CHAPTER 3

CARDIOVASCULAR DRUGS

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INTRODUCTION

Cardiovascular diseases were once regarded as major health concerns primarily in Western countries. Cardiovascular disorders, on the other hand, are becoming more prevalent in developing countries like India. Hypertension, congestive heart failure, angina pectoris, and cardiac arrhythmias are the most common cardiovascular disorders. Because most drugs currently available can reduce morbidity and mortality associated with these disorders, this chapter will focus on their pharmacology.

I. Antihypertensive Drugs

a. General consideration

- Hypertension is characterised by an increase in arterial blood pressure above a predetermined normal level. Hypertension is defined by the American Heart Association as a blood pressure reading of 140/90mmHg or higher (based on three measurements at different times).
- According to the level of diastolic blood pressure, hypertension can be divided into three categories.
- Mild hypertension- Diastolic blood pressure between 95-105 mmHg
- Moderate hypertension- Diastolic blood pressure between 105 – 115mmHg
- Severe hypertension- Diastolic blood pressure above 115mmHg.

Chronic arterial hypertension damages blood vessels in the kidneys, heart, and brain, increasing the risk of renal failure, cardiac failure, and stroke.

Effective pharmacologic blood pressure lowering prevents blood vessel damage and lowers morbidity and mortality rates. An understanding of the systems normally involved in monitoring and regulating blood pressure is required in order to understand the pathophysiology of hypertensive states and, as a result, the underlying rationale of drug therapy. Cardiac output (stroke volume x heart rate) and total peripheral resistance of the vasculature are two factors that influence blood pressure. The nervous, endocrine, and renal systems interact to control blood pressure.

Psychological stress, genetic inheritance, environmental and dietary factors, and others can all contribute to high blood pressure. Patients with essential hypertension, also known as primary hypertension, have no identifiable cause for their high blood pressure (accounts for 80-90 percent of cases). Secondary hypertension is caused by a variety of other conditions, including atherosclerosis, renal disease, endocrine disorders,

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and others. The goal of antihypertensive therapy, regardless of the cause, is to lower arterial blood pressure.

The treatment for hypertension is determined by a number of factors, including the patient's age, gender, race, body type, lifestyle, disease cause, other co-existing diseases, hypertension onset and severity, and the presence or absence of other cardiovascular risk factors (e.g. smoking, alcohol consumption, obesity, and personality type).

b. Antihypertensive Therapies

1. Non pharmacological therapy of hypertension

There are several non-pharmacological approaches to treating hypertension. These consist of:

- Weight reduction
- Exercise
- Low sodium chloride diet
- Cessation of smoking
- Decrease in excessive consumption of alcohol
- Psychological methods (relaxation, meditation …etc)
- Dietary decrease in saturated fats.

Patients' sensitivity to these non-pharmacological approaches varies, but on average, only modest blood pressure reductions (5 to 10 mmHg) can be achieved. For some mild hypertensive cases, this may be sufficient treatment. When compared to drug therapy, the main advantage of nonpharmacological approaches is their relative safety and lack of side effects.

2. Pharmacological therapy of hypertension.

The majority of patients with hypertension require medication to achieve long-term blood pressure reduction. Current drugs lower blood pressure by lowering cardiac output (CO), total peripheral vascular resistance (PVR), or both, though changes in one can affect the other indirectly. Physiological mechanisms, on the other hand, tend to oppose a drug-induced reduction in blood pressure.

Anti - Hypertensive drugs are classified based on their main regulatory site or mechanism of action. They consist of:

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.

Diuretics Include

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

Thiazide diuretics lower blood pressure by reducing blood volume and cardiac output due to a significant increase in urinary water and electrolyte excretion, particularly sodium. They lower blood pressure by lowering peripheral vascular resistance as cardiac output and blood volume gradually return to normal after 6-8 weeks of treatment. Most patients with mild to moderate hypertension and normal renal and cardiac function can benefit from thiazides.

