UNIT 4 DRUGS ACTION ON CARDIOVASCULAR SYSTEM

Structure

4.1 INTRODUCTION

The heart is a mechanical organ that pumps blood to different parts of the body. The heart, along with the arteries, veins and capillaries forms the cardiovascular system. There are various diseases that are associated with the malfunction of these individual components. Thickening of the coronary arteries leads to development of atherosclerosis and myocardial ischemia, decrease in the pumping capacity of the heart leads to the development of heart failure, conduction defects in the heart leads to the development of arrhythmias, and sustained contraction of the arterial smooth muscle leads to development of hypertension.

Objectives

After studying this unit, you should be able to:

- know about cardiac glycosides and their therapeutic uses;
- about the various drugs used in arrhythmia and their therapeutic uses;
- about the drugs used in angina pectoris and their therapeutic uses; and
- know the drugs used in hypertension and their therapeutic uses.

4.2 CARDIAC GLYCOSIDES AND ANTIARRHYTHMIC AGENTS

4.2.1 Cardiac Glycosides

Introduction

Cardiac glycosides are the drugs having cardiac inotropic property. They increase myocardial contractility and cardiac output in a hypodynamic heart without increase in oxygen consumption and overall myocardial efficiency is increased.

The cardiac glycosides are mainly obtained from plants e.g. digitalis, stropanthus and squill species and also present in certain other plants and animals. In 1776, William Withering, a Birmingham physician and botanist identified digitalis and other ingredients, which was found useful in the treatment of dropsy. In 1911, Mackenzie and Cushney studied the effect of digitalis on heart and its use in congestive heart failure.

Actions on Body Systems

Effect on Heart

Contractility: Digitalis increases the force of myocardial contraction without causing corresponding increase in the oxygen consumption. This action forms the basis of its use in treatment of Congestive Heart Failure.

Cardiac output: Digitalis increases the cardiac output in CHF patients by increasing the force of myocardial contraction.

Heart rate: Digitalis produces a decrease in heart rate.

Automaticity: It is the ability to generate propagated impulse. Digitalis increases the ability of the Purkinje cell and the ventricular muscle to initiate impulses.

Extracardiac Actions: Apart from the actions on the heart, cardiac glycosides also exert actions on various other body systems.

- Digitalis produces diuresis in CHF patients, it increases excretion of sodium and water by the kidney, thus shifting edema fluid into the circulation.
- Digitalis can produce nausea and vomiting which is probably due to the chemoreceptor trigger zone (CTZ) stimulation.

Therapeutic Uses

Digitalis is primarily used in the treatment of Congestive Heart Failure. Digitalis increases stroke volume and cardiac output. Digitalis by increasing the cardiac output brings about more complete emptying of the ventricles during systole. This reduces the pulmonary congestion and edema and decreases the systemic venous pressure. The cardiac glycosides primarily

correct systolic dysfunction. Other uses of digitalis are atrial fibrillation, atrial flutter, etc.

Other Positive Inotropic Drugs Used in CHF

Bipyridine Compounds: These drugs increase the force of contraction of the heart and also decrease the systemic vascular resistance by relaxing the arteries. The compounds used clinically are amrinone and milrinone.

SAQ 1

a) Digoxin is obtained from the plant _____.

b) Digoxin exerts its action by inhibiting the enzyme _____.

c) _____ and _____ are non glycoside drugs used in the treatment of CHF.

4.2.2 Antiarrhythmic Agents

The peculiarity of the heart tissue is that it can generate its own impulse. Under normal conditions, the normal pacemaker of the heart is the SA node. The impulse generated here is transmitted throughout the heart by a fine network of conducting fibres called the Purkinji fibres. During conditions like myocardial ischemia, mechanical injury to the heart, etc the myocardial fibres start generating their own impulse and arrhythmias set in. **Cardiac arrhythmias** is a group of disorder characterized by an abnormal cardiac rhythm and arise as a result of disorders of impulse formation or conduction or both.

Cardiac Arrhythmias

The different types of cardiac arrhythmias can be classified into two broad groups, depending on the rate of the heart beat. **Tachyarrhythmias** manifest as fast heart rate (more than 100 per minute) and **Bradyarrhythmias** manifest as slow heart rate (less than 50 to 60 beats per minute).

Important Antiarrhythmic Drugs

Quinidine

It is an alkaloid obtained from the bark of cinchona and is an isomer of anti-malarial drug ‘quinine’. Its sodium channel blocking property results in depression in the excitability of cardiac tissues, decreases pacemaker activity, and a decrease in the force of contraction of the heart. It is **indicated** in prevention of atrial and ventricular tachycardias.

Amiodarone

It is a long acting antiarrhythmic drug. It blocks inactivated sodium channels. It is **indicated** in tachyarrhythmias not responding to other agents.

