Cardiovasculer Disese

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This lectuer discusses the pharmacology of drugs used to reduce morbidity and mortality from cardiovascular diseases, particularly in western countries, such as hypertension, congestive heart failure, angina pectoris, and cardiac arrhythmias.

Hypertension:

Hypertension may be classified in to three categories, according to the level of **diastolic blood pressure**:

- **Mild** hypertension with a diastolic blood pressure between 95-105 mmHg
- **Moderate** hypertension with a diastolic blood pressure between 105 – 115mmHg
- **Severe** hypertension with a diastolic blood pressure above 115mmHg.A

- Sustained arterial hypertension damages blood vessels in kidney, heart, and brain, leading to increased incidence of renal failure, cardiac failure, and stroke.
- Effective pharmacologic lowering of blood pressure prevents vessel damage and reduces morbidity and mortality.

- Blood pressure is determined by cardiac output (stroke volume x heart rate) and total peripheral resistance of the vasculature.
- Elevated blood pressure is caused by psychological stress, genetic inheritance, environmental and dietary factors.
- Essential hypertension (80-90% of cases) and secondary hypertension arise from other conditions like atherosclerosis, renal disease, and endocrine diseases.

- Antihypertensive therapy aims to lower arterial blood pressure, regardless of the cause.
- Therapy choice depends on age, sex, race, body build, lifestyle, disease cause, co-existing diseases, onset and severity, and presence or absence of other cardiovascular disease risk factors.

Antihypertensive therapies.

1. Non pharmacological therapy of hypertension

Several non-pharmacological approaches to therapy of hypertension are available. These include:

- Low sodium chloride diet
- Weight reduction
- Exercise
- Cessation of smoking
- Decrease in excessive consumption of alcohol

- Psychological methods (relaxation, meditation …etc)
- Dietary decrease in saturated fats.

2. Pharmacological therapy of hypertension.

Most patients with hypertension require drug treatment to achieve sustained reduction of blood pressure.

Currently available drugs lower blood pressure by decreasing either cardiac output (CO) or total peripheral vascular resistance (PVR) or both.

Anti - hypertensive drugs are classified according to the principal regulatory site or mechanism on which they act. They include:

A)Diuretics:

which lower blood pressure by depleting the body sodium and reducing blood volume. Diuretics are effective in lowering blood pressure by 10 – 15 mmHg in most patients.

1\ **Thiazides and related drugs**: Reduce blood pressure by reducing blood volume and cardiac output. Chronic administration reduces blood pressure by decreasing peripheral vascular resistance.

increase in urinary water and electrolyte particularly sodium excretion. With chronic administration (6-8weeks), they decrease blood pressure by decreasing peripheral vascular resistance as the cardiac out put and blood volume return gradually to normal values. Thiazides are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function

2\ Loop diuretics: e.g. furosemide are more potent than thiazides as diuretics. The antihypertensive effect is mainly due to reduction of blood volum . Loop diuretics are indicated in cases of severe hypertension which is associated with renal failure, heart failure or liver cirrhosis.

3\ Potassium sparing diuretics:

e.g. spironolactone They are used as adjuncts with thiazides or loop diuretics to avoid excessive potassium depletion and to enhance the natriuretic effect of others. The diuretic action of these drugs is weak when administered alone.

B)Sympathoplegic agents (Depressants of sympathetic activity).

Based on the site or mechanism of action sympathoplegic drugs are divided into:

1-Centrally acting sympathetic depressants act by stimulating α2 - receptors located in the vasomotor centre of the medulla.

As a result, sympathetic out flow from the medulla is diminished and either total peripheral resistance or cardiac out put decreases. . Methyldopa is useful in the treatment mild to moderately severe hypertension.

2-Adrenoceptor antagonists, e.g propranolol (beta blocker), prazosin (alpha blocker), labetalol (alpha and beta blocker).

3-Blockers antagonize beta, receptors located on the myocardium and prevent the cardio acceleration.

The rate and force of myocardial contraction is diminished, decreasing cardiac out put and thus, lowering blood pressure.

An additional effect which can contribute to a reduction of blood pressure is that renin release is mediated by β receptors. Therefore, receptor blockade prevents angiotensin II formation and associated aldosterone secretion, resulting in a decrease in total peripheral resistance and blood volume.

C- Angiotensin converting enzyme inhibitors, e.g. captopril, enalapril, etc. The prototype is captopril. Captopril inhibits angiotensin converting enzyme that hydrolyzes angiotensin I (Inactive) to angiotensin II (Active), a potent vasoconstrictor, which additionally stimulates the secretion of aldosterone.

It lowers blood pressure principally by decreasing peripheral vascular resistance. The adverse effects include maculopapular rash, angioedema, cough, granulocytopenia and diminished taste sensation. Enalapril is a prodrug with effects similar to those of captopril.

D- Calcium channel blockers, e.g. nifedipine, verapamil, nicardipine, etc. The prototype is verapamil. The mechanism of action in hypertension is inhibition of calcium influx in to arterial smooth muscle cells, resulting in a decrease in peripheral resistance. Verapamil has the greatest cardiac depressant effect and may decrease heart rate and cardiac out put as well. The most important toxic effects for calcium channel blockers are cardiac arrest, bradycardia, atrioventricular block and congestive heart failure.

Lines of treatment of primary hypertension

The initial step in treating hypertension may be non-pharmacologic.

- Dietary salt restriction may be effective treatment for about half of the patients with mild hypertension.
- Weight reduction even without salt restriction normalizes blood pressure in up to 70% of obese patients with mild to moderate hypertension. Regular exercise may also be helpful in some hypertensive patients.

When non-pharmacologic approaches do not satisfactorily control blood pressure, drug therapy begins in addition to non-pharmacological approaches.

The selection of drug(s) depends on various factors such as the severity of hypertension, patient factors (age, race, coexisting diseases, etc.).

For most patients with mild hypertension and some patients with moderate hypertension monotherapy with either of the following drugs can be sufficient.

- Thiazide diuretics
- Beta blockers
- Calcium channel blockers
- Angiotensin converting enzyme inhibitors
- Central sympathoplegic agents

Notes :

- Beta-blockers preferred in young patients, high renin hypertension, and those with tachycardia or angina.
- Black patients respond better to diuretics and calcium channel blockers than beta-blockers and ACE inhibitors.
- If mono-therapy fails, combination of two drugs with different action sites may be used.
- If hypertension is not under control, a third drug like vasodilator may be combined.

• When three drugs are required, a combination of diuretic, sympathoplegic agents, ACE inhibitor, and direct vasodilator or calcium channel block is effective.

• Treatment of hypertensive emergencies usually starts with furosemide, diazoxide, sodium nitroprusside, hydralazine, trimethaphan, and labetalol.

Thank you