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Cardiovascular drugs & Renal Drugs

The most commonly encountered cardiovascular disorders include hypertension, congestive heart failure, angina pectoris and cardiac arrhythmias. Most drugs available currently are able to reduce the morbidity and mortality due to these disorders.

Antihypertensive drugs

Hypertension is defined as an elevation of arterial blood pressure above an arbitrarily defined normal value. The American Heart Association defines hypertension as arterial blood pressure higher than 140/90mmHg (based on three measurements at different times).

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.

Sustained arterial hypertension damages blood vessels in kidney, heart and brain and leads to an increased incidence of renal failure, cardiac failure, and stroke.

Effective pharmacologic lowering of blood pressure prevents the damage to blood vessels and reduces the morbidity and mortality rate.

In order to understand the pathophysiology of hypertensive states and, in turn, the underlying rationale of drug therapy, an

appreciation of the systems normally involved in monitoring and regulating blood pressure is required.

Two factors which determine blood pressure are cardiac output (stroke volume x heart rate) and total peripheral resistance of the vasculature. Blood pressure is regulated by an interaction between nervous, endocrine and renal systems

Elevated blood pressure is usually caused by a combination of several abnormalities such as psychological stress, genetic inheritance, environmental and dietary factors and others.

Patients in whom no specific cause of hypertension can be found are said to have essential hypertension or primary hypertension (accounts for 80-90 % of cases).

Secondary hypertension arises as a consequence of some other conditions such as, atherosclerosis, renal disease, endocrine diseases and others. The central issue of antihypertensive therapy is to lower arterial blood pressure, irrespective of the cause.

The choice of therapy of a patient with hypertension depends on a variety of factors: age, sex, race, body build, life-style of the patient, cause of the disease, other co-existing disease, rapidity of onset and severity of hypertension, and the presence or absence of other risk factors for cardiovascular disease (e.g. smoking, alcohol consumption, obesity, and personality type).

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

This may be sufficient for the treatment of some mild hypertensive cases.

The major advantage of non-pharmacological approaches is the relative safety and freedom from side effects, compared with drug therapy.

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 although changes in one can indirectly affect the other. Anti - hypertensive drugs are classified according to the principal regulatory site or mechanism on which they act. They include:

1-) **Diuretics**, which lower blood pressure by draining the body sodium and reducing blood volume. Diuretics are effective in lowering blood pressure by 10 – 15 mmHg in most patients. Diuretics include:

a) **Thiazides** and related drugs, e.g. hydrochlorthiazide bendrofluazide, chlorthalidone, etc.

Initially, thiazide diuretics reduce blood pressure by reducing blood volume and cardiac output as a result of a pronounced 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 output 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.

b) **Loop diuretics**, e.g. furosemide, ethacrynic acid, etc.

Loop diuretics are more potent than thiazides as diuretics. The antihypertensive effect is mainly due to reduction of blood volume.

Loop diuretics are indicated in cases of severe hypertension which is associated with renal failure, heart failure or liver cirrhosis.

c) **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.

2-) **A sympatholytic** (or sympathoplegic) drug is **a medication that opposes the sympathetic nervous system (SNS)**.

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

a) **Centrally acting antihypertensive agents** e.g. methyldopa, clonidine

Centrally acting sympathetic depressants act by stimulating α_2 receptors located in the vasomotor center of the medulla. As a result, either total peripheral resistance or cardiac output decreases. . Methyldopa is useful in the treatment mild to moderately severe hypertension.

The side effects of methyldopa include sedation, vertigo, dry mouth, nausea, vomiting, diarrhea, postural hypotension,

impotence, hemolytic anemia, weight gain and hypersensitivity reactions (fever, liver damage, thrombocytopenia).

b) **Adrenoceptor antagonists**, e.g propranolol (beta blocker), prazosin (alpha blocker), labetalol (alpha and beta blocker).

beta 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.

The principal action of alpha adrenergic blocking drugs is to produce peripheral vasodilation.

Treatment with prazosin should be initiated with low dose (1mg 3 times daily) to prevent postural hypotension and syncope or be given at bed time.

c) **Adrenergic neuron – blocking agents**, e.g. guanethidine

Guanethidine blocks adrenergic nerve transmission, preventing the release of transmitter. It lowers blood pressure by reducing both cardiac output and total peripheral resistance.

d) **Drugs which deplete catecholamine stores**, e.g. reserpine.

Reserpine interferes with the storage of endogenous catecholamines in storage vesicles as a result of which little neurotransmitter is released upon stimulation. It leads to reduction of cardiac out put and peripheral vascular resistance. Reserpine is a second-line drug for treatment of hypertension.

e) **Ganglion blockers**, e.g. trimethaphan, trade name **Arfonad** is ganglion blocking drug which is reserved for use in hypertensive emergencies only.

