ANTI-HYPERTENSIVE DRUGS

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Overview

- The normal physiological function of the body requires blood circulation
- This is vital in enhancing the subsequent circulation of oxygen and other nutrients to the rest of the body
- This circulation is supposed to be done at a certain blood pressure (BP)
- Currently the pressure from 110/70mmHg and the upper limit of less than 140/90mmHg being the acceptable normal

Definition of Hypertension

- Hypertension is a common chronic disease which involves a persistent elevated arterial blood pressure(BP) of more that 140/90mmHg
- The targeted BP is 140/90mmHg though 130/80mmHg is currently the target in those with Cardiovascular conditions and diabetes
- For each 20mmHg systolic or 10mmHg diastolic BP increase, there is a 2 fold increase in risk of Cardiovascular diseases
- Increasing awareness and diagnosis of hypertension, and improving control of BP with appropriate treatment, are considered critical public health initiatives to reduce CV morbidity and mortality

Types of hypertension (ETIOLOGY)

Essential or primary hypertension

- Forms 90% of hypertension of the cases n most patients, hypertension results from an unknown pathophysiologic etiology

- This form of hypertension cannot be cured, but it can be controlled

Non essential or secondary hypertension)

- A small percentage (10%) of patients have a specific cause of their hypertension

- There are many potential secondary causes that are either concurrent medical conditions or are endogenously induced

- If the cause can be identified, hypertension in these patients has the potential to be cured

Factors controlling BP

- Multiple factors that control BP are potential contributing component;

i. Humoral - can either be the renin–angiotensin–aldosterone system [RAAS]) or vasodepressor mechanism

ii. Abnormal neuronal mechanisms

iii. Defects in peripheral auto regulation

iv. Disturbances in sodium, calcium, and natriuretic hormones

- Many of these factors are cumulatively affected by the multifaceted RAAS, which ultimately regulates arterial BP
- It is probable that none of these factors is solely responsible for essential hypertension
- However, most anti-hypertensives specifically target these mechanisms and components of the RAAS

Secondary causes of Hypertension

- The following are notable secondary causes of hypertension;

1. Diseases

2. Drugs
   - Prescription drugs
   - Street drugs and other natural products

3. Food substances

Diseases as causes of hypertension

- Chronic kidney disease
- Cushing's syndrome
- Coarctation of the aorta
- Obstructive sleep apnea
- Parathyroid disease
- Pheochromocytoma
- Primary aldosteronism
- Renovascular disease
- Thyroid disease

Drugs that can cause hypertension

Prescription drugs

- Adreneal steroids e.g prednisolone, fludrocortisone, triamcinolone
- Amphetamines or anorexiants
- Decongestants phenylephrine, pseudoephedrine
- NSAIDs e.g. ibuprofen, diclofenac, Valecoxibetc

Others:

- Bromocriptine, clozapine
- Beta blockers or or centrally acting alpha agonists
- Beta blockers without alpha blockers first when treating pheochromocytomawhen stopped abruptly when

Street drugs and other natural products

- Cocaine and cocaine withdrawal Ephedra alkaloids (e.g., Ma-huang),
- "herbal ecstasy," other phenylpropanolamine analogsa Nicotine withdrawal
- Anabolic steroids
- Narcotic withdrawal
- Methylphenidate
- Phencyclidine
- Ketamine
- Ergotamine and other ergot-containing herbal products
- St. John's wort

Food substances that can cause hypertension

- Sodium
- Ethanol
- Licorice
- Tyramine-containing foods if taking a monoamine oxidase inhibitor

Blood pressure as a mathematical product

- Blood pressure = cardiac output x Peripheral resistance
- Cardiac output relates to blood volume while peripheral resistance is the resistance or friction the blood has to go against as it moves along the blood vessel
- Elevated blood pressure can result from increased cardiac output and or increased total peripheral resistance

Stages of hypertension

BP Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)	Lifestyle Modification
Normal	< 120	AND	< 80	Encourage
Prehypertension	120–139	OR	80–89	Yes
Stage 1 hypertension	140–159	OR	90–99	Yes
Stage 2 hypertension	≥ 160	OR	≥ 100	Yes

BP = blood pressure.

