibition of NE release from presynaptic neuron ➔Activation beta receptors will increase BP **(Act,beta.inc.BP)للحفظ**		
Alpha-methyldopa	LOWER BP by binding to its receptor .	**- safe** to be used with **pregnancy** for hypertension	- Prevent the synthesis of NE ,and synthsis **alpha-methyldopaNE** -Lowers BP but not CO or renal blood flow	We give it as alternative to **ARBs & ACEI** coz these two not used in pregnancy.	**-Old drug** **-Work centrally and peripherally**