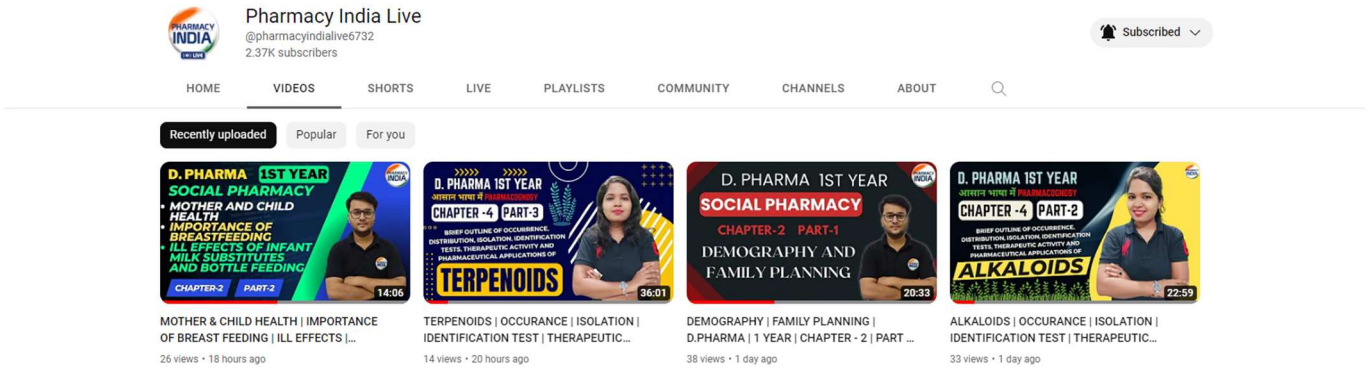
PHARMACOLOGY

MODEL PAPER – 2

Syllabus to be covered in this module are-

- ❖Chapter-5 Drugs Acting on the Cardiovascular System
- ❖Chapter-6 Drugs Acting on Blood and Blood Forming Drugs
- ❖Chapter-7 Drugs Acting on Respiratory System
- ❖Chapter-8 Drugs Acting on the Gastro-Intestinal Agents



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Questions

Long Questions-

Ques.1 Write in detailed about anti-anginal agents.

Ques.2 Explain in detail about congestive heart failure.

Ques.3 Discuss drug therapy for shock in detail.

Ques.4 Explain bronchodilators in detail.

Ques.5 Write in detailed about laxatives & purgatives.

Short Questions

Ques.1 Give the classification of anti-hypertensive agents.

Ques.2 Give the complete classification of anti-arrhythmic agents.

Ques.3 What are the pharmacological actions of CHF?

Ques.4 Give the pharmacokinetics of calcium channel blockers.

Ques.5 Write a short note on anti-platelet agents.

Ques.6 What are expectorants and mucolytic agents?

Ques.7 Explain nasal decongestants.

Ques.8 Write a short note on proton pump inhibitors & ulcer protectives.

Long Answers

Ques.1 Write in detailed about anti-anginal agents.

Ans- ANTI-ANGINAL AGENTS

Angina pectoris refers to a strangulating or pressure-like pain caused by cardiac ischemia. The pain is usually located sub-stern ally but is sometimes perceived in the neck, shoulder and arm, or epigastrium. Anti-anginal drugs are those that prevent, abort, or terminate attacks of angina pectoris.

Types of anginas are:

1. Atherosclerotic angina (classic angina/common form): Attacks are predictably provoked (stable angina) by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn, rest, by reducing cardiac work, usually leads to complete relief of the pain within 15 min. Atherosclerotic angina constitutes about 90% of angina cases.

2. Vasospastic angina (rest angina, variant angina, or Prinzmetal's anginal uncommon form): Attacks occur at rest or during sleep and are unpredictable. Vasospastic angina is responsible for less than 10% of angina cases. Coronary artery calibre changes in classical and variant angina.