Complications of hypertension

- When not well controlled hypertension can cause a number of complications that can be life threatening

- Be low are the major four hypertensive complications;

i. Congestive cardiac failure
ii. Renal failure
iii. Hypertensive retinopathy
iv. Stroke

NB:

Other cardiovascular complications have also been known to occur as complications

Treatment of hypertension

Goals o treatment

i. Reduce mortality and morbidity associated to hypertension
ii. Improve quality of life of patients
iii. Prevent end organ damage e.g., CV events, heart failure, and kidney disease)

- Reducing risk remains the primary purpose of hypertension therapy and the specific choice of drug therapy is significantly influenced by evidence demonstrating such risk reduction

Benefits of controlling BP

- 40% decrease in stroke
- 25% decrease in myocardial infarction
- 50% decrease in heart failure

Approaches to treatment

- After a definitive diagnosis of hypertension is made, most patients should be placed on both lifestyle modifications and drug therapy concurrently

- Lifestyle modification alone is considered appropriate therapy for patients with prehypertension

- However, lifestyle modifications alone are not considered adequate for patients with hypertension and additional CV risk factors

- These patients have BP goals of less than 130/80 mm Hg (e.g., diabetes, coronary artery disease, chronic kidney disease) or less than 120/80 mm Hg i.e. left ventricular dysfunction)

Non Pharmacological treatment of hypertension

Modification	Recommendation
Weight loss	Maintain normal body weight (body mass index 18.5–24.9 kg/m2)
DASH(Dietary approaches to stop Hypertension)	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat
Reduced salt intake	Reduce daily dietary sodium intake as much as possible, ideally to ≈65 mmol/day (1.5 g/day sodium, or 3.8 g/day sodium chloride)
Physical activity	Regular aerobic physical activity (at least 30 min/day, most days of the week)
Moderation of alcohol intake	Limit consumption to ≤2 drinks/day in men and ≤1 drink/day in women and lighter-weight persons

Types of anti-hypertensive drugs

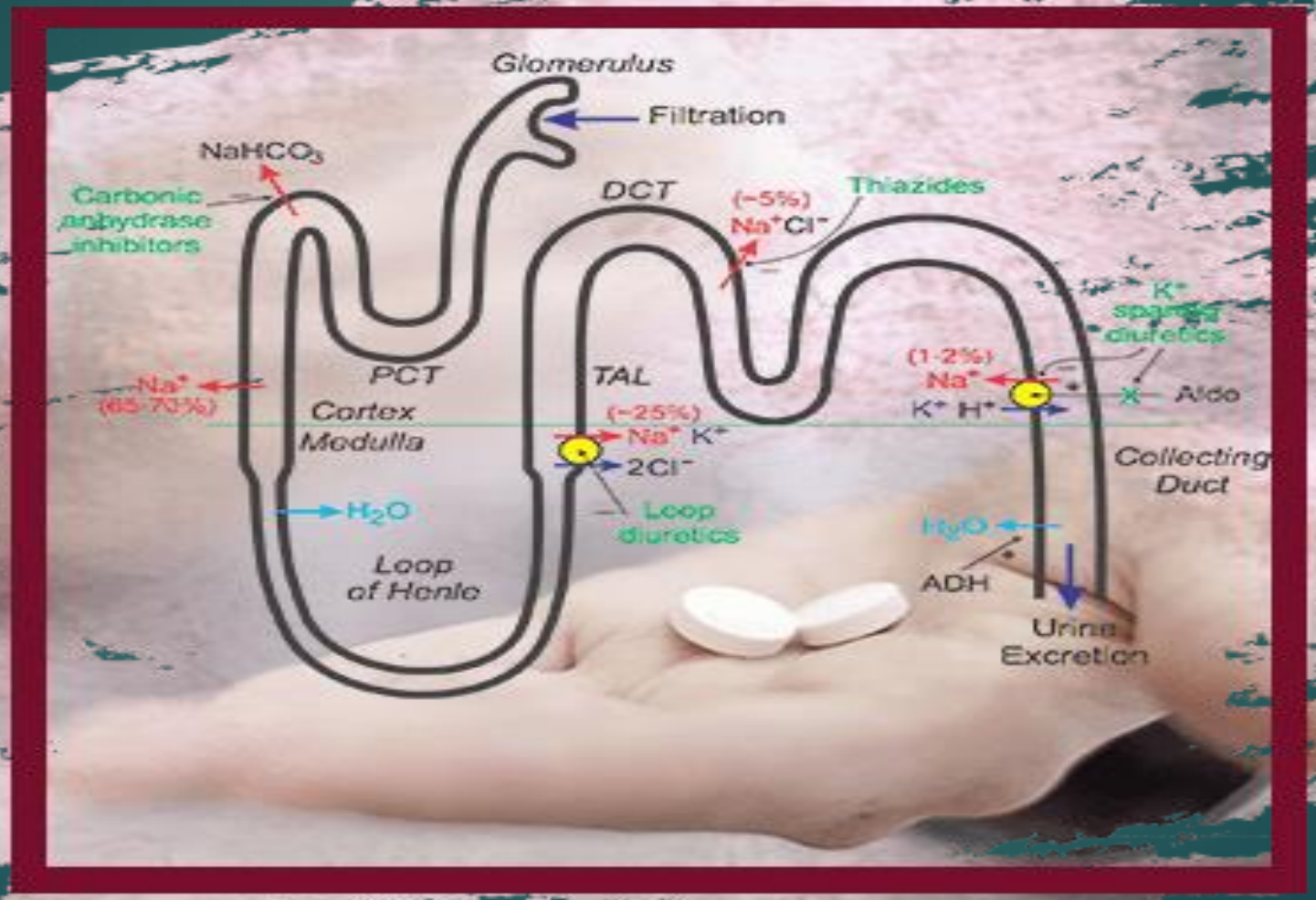
- The following groups of drugs are used in hypertension;
- Diuretics
  - Thiazides diuretics
  - Loop diuretics
  - Potassium sparing diuretics
  - Osmotic diuretics
  - Carbonic anyhydrase inhibitors
- Angiotensin converting enzyme inhibitors (ACE-Is)
- Angiotensin receptor blockers (ARBs)
- Calcium channel blockers
- Beta blockers
- Alpha receptor blockers
- Centrally acting drugs