Bretylium

It has direct action on myocardium and interferes with the neuronal release of catecholamines and has direct antiarrhythmic property. It is used in the treatment of ventricular tachycardia and ventricular fibrillation.

SAQ 2

a) Tachyarrhythmias is sinus rate more than _____ per minute.

b) Beta blockers are classified under Class _____ antiarrhythmics.

c) Define Cardiac arrhythmias.

4.3 ANTIANGINAL AGENTS

4.3.1 Introduction

Angina pectoris is a symptom of ischaemic heart disease. It develops as a result of an imbalance between the oxygen supply and oxygen demand of the myocardium. Decrease in myocardial perfusion is due to deposition of atherosclerotic plaques in blood vessels. These plaques are due to accumulation of cholesterol and other lipid compounds which develop as patches on inner side of blood vessels.

4.3.2 Nitrates

Glyceryl trinitrate (GTN) is the prototype member of this drug group. It releases nitrite ion (NO_2^-) which is further metabolized to NO by enzymatic step in vascular smooth muscles. NO released by GTN leads to relaxation of the blood vessels. Both large arteries and veins are dilated by GTN, but the action on veins is more prominent. GTN is used as a sublingual tablet in the emergency management of Angina pectoris. It is used intravenously in the management of Unstable angina, coronary vasospasm, left ventricular failure accompanying MI, hypertension and during cardiac surgery. It is used in the form of Ointment/transdermal patch for the prevention of angina pectoris. Isosorbide mononitrate has the longest duration of action and is generally preferred for the prophylaxis of angina in susceptible individuals.

4.3.3 Other Antianginal Drugs

Dipyridamole

It is a coronary dilator and claimed to dilate coronary resistance vessels. It probably acts by inhibiting the uptake and degradation of adenosine (a local mediator involved in auto regulation of coronary flow in response to ischemia). It also has platelet inhibitory properties.

It has been employed for prophylaxis of coronary and cerebral thrombosis in post MI and post stroke patients, as well as to prevent thrombosis in patients with prosthetic heart valves.

SAQ 3

a) _____ is given by the sublingual route for the treatment of angina pectoris.

b) _____ has the longest duration of action among organic nitrates used in the treatment of angina.

4.4 ANTIHYPERTENSIVES AND VASODILATORS

4.4.1 Introduction

Hypertension is the most common cardio-vascular disease and pathophysiologically hypertension can be classified into two main groups.

a) **Essential** or **primary hypertension**, where the cause for rise in blood pressure is not known. Responsible for majority of cases.

b) **Secondary hypertension**, where rise is due to renal disease e.g. chronic diffuse glomerulonephritis, pyelonephritis; due to some vascular disease e.g. renal artery disease or due to some endocrinal disorders e.g. pheochromocytoma, Cushing's syndrome and primary aldosteronism.

Systemic arterial blood pressure is determined by cardiac output and total peripheral resistance. In most of the cases, rise in BP is due to increase in total peripheral resistance.

Clinically, hypertension can be divided into three stages e.g. mild, moderate and severe hypertension. The diastolic blood pressure between 90-104 mmHg is graded as mild, 105-114 mmHg is graded as moderate and above 115 mmHg is graded as severe hypertension.

The blood pressure is mainly controlled by two systems. Firstly through the baro-receptors and the adrenergic nervous system. The baroreceptor reflexes protect the circulation against stresses which shows the changes in the arterial blood pressure. Secondly through renin angiotensin system, this is involved in the pathogenesis of some forms of secondary hypertension. Renin is a proteolytic enzyme released from the juxtaglomerular cells of kidneys. The reaction between renin and plasma protein, serum globulin (angiotensinogen) forms an inactive compound 'angiotensin I' (decapeptide), which further changed into 'angiotensin II' (octapeptide) by the action of angiotensin converting enzyme (ACE) and is the most powerful vasoconstrictor agent.

4.4.2 Important Antihypertensive Drugs

Clonidine/Methyldopa: These agents stimulate, alpha receptors in vasomotor centre of brain and decrease the sympathetic outflow which results in fall of blood pressure and bradycardia.

They are indicated in hypertension of all grades except pheochromocytoma, glaucoma and migraine.

Reserpine: It is an alkaloid known to deplete the catecholamines – adrenaline, noradrenaline and dopamine from the various sites in the body. As a result the sympathetic tone in the body decreases.

Prazosin/Terazocin: The detailed pharmacology of alpha blockers is already discussed in chapter 'adrenergic blocking agents'. Decrease in blood pressure is brought about by blockade of alpha receptors that leads to relaxation of smooth muscles of the blood vessels.

Propranolol/Metoprolol: The detailed pharmacology of alpha blockers is already discussed in chapter 'adrenergic blocking agents'. Decrease in blood pressure is brought about by reducing heart rate and force of contraction.