3. Unstable angina (crescendo angina, also known as acute coronary syndrome): It is characterized by increased frequency and severity of attacks that result from a combination of atherosclerotic plaques, platelet aggregation at fractured plaques, and vasospasm.

Drugs used in angina exploit two main strategies: reduction of oxygen demand and increase of osym delivery to the myocardium.

CLASSIFICATION OF ANTI-ANGINAL DRUGS

1. Nitrates

- **Short acting:** Glyceryl trinitrate (GTN, Nitroglycerine)
- **Long acting:** Isosorbide dinitrate (short acting by sublingual route), Isosorbide, mononitrate, Erythrityl, tetranitrate, Pentaerythritol tetranitrate

2. β Blockers: Propranolol, Metoprolol, Atenolol, and others.

3. Calcium channel blockers:

- **Phenyl alkylamine:** Verapamil
- **Benzothiazepine:** Diltiazem
- **Dihydropyridines:** Nifedipine, Felodipine, Amlodipine, Nimodipine

4. Potassium channel opener: Nicorandil

5. Others: Dipyridamole, Trimetazidine, Ranolazine, Ivabradine, Oxyphedrine

CLINICAL CLASSIFICATION:

1. Used to abort or terminate attack: GTN, Isosorbide dinitrate (sublingually).

2. Used for chronic prophylaxis: All other drugs.

Nitrates/Organic Nitrates Preload reduction: Peripheral pooling of blood decreased venous return (preload reduction).

Afterload reduction: Nitrates also produce some arteriolar dilatation→ slightly decrease total peripheral resistance or afterload on heart.

Redistribution of coronary flow: In the arterial tree, nitrates relax bigger conducting (angiographically visible) coronary arteries than arterioles or resistance vessels.

Pharmacokinetics

Organic nitrates are lipid soluble, well absorbed from buccal mucosa, intestines, and skin. Ingested orally, all except isosorbide mononitrate undergo extensive and variable first pass metabolism in liver. They are rapidly denigrated by a glutathione reductase and a mitochondrial aldehyde dehydrogenase.

Adverse Effects

- Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.
- Phosphodiesterase type 5 inhibitors such as sildenafil potentiate the action of the nitrates, this combination is contraindicated.
- Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug.
- Sudden withdrawal after prolonged exposure has resulted in spasm of coronary and peripheral blood vessels. Withdrawal of nitrates should be gradual.

Uses

1. Angina pectoris: GTN produces relief within 3 min in 75% patients, the rest may require another dose or take longer (up to 9 min).

2. Acute coronary syndromes: Nitrates are useful by decreasing preload as well as by increasing coronary flow,

3. Myocardial infarction (MI): GTN is frequently used during evolving MI with the aim of relieving chest pain, pulmonary congestion and limiting the area of necrosis by favourably altering O_2 balance in the marginal partially ischaemic zone.

4. CHF and acute LVF: Nitrates afford relief by venous pooling of blood → reduced venous → return (preload) → decreased end diastolic volume → improvement in left ventricular function.

5. Biliary colic & Esophageal spasm

6. Cyanide poisoning: Nitrates generate methaemoglobin which has high affinity for cyanide radical and forms cyanomethaemoglobin.

***β* Blockers:** β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking B, receptors, resulting in decreased heart rate, contractility, cardine output, and blood pressure. All β_1 blockers are nearly equally effective in decreasing frequency and severity of attacks and in increasing exercise tolerance in classical angina, but cardio-selective agents (atenolol, metoprolol) are preferred over non-selective β_1+β_2 blockers (e.g. propranolol). Agents with intrinsic sympathomimetic activity (ISA) such as pindolol should be avoided in patients with angina and those who have had a MI.

Ques.2 Explain in detail about congestive heart failure.

Ans- CONGESTIVE HEART FAILURE

Cardiotonic are glycosides having cardiac inotropic property i.e., drugs that increase force of contraction of heart without a proportionate increase in O_2 consumption. An ideal cardiotonic agent should not increase heart rate & should be devoid of toxic effects.