DIURECTICS

Mechanism of Action and Sites

- Diuretics are drugs that slow down the absorption of salts and fluids in the kidney tubules, thereby increasing the volume of fluid excreted by the urinary system
- These drugs accelerate the flow of urine
- Their effect is based on the ability to inhibit the reabsorption of electrolytes by the kidneys
- Enhanced elimination of electrolytes is accompanied by an increase in the volume of fluid excreted from the body through osmotic pressure
- All this achieved at different sites of the nephron i.e. the proximal convoluted tubule, ascending loop of henle, distal convoluted tubule and the collecting duct

Different sites of diuretic actions



Loop diuretics

- **Examples** – Furosemide, Torasemide, Bumetanide, Ethacrynic acid

- **Site of Action**

- Ascending loop of henle where they inhibit the protein or enzyme **$Na^+/K^+/2Cl^-$ transporter** and thus preventing absorption of the said ions, with water following by osmosis
- Also work by a secondary mechanism namely; **dilatation of capacitance veins**, an effect which reduces preload and enhances the contractile ability of cardiac muscle

Indications

- Hypertension
- Congested cardiac failure
- Pulmonary edema
- Liver renal dysfunction – treating fluid build up associated with these conditions (Ascites)

Side effects

- Hypotension, hypokalemia, hypocalcemia, dehydration, hyperglycemia, electrolyte loss, dizziness, faintness, elevated serum creatinine concentration, ototoxicity, nephrotoxicity

Contraindications of loop diuretics

- Dehydration or severe hypovolemia
- Patients taking aminoglycosides like gentamycin, amikacin and the like due to the increase risk of ototoxicity and nephrotoxicity
- Hepatic encephalopathy where hypokalemia can worsen coma
- Patients with gout as reduces the excretion of uric acid when taken for a long time
- Recommended to be taken early in the day to avoid nocturia which can affect the quality of sleep
- Pregnancy – belong to category C and thus risk cannot be ruled out
- Combination with ACE inhibitors and NSAIDs – leads to triple whammy effect and hence heightening risk of kidney failure
- Patients with know history of sulfa allergies except ethacrynic acid which is a not a sulfa drug

Thiazide diuretics

Examples

- Hydrichlorothiazide, bendroflumethiazide, indapamide, metalazone

Site of action

- Distal convoluted tubule

Indication

- First line treatment of hypertension

Side effects

- Hypovolemia, hypokalemia, metabolic alkalosis, hyperuricemia, hypercalcemia, glucose intolerance