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

As diuretics, loop diuretics are more effective than thiazides. The reduction of blood volume is primarily responsible for the antihypertensive effect. In cases of severe hypertension associated with renal failure, heart failure, or liver cirrhosis, loop diuretics are prescribed.

c) Potassium sparing diuretics, e.g. spironolactone

They're used in combination with thiazides or loop diuretics to avoid potassium depletion and to boost the natriuretic effect of others. When used alone, these drugs have a weak diuretic effect.

B. Sympathoplegic agents (Depressants of sympathetic activity). Based on the site or mechanism of action sympathoplegic drugs are divided into:

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

Sympathetic depressants that act centrally work by stimulating 2 - receptors in the medulla's vasomotor centre. As a result, sympathetic outflow from the medulla decreases, lowering total peripheral resistance or cardiac output. Methyldopa is effective in the treatment of mild to moderate hypertension.Methyldopa is a prodrug that must be converted to active methylnorepinephrine in the CNS in order to have an effect on blood pressure. Sedation, vertigo, dry mouth, nausea, vomiting, diarrhoea, postural hypotension, impotence, haemolytic anaemia, weight gain, and hypersensitivity reactions are all side effects of methyldopa (fever, liver damage, thrombocytopenia).

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

Blockers antagonize beta, receptors located on the myocardium and prevent the cardio acceleration, which follows sympathetic stimulation.

The rate and force of myocardial contraction is reduced, lowering blood pressure and decreasing cardiac output. Renin release is mediated by receptors, which has an additional effect that can help lower blood pressure. As a result, receptor blockade reduces total peripheral resistance and blood volume by preventing angiotensin II formation and associated aldosterone secretion.

The main effect of alpha adrenergic blockers is that they cause peripheral vasodilation. By dilating both resistance and capacitance vessels, alpha blockers lower arterial pressure. To avoid postural hypotension and syncope, prazosin should be started at a low dose (1 mg three times daily) or given at bedtime. Guanethidine is an adrenergic neuron blocker that is prescribed for the treatment of severe hypertension.

c) Adrenergic neuron – blocking agents, e.g. guanethidine Guanethidine is an adrenergic neuron blocker that is prescribed to treat severe hypertension. Guanethidine inhibits the release of transmitter by blocking adrenergic nerve transmission. It reduces both cardiac output and total peripheral resistance, lowering blood pressure.

d) Drugs which deplete catecholamine stores, e.g. reserpine. Reserpine prevents endogenous catecholamines from being stored in storage vesicles, resulting in less neurotransmitter being released upon stimulation. It lowers cardiac output and lowers peripheral vascular resistance. Reserpine is a second-line antihypertensive medication.

e) Ganglion blockers, e.g. trimethaphan

Trimethaphan is ganglion blocking drug which is reserved for use in hypertensive emergencies only.

C. **Direct vasodilators. These include**

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

Hydralazine: Arterioles are dilated, but veins are not. It is used to treat severe hypertension in particular.

Headache, nausea, anorexia, palpitations, sweating, and flushing are the most common side effects of vasodilators.

Sodium Nitroprusside: It's a potent vasodilator that's used to treat hypertensive emergencies and severe heart failure. It reduces peripheral vascular resistance and venous return by dilation of both arterial and venous vessels. Nitroprusside is an intravenous infusion that lowers blood pressure quickly. Metabolic acidosis, arrhythmias, excessive hypotension, and death are among the most serious side effects.

D. Angiotensin-converting enzyme inhibitors, such as captopril, enalapril, and others. Captopril is the prototype. Captopril inhibits the angiotensin converting enzyme, which converts inactive angiotensin I to active angiotensin II, a potent vasoconstrictor that also stimulates aldosterone secretion. It works by lowering blood pressure by lowering peripheral vascular resistance. Maculopapular rash, angioedema, cough, granulocytopenia, and diminished taste sensation are some of the side effects. Enalapril is a prodrug that works in a similar way to captopril.

B) Calcium channel blockers, e.g. nifedipine, verapamil, nicardipine, etc.