Source

- **Digitalis Purpurea -** Digitoxin, Gitoxin, Gitalin
- **Digitalis Lanata -** Digitoxin, Gitoxin, Digoxin
- **Strophanthus gratus** (seed) -Strophanthin-G (ouabain)
- **Urginea** (scilla); Maritima (bulb) -Proscillaridin A
- **Thevetia neriifolia** (nut) –Thevetin
- **Convallaria majalis** –Convallotoxin
- **Bufo vulgaris** (Toad skin) –Bufotoxin

Chemistry

All are glycosides; consist of an aglycone (genin) to which are attached one or more sugar (glucose or digitoxose) moieties. Aglycon consists of cyclopentanoperhydrophenanthrene (steroid) ring 5 or 6 membered unsaturated lactones ring. One or more hydroxyl & other substitution are present on aglycon & determine its polarity e.g. digoxigenin has an additional OH group than digoxigenin & is more polar.

Mechanism of Action

Digitalis increases force of cardiac contraction by a direct action independent of innervations. It selectively binds to extra cellular face of membrane associated Na^+ /K^+/ATPase of myocardial fibres & inhibits this enzyme. Inhibition of this cation pump results in progressive accumulation of Na^+ intracellularly. This indirectly results in intracellular Ca^{2+} accumulation via the Na^+ /Ca^{++} exchange system (essential for maintaining sodium and calcium homeostasis). In the heart, increased intracellular calcium causes more calcium to be released by the sarcoplasmic reticulum, thereby making more calcium available to bind to troponin-C, which increases contractility (intropy) without increasing heart energy expenditure.

Pharmacological Actions

All digitalis glycosides have qualitatively similar action; there are only quantitative & pharmacokinetic differences. Digoxin is described as prototype.

1. Heart:

(a) Force of contraction: It increases force of contraction of heart, a positive inotropic. In normal individual, it constricts blood vessels of arteries & veins. In CCF there is decrease force of contraction of heart, this result in decrease cardiac output & decrease stroke volume

(b) Tone: Maximum length of fibre at a given filling pressure or resting tension in the muscle fibre. This is not affected by therapeutic doses of digitalis.

(c) Rate: Heart rate is decreased by digitalis (-ve chronotropic), Bradycardia is more marked in CHF patients; improved circulation (due to ve inotropic action) restores the diminished vagal tone & abolishes

sympathetic over activity. Vagal tone is increased by direct stimulation of vagal centre & sensitization of SA node to Ach.

(d) Conduction velocity & refractory period: smaller doses produce increase in conduction velocity due to vagal action whereas; larger doses of digitalis produce decrease in conduction velocity because of direct action. The decrease in conduction in AV node is therapeutically useful in conditions of atrial flutter & fibrillation. The refractory period in atria is shortened in lower doses whereas, in larger doses digitalis prolongs the refractory period. The refractory period of AV node is prolonged by vagal impulse & also by direct action of digitalis.

(e) Electrocardiogram (ECG): Digitalis produces depression of ST segment (at high dose), innervations of T wave (decreased amplitude), increased P-R interval (slowing of A-v conduction), A-V block at toxic doses shortening of QT interval. ST segment (due to interference with repolarization).

2. Blood Vessels: Blood vessels Digitalis has mild direct vasoconstrictor action peripheral resistance is decreased in normal individuals. Digitalis has no prominent effect on BP, systolic BP may increase & diastolic may fall in CHF patients pulse pressure increases. Hypertension is no contraindication to the use of digitalis.

3. Kidney: In CCF there is decrease in renal blood flow resulting in sodium retention & oedema. Digitalis by improving renal circulation & decreasing venous pressure increases the formation of urine. This results into increased excretion of Na^+ & decrease in oedema and produces a prominent diuretic effect.

4. CNS: Digitalis has little apparent CNS effect in therapeutic dose. Higher doses cause CTZ activation-nausea, vomiting. Still higher doses produce mental confusion, visual disturbance, diarrhoea, central sympathetic stimulation hyperpnoea, disorientation.