Potassium sparing diuretics

Examples

- Spironolactone, Eplerenone, Amloride, Triamterene

Site of action

- Collecting duct or later part of the distal convoluted tubule

Indication

- Congestive cardiac failure
- Hypertension

Side effects

- Hyperkalemia

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-Is)

Examples

- Enapril, Ramipril, Lisinopril, Perindopril, Captopril, Fosinopri

Mechanism of action

- They work by inhibiting the enzyme, **angiotensin-converting enzyme** (ACE), an enzyme responsible for converting angiotensin I to angiotensin II
- Angiotensin II is a potent vasoconstrictor and blocking its formation helps of peripheral resistance
- Furthermore, by blocking ACE, these drugs prevent aldosterone release from the adrenal cortex and eliminate sodium ions (along with water) from the kidneys
- These two cumulative effects serve to reduce blood volume and blood pressure.

Indications

- Hypertension - ACE inhibitors reduce the risk of serious cardiovascular events, such as heart attack and stroke. They may be used first or second-line, usually in combination with another drug

- Iscaemic heart disease – Reduce risk of cardiovascular events and stroke

- Chronic cardiac failure – symptomatic relief and overall prognosis

- Diabetic nephropathy – prevent nephropathy from progressing in diabetic patients . Also used for chronic kidney disease to reduce proteinuria

NB

- They are the best choice in hypertensive patients with diabetes co-morbidity

Side effects

- **Hypotension** – first-dose hypotension is prevalent with ACE inhibitors
- **Persistent, dry cough** – due to pulmonary kinin accumulation
- **Hyperkalemia** – ACE inhibitors promote potassium retention
- Angioedema – the drug should be stopped immediately if this occurs
- **Other** – fatigue, nausea, dizziness, headache

NB:

- Because ACE inhibitors cause hyperkalemia, patients should not be prescribed other potassium-elevating drugs or supplements

ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

Examples

- Candesartan
- Irbesartan
- Losartan
- Telmisartan

- Mechanism of Action
- Angiotensin-receptor blockers have a similar mechanism of action to ACE inhibitors.
- Whereas ACE inhibitors block the conversion of angiotensin I into angiotensin II, ARBs work by **blocking the action of angiotensin II at the AT_1 receptor**. Because angiotensin II promotes aldosterone secretion and acts as a vasoconstrictor, its blockage reduces peripheral vascular resistance and lowers blood pressure.

Side effects of ARBs

- **Hypotension**
- **Hyperkalemia**
- **Renal failure** (as with ACE inhibitors)
- **Cough** – though less likely than with an ACE inhibitor

- Due to the risk of hyperkalemia, other potassium-elevating drugs should not be prescribed including potassium supplements, potassium-sparing diuretics

- As with ACE inhibitors, taking ARBs with NSAIDs increases the risk of renal failure

CALCIUM CHANNEL BLOCKERS (CCBs)

Types of Calcium Channel blockers

Dihydropyridines

- Amlodipine
- Nifedipine (safe in gestational hypertension!)
- Felodipine
- Nimodipine

Non - dydropyridines

Diphenyl alkylamines

- Verapamil

Benzothiazepines

- Diltiazem

Dihydropyridines have greater selectivity for the vasculature in contrast to non-dihydropyridines which have greater selectivity for the heart

Mechanism of action of CCBs

- Calcium channel blockers reduce calcium entry into vascular and cardiac cells
- This leads to reduced intracellular calcium concentration which, in turn, causes relaxation and vasodilation in arterial smooth muscle
- Calcium channel blockers also reduce myocardial contractility in the heart and suppress cardiac conduction at the AV node
- Reduced cardiac rate, contractility and afterload lower myocardial oxygen demand and thus preventing angina

Indications of CCBs

- Hypertension (Forms part of the first line agents)
- Angina pectoris
- Nifedipine is also used as a tocolytic agent

Side effects of CCBs

- Flushing, headache, ankle swelling, palpitations, light headedness, shortness of breath, constipation (most common with verapamil), **gingival hyperplasia** (gum overgrowth)

NB:

- CCBs especially non dihydropyridines should not be combined with beta-blockers except under specialist supervision as both drug classes are negatively inotropic and negatively chronotropic

- Taken together, this can lead to heart failure, bradycardia and asystole

BETA BLOCKERS

Examples

- Acebutelol
- Metoprolol
- Bisoprolol
- Labetalol (safe in gestational hypertension)
- Nebivolol
- Propanolol
- Timolol
- Betaxolol
- Carvedilol