The prototype is verapamil. The inhibition of calcium influx into arterial smooth muscle cells causes a decrease in peripheral resistance, which is the mechanism of action in hypertension. Verapamil is the strongest cardiac depressant, and it can also lower heart rate and cardiac output. Cardiac arrest, bradycardia, atrioventricular block, and congestive heart failure are the most serious side effects of calcium channel blockers. Lines of treatment of primary hypertension Treatment for hypertension may begin without the use of drugs. For about half of patients with mild hypertension, dietary salt restriction may be an effective treatment. In up to 70% of obese patients with mild to moderate hypertension, weight loss without salt restriction normalises blood pressure. Some hypertensive patients may benefit from regular exercise. When non-pharmacologic methods fail to control blood pressure adequately, drug therapy is used in addition to non-pharmacologic methods. The drug(s) chosen are determined by a number of factors, including the severity of hypertension and patient characteristics (age, race, coexisting diseases, etc.).

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

- Thiazide diuretics
- Beta blockers
- Calcium channel blockers

- Angiotensin converting enzyme inhibitors
- Central sympathoplegic agents

In young patients with high renin hypertension, tachycardia or angina, and hypertension, beta-blockers are preferred. Diuretics and calcium channel blockers work better for black patients than beta-blockers and ACE inhibitors. If monotherapy fails, a combination of two drugs with opposing mechanisms of action may be used. A beta-blocker, calcium channel blocker, or an angiotensin converting enzyme inhibitor may be combined with thiazide diuretics. If hypertension persists, a third drug, such as a vasodilator such as hydralazine, may be added.

Combining a diuretic, a sympathoplegic agent or an ACE inhibitor, and a direct vasodilator or calcium channel block is effective when three drugs are required. The treatment of hypertensive emergencies is usually started with furosemide given by parenteral route at dose of 20-40mg. In addition, parenteral use of diazoxide, sodium nitroprusside, hydralazine, trimethaphan, labetalol can be indicated.

II. DRUG USED IN HEART FAILURE

Congestive heart failure occurs when the heart is unable to maintain a sufficient cardiac output to meet the needs of the metabolising tissues.

The following are the most common causes of heart failure:

- Ischaemic heart disease,
- Valvular heart disease
- Heart muscle disorders and
- Hypertension

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

Positive inotropic drugs increase the force with which the heart muscle contracts. These consist of:

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

- Methylxanthines

1. Cardiac glycosides

Cardiac glycosides are a class of steroid compounds that can boost cardiac output while also altering electrical functions. Digoxin and digitoxin are two cardiac glycosides that are commonly used.

The inhibition of the membrane-bound Na+/K+ ATPase, also known as the "Sodium Pump," is the mechanism of inotropic action of cardiac glycosides. This causes an increase in intracellular sodium movement and sodium accumulation in the cells. Because of the increased intracellular sodium, transmembrane sodium and calcium exchange is reduced, resulting in an increase in intracellular calcium that acts on contractile proteins.

The pharmacodynamic properties of all cardiac glycosides are similar, but their pharmacokinetic properties differ. Digitoxin, for example, is more lipid soluble and has a longer half-life than digoxin.

Therapeutic uses of cardiac glycosides include:

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

Toxicity of cardiac glycosides include:

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

Mild side effects like gastrointestinal and visual disturbances can be managed by lowering the drug's dose.

Potassium supplementation, administration of anti-arrhythmic drugs (e.g. lidocaine), and use of digoxin antibodies can all help with arrhythmias or serious toxicity.

2. Bipyridine derivatives, e.g. amrinone, milrinone. These medications have both inotropic and vasodilator properties. The inhibition of an enzyme called phophodiesterase, which is responsible for the inactivation of cyclic AMP, is thought to be the mechanism of action. When these enzymes are inhibited, cAMP levels rise. In cases of heart failure resistant to treatment with cardiac glycosides and vasodilators, bipyridine derivatives are used.
3. **Beta - adrenergic stimulants** e.g. dobutamine, dopamine Beta stimulants increase cardiac output by increasing myocardial contractility. However, in patients with ischaemic heart disease, the positive chronotropic effect of these agents reduces the benefit. Dobutamine has a proportionally greater positive inotropic effect than it has on heart rate. It's only used to treat acute failure or failure that hasn't responded to other oral medications.
4. **Methylxanthines,** e.g. theophylline in the form of aminophylline Aminophylline has a favourable inotropic effect, a bronchodilating effect, and a minor effect on renal blood flow. It's used to treat pulmonary edoema or acute left ventricular failure.