Pharmacokinetics

Amongst various cardiac glycosides used, digoxin & digitoxin are very common. Absorption is confined to small intestine. Digoxin absorption is variable (60-80%), digitoxin is absorbed almost (100%). Digitoxin is the most lipid soluble, digoxin is relatively polar, while ouabain has highest polar character. Digitoxin metabolized in liver, partly to digoxin & undergoes some enterohepatic circulation. Digoxin excreted by kidney; mainly by glomerular filtration; rate of excretion is altered parallel to creatinine clearance.

Therapeutic Uses

1 Digitalis is useful in low output failure such as hypertension & ischemic heart disease.

2. Atrial fibrillation: Digitalis is drug of choice for controlling ventricular rate in AF, it reduces the ventricular rate in AF by decreasing the number of impulses that are able to pass down the A-V node & bundle of His.

3. Atrial flutter (AFI): The atrial rate is 200-350/min but atrial contractions are regular. A variable degree of A-V node, is naturally established. Digitalis enhance this AV block reduces ventricular rate & prevents sudden shift of A-V block to a lower degree. Digitalis may convert AFI-AF by reducing atrial ERP & making it inhomogeneous. In nearly $^1/_2$ of the patients when digitalis is stopped this induced AF reverts to sinus rhythm since the cause of atrial inhomogenecity is gone.

4. Paroxysmal supraventricular tachycardia (PSVT): It is common arrhythmia with rate 150-200/min & 1:1 A-V conduction. It is mostly due to re-entry involving the SA (or) AV node. A parenteral glycoside

may be injected iv increase vagal tone & depress the path through SA/AV node. Verapamil /Adenosine are more effective, less toxic & act faster.

Adverse Effects

Toxicity of digitalis is high, margin of safety is low (therapeutic index: 15-3) Higher cardiac mortality has been reported among patients with steady-state plasma digoxin levels more than 11 ng /ml during maintenance therapy.

- Extra cardiac - anorexia, nausea, vomiting, abdominal pain is usually reported first, are due to gastric irritation, mesenteric vasoconstriction & CTZ stimulation Restlessness hyperapnoea, disorientation, psychosis and visual disturbances are the other complaints
- Cardiac - almost every type of arrhythmis can be produced by digitalis, pulses bigeminus, nodal & ventricular extra systoles, ventricular tachycardia & terminally fibrillation. Partial to complete A-V block may be the sole cardiac toxicity or it may accompany other arrhythmias.

TREATMENT OF CHF

There are two distinct goals of drug therapy in CHF:

(a) Relief of congestive/low output symptoms and restoration of cardiac performance:

- **Inotropic drugs**-digoxin, dobutamine/dopamine, amrinone/milrinone
- **Diuretics**-furosemide, thiazides
- **Vasodilators**-ACE inhibitors/ AT_1, antagonists, hydralazine, nitrate, nitroprusside
- β blocker-Metoprolol, bisoprolol, carvedilol

(b) Arrest/reversal of disease progression and prolongation of survival:

- ACE inhibitors/AT, antagonists (ARBS)
- β blockers
- **Aldosterone antagonist**-Spironolactone

Important non-pharmacological measures are rest and salt restriction.

Ques.3 Discuss drug therapy for shock in detail.

Ans- DRUG THERAPY FOR SHOCK

It is an abnormal physiological state resulting from a widespread and serious reduction of tissue perfusion that if prolonged will lead to generalized impairment of cellular function. A life-threatening clinical syndrome of cardiovascular collapse characterized by:

- An acute reduction of effective circulating blood volume (hypotension)
- Inadequate perfusion of cells and tissues (hypoperfusion)

If uncompensated, these mechanisms may lead to impaired cellular metabolism and death. The clinical manifestations of shock are the result of stimulation of the sympathetic and neuroendocrine stress responses, inadequate oxygen delivery end-organ dysfunction.