Mechanism of action

- reduce renin secretion from the kidney – an effect ordinarily mediated by beta-1 receptors.
- Direct blockage of the beta 1 receptors reduce the heart rate and contractility

Specific properties

- Compairing the drugs; propranolol, nadolol, pindolol and timolol some specific properties are found with individual drugs
- Pindolol is found to have intrinsic sympathomimetic activity or partial agonist activity which enables it to exert a weak agonist effect on β – adrenoceptors
- Although propranolol and pindolol have membrane stabilizing effects (Local anesthetic activity), nadolol and timolol do not
- This membrane stabilizing activity causes the blockage of sodium channels in nerves and heart tissue thereby, slowing conduction velocity
- Propranolol the first β-blocker approved (Prototype) for clinical use is distinguished by it high lipid solubility and CNS penetration and hence a higher incidence of side effects such as headache, psychosis, nightmares, sleep disturbances, vertigo, visual disturbance

Indications Non selective β-blockers

Pindolol

- Approved for hypertension treatment

Propranolol

- Treatment of hypertension, angina pectoris and cardiac arrhythmias
- Prevention of migraine headaches and as adjunctive therapy in treatment of acute thyrotoxicosis, acute myocardial function and pheochromocytoma

Nadolol

- Treatment of hypertension, angina pectoris and prevention of migraine headache

Timolol

- Administered orally for treatment of hypertension, to reduce risk of death in patients with acute myocardial infarction and prevention of migraine headache

- Ocular topical application for treatment of glaucoma and is suitable because it does not have local anesthetic effect and hence cannot anesthetize the cornea when instilled into the eye

Selective β_1-blockers

- These have a greater affinity for β_1 than for β_2 adrenoceptors and because β_1 are primarily located in the cardiac tissue, β_1-blockers are also known as cardio selective β-blockers

- Examples are acebutolol, atenolol, esmolol and metoprolol

- Comparing with non selective β-blockers, selective β_1-blockers produce less bronchoconstriction and other mediated effects

- Their selectivity for β_1 adrenoceptors is not absolute and therefore, blockade of β_2-receptors increases with dose and hence β_1 should be used with caution in patients with asthma

NB: with the last point in mind, it is important to appreciate that cardio selectivity is not the same as cardio specificity

Specific properties and indications for selective β1-blockers

Acebutolol

- Administered orally for treatment of hypertension and cardiac arrhythmias

Atenolol

- Shows less variability in its oral absorption than do other β – blockers and is largely excreted unchanged in the urine and has lower lipid solubility
- Administered orally for treatment of hypertension, angina pectoris and acute myocardial infaction

Esmolol

- Has shorter half life compared to others β – blockers and is administered intravenously for treatment of hypertension and acute supraventricular tachycardia when these occur during surgery

Metoprolol

- Used to treat hypertension, angina pectoris and acute myocardial infarction

- Administered orally or parenterally and is extensively metabolized by CYP450 enzymes before undergoing renal excretion

Other β_1- selective antagonists

- These include bisoprolol and betaxolol

- Both of these drugs are administered orally for treatment of hypertension

- Topical application of betaxolol also reduces aqueous humour secretion while producing negligible systemic β-adrenoceptors and hence it is used in treatment of chronic open angle glaucoma

α and β – Adrenoceptor Antagonists

- These block both α and β adrenoceptors and they include carvedilol and labetalol

Carvedilol

- Carvedilol blocks β_1, β_2 and α_1 adrenoceptors and also possesses antioxidant activity
- Each of these properties offer the cardioprotective effect

Antioxidant effects of carvedilol

- Inhibition of lipid peroxidation in myocardial membranes
- Scavenging of free radicals
- Prevention of neutrophil release of O_2
- Additionally carvedilol has antiapoptotic effect which helps prevent myocyte death and reduce infarct size in persons with myocardial ischaemia

Indications of carvedilol

- Carvedilol is therefore referred to as third generation β-blockers and neurohumoral antagonists and its value in treating myocardial infarction has been established

- Carvedilol is used in management of hypertension

Labetalol

- This is a non selective β blocker and selective α_1 blocker that is primarily used in the treatment of hypertension

- Labetalol decreases heart rate and cardiac output as a result of β_1-adrenoceptor blockade and it reduces peripheral vascular resistance as a result of α_1-adrenoceptor blockade