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 the first line of treatment for heart failure patients. A thiazide may be sufficient in mild failure, but they are ineffective at low glomerular filtration rates. A loop diuretic is required in moderate or severe failure.

Diuretics play an important role in acute failure by lowering ventricular preload. The reduction in venous pressure reduces edoema and its symptoms, as well as the size of the heart, resulting in improved pump function.

2. Vasodilators

Vasodilators are effective in the treatment of acute heart failure because they reduce preload (via venous dilation), afterload (via arteriolar dilation), or both. Hydralazine works as a direct vasodilator in the arterial bed. A significant increase in cardiac output occurs when systemic vascular resistance is reduced. Sodium

nitroprusside is a venous and arteriolar dilator that can also be used to lower blood pressure quickly. Patients who are intolerant of or have contraindications to ACE inhibitors are usually prescribed vasodilators.

Angiotensin converting enzyme (ACE) inhibitors: Reduction of angiotensin II has beneficial effects on the course of the disease because of its widespread involvement in the undesirable compensatory responses to heart failure.

These drugs reduce afterload by lowering peripheral resistance and preload by lowering sodium and water retention by lowering aldosterone secretion. In the treatment of chronic heart failure, they are now considered a head of cardiac glycosides. Long-term management of chronic heart failure requires the following: Change your cardiovascular risk factor profile, such as smoking, obesity, and salt consumption. Anemia, hypertension, and valvular disease are examples of underlying causes that should be treated. If this isn't enough, a diuretic should be given. Give digitalis and an ACE inhibitor (ACE inhibitors may be used before digitalis). Patients with persistent symptoms should be given vasodilators in addition to increasing their diuretic and ACE inhibitor doses.

Pharmacotherapy of Angina pectoris

Angina pectoris occurs when there is a mismatch between the oxygen supply and demand of the myocardium. Myocardial ischemia causes this symptom. Angina develops when the increased coronary blood flow is insufficient to meet the increased oxygen demand. The importance of coronary artery spasm in the development of angina has been discovered.

Drugs used in angina pectoris

Organic nitrates e.g. nitro-glycerine, isosorbide dinitrate, etc. Beta adrenergic blocking agents e.g. propranolol, atenolol, etc. Calcium channel blocking agents e.g. verapamil, nifedipine, etc. Miscellaneous drugs e.g. aspirin, heparin, dipyridamole

Organic nitrates: 1.Organic nitrates are powerful vasodilators that have been used to treat angina pectoris for over a century. Nitrates exert their effects by acting as a direct relaxant on smooth muscles. Endothelium derived relaxing factor (EDRF), also known as nitric oxide, is thought to act as a vasodilator in the presence of nitrates. Organic nitrates are converted to organic nitrites, which are then converted to nitric oxide, a vasodilator. When chewed or held under the tongue, the action of nitrates begins after 2-3 minutes and lasts for 2 hours. Different nitrates and pharmaceutical preparations have different onsets and durations of action. Flushing, weakness, dizziness, tachycardia,

palpitation, vertigo, sweating, syncope localised burning, and contact dermatitis with ointment are some of the side effects.

Angina pectoris, post myocardial infarction, coronary insufficiency, and acute LVF are all treated with this drug (left ventricle failure)

Adrenergic blocking agents

Through increased sympathetic activity, exercise and emotional excitement cause angina in susceptible subjects by increasing heart rate, blood pressure, and myocardial contractility.

All of these effects are blocked by beta receptor blocking agents, which prevent angina. In most patients, atenolol, propranolol, metoprolol, and labetolol have a beneficial effect on cardiac workload and myocardial oxygen consumption.

Adverse effects: Lethargy, fatigue, rash, cold hands and feet, nausea, breathlessness, nightmares, and bronchospasm are some of the symptoms you may experience. Beta blockers that are selective have fewer side effects.