Types of Shock

1. Hypovolemic shock

2. Cardiogenic shock

3. Septic shock

4. Neurogenic shock

5. Anaphylactic shock

Management of Shock

- **Ionotropic:** An agent that changes myocardial contractility.
- **Vasopressor:** An agent that increases blood pressure.
- **Chronotropic:** An agent that changes heart rate.
- **Dromotropic:** An agent that increases cardiac conduction velocity.

Norepinephrine

- Most widely used vasopressor.
- Potent α_1 agonist causing vasoconstriction in tissue beds.
- The resultant increase in SVR causes a rise in blood pressure.
- The Standard dose 4 mg in 50 ml (0.08 mg/ml).

Epinephrine

- Nature's vasopressor.
- Most commonly used during resuscitation cardiac arrest and anaphylaxis.
- α_1: Increases SVR.
- β_1: Increases IR and myocardial contractility.
- β_2: Bronchial smooth muscle relaxation.
- Standard dose: 10 mg in 50 ml (0.2 mg/ml).

Dopamine

- Vasopressor agent.
- Use in cardiogenic and septic shock.
- Receptor stimulation depends on the dose given.

Dobutamine

- A synthetic catecholamine.
- β_1 stimulation: Increase HR and increase cardiac contractility.
- β_2 mediated vasodilatations.
- Reduction in Mean Arterial Pressure is common with dobutamine.
- NE usually needed to offset vasodilatation.

Vasopressin:

- Peptide hormone is released from the posterior pituitary.
- Causes increase in the permeability of distal convoluted tubules and CT, increases water retention (V2 receptor).
- VI receptor present in the smooth muscle of an arteriolar wall and stimulation causes smooth muscle contraction and vasoconstriction.

PHARMACOLOGY

1. HYPOVOLEMIC SHOCK

Improper tissue perfusion as a result of severe loss of blood or other fluid from the body or inadequate fluid intake, any of which decrease intravascular volume.

Causes

- ❖ Haemorrhagic (acute blood loss
- ❖ Burns
- ❖ Excessive vomiting and diarrhoea

Pathophysiology of Hypovoleraic shock

↓

Haemorrhage from small venules and veins (50%)

↓

Decreased filling of right heart

↓

Decreased filling of the pulmonary vasculature

↓

Decreased filling of left atrium and ventricle

↓

Left ventricular stroke volume decreases (Frank-Starling)

↓

Drop-in arterial blood pressure and tachycardia

↓

Poor perfusion to pulmonary arteries

↓

Cardiac depression and pump failure

Management

(a) Increase Cardiac Output

(b) Increase Tissue Perfusion

(c) Adequate fluid replacement

(d) Improving myocardial contractility

(e) Correcting acid-base disturbances

Drugs: Sedatives, Chronotropic agents, Inotropic agents

2. CARDIOGENIC SHOCK

A state of inadequate cardiac output despite the adequate intravascular volume, resulting in hypoxia.

- Cool, mottled skin
- Hypotension
- Tachypnoea
- Altered mental status
- Narrowed pulse pressure

Pathophysiology

- Often after ischemia, loss of LV function
- CO reduction = lactic acidosis, hypoxia
- Stroke volume is reduced
- Tachycardia develops as compensation
- Ischemia and infarction worsen

Treatment

- Aspirin, beta-blocker, morphine, heparin
- If no pulmonary oedema, IV fluid
- If pulmonary oedema- Dopamine- will ↑ HR and thus
- Dobutamine-May drop blood pressure
- Combination therapy may be more effective
- Thrombolytics (streptokinase, rt-PA)

3. SEPTIC SHOCK

A type of distributive shock resulting from sepsis:

Sepsis: An abnormal body-wide inflammatory response to an infection that can result in death.