Captopril/Enalapril: These drugs act primarily by suppressing renin-angiotensin-aldosterone system. The main action of all ace inhibitors is to inhibit conversion of angiotensin I (inactive) to angiotensin II (active). They inhibit the angiotensin converting enzyme (ACE). Hence, angiotensin II production is inhibited. Decrease in angiotensin ii results in dilatation of peripheral vessels leading to a reduction in systemic vascular resistance and a decreased aldosterone secretion.

Losartan/Irbesartan: Angiotensin II is a potent vasoconstrictor, stimulant of aldosterone secretion and an important component in the pathophysiology of hypertension. Losartan blocks the binding of angiotensin with its receptor.

Verapamil/Diltiazem/Nifedipine: Calcium channel blockers interfere with the calcium entry into the myocardial cells (leads to decrease in force of contraction of the heart) and vascular smooth muscles (blood vessel relaxation). As a result, the blood pressure decreases.

Hydralazine/Sodium Nitroprusside: These agents release NO (nitric oxide) in the body and have action similar to that of Glyceryl trinitrate. The released NO leads to vascular smooth muscle relaxation and decrease in blood pressure. The onset of action of these agents is very fast and duration of action is very less. Therefore these agents are used by the intravenous route in the management of hypertensive emergencies (known as "Hypertensive crisis").

SAQ 4

a) The main action of all ACE inhibitors is to inhibit conversion of _____ to _____.

b) Sodium nitroprusside is administered by the _____ route in hypertensive emergencies.

c) Define essential hypertension.

4.5 SUMMARY

- Cardiac glycosides are the drugs having cardiac inotropic property. They increase myocardial contractility and cardiac output in a hypodynamic heart without increase in oxygen consumption and overall myocardial efficiency is increased.
- Digitalis increases the cardiac output in CHF patients by increasing the force of myocardial contraction.
- Primary indications for digitalis include CHF, artial and ventricular failure.
- Cardiac arrhythmias is a group of disorder characterized by an abnormal cardiac rhythm and arise as a result of disorders of impulse formation or conduction or both.

- Angina pectoris is a symptom of ischaemic heart disease. It develops as a result of an imbalance between the oxygen supply and oxygen demand of the myocardium.
- Hypertension can be classified into two main groups.
  a) **Essential** or **primary hypertension**, where the cause for rise in blood pressure is not known responsible for majority of cases.
  b) **Secondary hypertension**, where rise is due to renal disease, due to some vascular disease or due to some endocrinal disorders
- ACE inhibitors block the rennin-angiotensin-aldosterone system by inhibiting the conversion of angiotensin I into the active angiotensin II.
- Calcium channel blockers depress the contractility of the myocardium and decrease the cardiac work and the requirement of oxygen.

4.6 TERMINAL QUESTIONS

1. What do you understand by the term "cardiac glycoside"?
2. Elaborate the mechanism of action of nitrates.
3. What are the drugs used in the treatment of essential hypertension?
4. What are the drugs used in the treatment of hypertensive emergencies? Why are they preferred?

4.7 ANSWERS

Self Assessment Questions

1. a) Digitalis sp. b) $Na^+ K^+$-ATPase c) Amrinone and milrinone
2. a) 100
   b) II
   c) Cardiac arrhythmias is a group of disorder characterized by an abnormal cardiac rhythm and arise as a result of disorders of impulse formation or conduction or both.
3. a) Glyceryl trinitrate b) Isosorbide mononitrate
4. a) Angiotensin I to angiotensin II
   b) Intravenous
   c) When the cause for rise in blood pressure is not known, it is known as essential hypertension.

Terminal Questions

1. **Cardiac glycosides** are the drugs having cardiac inotropic property. They increase myocardial contractility and cardiac output in a hypodynamic heart without increase in oxygen consumption and overall myocardial efficiency is increased. The cardiac glycosides are mainly obtained from plants e.g. digitalis, stropanthus and squill species.

2. Nitrates releases nitrite ion (NO_2^-) which is further metabolized to NO by enzymatic step involving reaction with tissue sulphydryl (–SH) groups in vascular smooth muscles. This NO released by GTN activates soluble, cytosolic form of guanylyl cyclase in vascular smooth muscles by interacting with haem group in the enzyme. This converts GTP to cGMP. cGMP dephosphorylates myosin light chain kinase and prevent myosin interaction with actin leading to relaxation.

3. Drugs used in the treatment of essential hypertension are as follows:
   i) Clonidine and Methyldopa
   ii) Reserpine
   iii) Prazosin and Terazocin
   iv) Propranolol and Metoprolol
   v) Captopril and Enalapril
   vi) Losartan and Irbesartan
   vii) Verapamil, Diltiazem and Nifedipine

4. Direct vasodialators like hydralazine and sodium nitroprusside are given by the intravenous route in the management of hypertensive emergencies. The onset of action of these agents is very fast and duration of action is very less. Therefore these agents are used in the management of hypertensive emergencies.