Therapeutic uses other than angina include hypertension, Cardiac arrhythmias, post myocardial infarction and pheochromocytoma.

1. **Calcium channel blockers**: Calcium is required for the cardiac and smooth muscle excitation contraction coupling. Calcium channel blockers, such as nifedipine, felodipine, verapamil, and diltiazem, appear to interfere with calcium entry into myocardial and vascular smooth muscle, lowering intracellular calcium availability.

Other therapeutic uses: hypertension, acute coronary insufficiency, tachycardia,

Adverse effects: flushing nausea/vomiting, headache, Ankle swelling, dizziness, constipation, etc.

2. **Miscellaneous drugs,e.g. Acetylsalicylic acid**

Low doses of acetylsalicylic acid (aspirin) given intermittently reduce thromboxne A2 synthesis without drastically reducing prostacylin synthesis. It can thus produce antiplatelet activity and reduce the risk of myocardial infarction in anginal patients at doses of 75 mg per day.

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Anti - arrhythmics

Electrophysiology of cardiac muscle: The pathophysiological mechanisms that cause cardiac arrhythmias are poorly understood. However, cardiac arrhythmias are thought to be caused by either of these factors.

a) Disorders of impulse formation and/ or

b) Disorders of impulse conduction.

Pharmacotherapy of cardiac arrhythmias Antiarrhythmic drugs are used to prevent or treat arrhythmias in the hear (tachyarrhythmias). Drugs used in the treatment of cardiac arrhythmias are traditionally classified into:

Class

I. (Sodium channel blockers which include quinidine, lidocaine, phenytion, flecainide, etc.
II. Beta adrenergic blockers which include propranolol, atenolol, etc. Class
III. Potassium channel blockers e.g. amiodarone, bretylium.
IV. Calcium channel blockers e.g. verapamil, etc.
V. Digitalis e.g.digoxin.

Class – I drugs

Quinidine: Quinidine works by blocking sodium channels and raising the excitability threshold. Orally, it is well absorbed

Adverse effects: The therapeutic ratio is low. SA block, cinchonism, severe headache, diplopia, and photophobia are the most common side effects.

Lidocaine, a common local anaesthetic, reduces automaticity by blocking both open and inactivated sodium channels. It is administered intravenously.

Adverse effects: Excessive doses cause cardiac arrest, dizziness, drowsiness, seizures, and other side effects.

Flecainide is a procainamide analogue that is easily absorbed when taken orally. In patients with normal left ventricular function, it is used to treat ventricular ectopic beats.

Class –II drugs: Beta-adrenergic receptor blockers

Propranolol: Automaticity, A.V. conduction velocity, and the refractory period all improve with myocardial sympathetic beta receptor stimulation. These effects can be

reversed with propranolol. Other antiarrhythmics' negative inotropic effects may be amplified by beta blockers.

Therapeutic uses: This is beneficial in the treatment of tachyarrhythmias, pheochromocytoma, and thyrotoxicosis crises. It can also help patients who are resistant to digitalis and have atrial fibrillation or flutter.

Class – III: Potassium channel blockers

AMIODARONE: Ventricular tachyarrhythmias and refractory supraventricular tachyarrhythmias are treated with this drug. The function of the sinus, atrial, and A.V nodes is all affected. The most common side effects of this medication are anorexia, nausea, abdominal pain, tremor, hallucinations, peripheral neuropathy, and A.V. block.

Class IV drugs: Calcium channel blockers

Verapamil: This drug works by preventing calcium ions from moving through the channels. Patients taking beta blockers, quinidine, or disopyramide should not take it. It is the drug of choice for rapid sinus rhythm conversion in cases of paroxysmal supraventricular tachycardia.

Class - V drugs

Small doses of digoxin cause a shortening of the atrial refractory period (vagal action), while larger doses cause a prolongation (direct action). It directly and indirectly prolongs the effective refractory period of the A.V node. In patients with atrial fibrillation, this action is critical for slowing the rapid ventricular rate.