3-) **Direct vasodilators**. These include:-

- Arterial vasodilators, e.g. hydralazine
- Arteriovenous vasodilators, e.g. sodium nitroprusside

Hydralazine: It dilates arterioles but not veins. It is used particularly in severe hypertension. The most common adverse effects are headache, nausea, anorexia, palpitations, sweating and flushing which are typical to vasodilators.

Sodium nitroprusside: It is a powerful vasodilator that is used in treating hypertensive emergencies as well as severe cardiac failure. It dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return. Nitroprusside rapidly lowers blood pressure and it is given by **intravenous infusion.**

The most serious toxicities include metabolic acidosis, arrhythmias, excessive hypotension and death.

4-) **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.

5-) **Calcium channel blockers**, e.g. nifedipine brand name Adalat , verapamil, nicardipine, etc.

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 output 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 treatment of hypertensive emergencies is usually started with furosemide given by parenteral route at dose of 20-40mg. In addition, parenteral use of sodium nitroprusside, hydralazine can be indicated.

Drug used in heart failure

Congestive heart failure occurs when there is an inability of the heart to maintain a cardiac output sufficient to meet the requirements of the metabolizing tissues.

Heart failure is usually caused by one of the following:

Ischaemic heart disease, Hypertension, Heart muscle disorders, & Valvular heart disease.

Drugs used to treat heart failure can be broadly divided into:

A. Drugs with positive inotropic effect.
B. Drugs without positive inotropic effect.

A. **Drugs with positive inotropic effect**:-

Drugs with positive inotropic effect increase the force of contraction of the heart muscle. These include:

- Cardiac glycosides,
- Bipyridine derivatives,
- Sympathomimetics, and
- Methylxanthines

1. **Cardiac glycosides:** Cardiac glycosides comprise a group of steroid compounds that can increase cardiac output and alter the electrical functions. Commonly used cardiac glycosides are **digoxin & digitoxin**. Digitoxin is a cardiac glycoside sometimes used in place of DIGOXIN. **It has a longer half-life than digoxin**

Therapeutic uses of cardiac glycosides include:

- Congestive heart failure
- Atrial fibrillation,
- Atrial flutter, and
- Paroxysmal atrial tachycardia.

Toxicity of cardiac glycosides include:

- Gastrointestinal effects such as anorexia, nausea, vomiting, diarrhoea
- Cardiac effects such as bradycardia, heart block, arrhythmias
- CNS effects such as headache, malaise, hallucinations, delirium, visual disturbances (yellow vision)

2. **Bipyridine derivatives**, e.g. amrinone, milrinone.

These drugs possess both positive inotropic effect and vasodilator effects.

Bipyridine derivatives are used in cases of heart failure resistant to treatment with cardiac glycosides and vasodilators.

3. **Beta - adrenergic stimulants** e.g. dobutamine, dopamine

The increase in myocardial contractility by beta stimulants increase the cardiac output. It is reserved for management of acute failure or failure refractory to other oral agents.

4. **Methylxanthines,** e.g. theophylline in the form of aminophylline

Aminophylline has a positive inotropic effect, bronchodilating effect and a modest effect on renal blood flow. It is used for management of acute left ventricular failure or pulmonary edema.

B. Drugs without positive inotropic effect. These include:

- Diuretics, e.g. hydrochlorothiazide, furosemide
- Vasodilators, e.g. hydralazine, sodium nitroprusside
- Angiotensin converting enzyme inhibitors e.g. captopril, enalapril

1. **Diuretics**: Diuretics are first – line drugs for treatment of patients with heart failure. In mild failure, a thiazide may be sufficient but are ineffective at low glomerular filtration rates. Moderate or severe failure requires a loop diuretic.In acute failure, diuretics play important role by reducing ventricular preload.
2. **Vasodilators:** The vasodilators are effective in acute heart failure because they provide a reduction in preload (through venous dilation), or reduction in after-load (through arteriolar dilation), or both. Vasodilator agents are generally reserved for patients who are intolerant of or who have contraindications to ACE inhibitors.
3. **Angiotensin converting enzyme (ACE) inhibitors**. These drugs reduce after load by reducing peripheral resistance and also reduce preload by reducing salt and water retention by way of reduction in aldosterone secretion.

The following are essential for long-term management of chronic heart failure:

Modify cardiovascular risk factor profile, e.g. cigarette smoking, obesity, salt intake Underlying causes should be treated, e.g. anemia, hypertension, valvular disease If this proves inadequate, diuretic should be given.

Give ACE inhibitor and digitalis (ACE inhibitors may be used before digitalis). In patients with persisting symptoms give vasodilators besides increasing the dose of diuretic and ACE inhibitors.