Clinical Signs

- Hyperthermia
- Tachycardia
- Wide pulse pressure
- Low blood pressure (SBP <90)
- Mental status changes

Treatment

- Fluid replacement.
- Supplemental oxygen.
- Antibiotics: Survival correlates with how quickly the correct drug is given one gram-positive and gram-negative bacteria.
- Ceftriaxone 1 gram IV BD or Imipenem 1 gram IV TDS.
- Pseudomonas: Gentamicin or Cefepime.

4. ANAPHYLACTIC SHOCK

It develops following exposure to Allergen and cross-links IgE on mast cells causing media release (release of Histamine, Eicosanoids-LTs, PGs).

Clinical Presentation

- Urticaria and angioedema.
- Hypertension and CV collapse.
- Bronchospasm.

Treatment

- Epinephrine is 1st line drug
- Standard Dose: Inj. 0.5 ml (1:1000) IM.
- Repeat every 5-10 min if not improve.
- Inj. 0.5 ml (1:10000),(1:100000) IV

Antihistaminic

- Diphenhydramine (HI) administered IV.
- Ranitidine (H2) administered IV.
- β_2 agonist: Salbutamol,
- Corticosteroid: Hydrocortisone 200 mg IV followed by oral prednisolone for 3 days

NEUROGENIC SHOCK

Develops secondary to a sudden loss of Autonomic Nervous System functions following sp and injury resulting in vasomotor tone and impaired cellular metabolism.

Clinical Features

- Hypotension
- Poikilothermia
- Bradycardia

Management:

- Airway support.
- Fluid replacement.
- Dopamine (>10 mcg/kg/min).
- Ephedrine (12.5-25 mg IV every 3-4 hr).
- Atropine for bradycardia, (0.5 mg IV every 3 to 5 mins - 3 mg).
- Treatment of the underlying cause.

Ques.4 Explain bronchodilators in detail.

Ans- BRONCHODILATORS

Bronchial asthma is characterised by hyper responsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion mucosal oedema and mucus plugging. Symptoms include dyspnoea, wheezing, cough and may be limitation of activity.

Classification

I. Bronchodilators

(a) Sympathomimetics: Salbutamol, Terbutaline, Bambuterol, Salmeterol, Ephedrine

(b) Methylxanthines: Theophylline (anhydrous), Aminophylline, Doxophylline

(c) Anticholinergics: Ipratropium bromide, Tiotropium bromide

II. Leukotriene antagonists: Montelukast, Zafirlukast.

III. Mast cell stabilizers: Sodium cromoglycate, Ketotifen.

IV. Corticosteroids

(a) Systemic: Hydrocortisone, Prednisolone, and others.

(b) Inhalational: Beclomethasone dipropionate, Budesonide, Fluticasone propionate

V. Anti-IgE antibody: Omalizumab

BRONCHODILATORS

Sympathomimetics

The selective β_2 agonists are the primary bronchodilators used in the treatment of asthma /acute asthmatic attacks. $\beta_2$adrenergic receptor agonist stimulates the beta receptor, increasing the CAMP concentration in smooth muscle and causing bronchodilation. It also increases the conductance of large Ca^{2+} Ca sensitive K^+ channels in airway smooth muscle, leading to membrane hyperpolarization and relaxation. The selective β_2 agonist relax the bronchial smooth muscle without affecting cardiac function. In higher doses selective $\beta_2$agonist increasing the heart rate by stimulating the cardiac β_1 receptor. The selective β_2 agonist produce hypertension to patient those receiving digitalis. Side effects are palpitation, restlessness, nervousness, throat irritation and ankle edema.

Methylxanthines

They inhibits cyclic nucleotide phosphodiesterase (PDEs), thereby preventing conversion of cAMP and cGMP to 5'-AMP and 5, -GMP, respectively. Inhibition of PDEs will lead to an accumulation of intracellular CAMP and CGMP Bronchodilation, cardiac stimulation and vasodilation occur when CAMP level rises in the concerned cells. Theophylline and related methylxanthines are relatively non-selective in the PDE subtypes inhibitor.

Pharmacological Actions

CNS: Stimulant, affects higher centre, Caffeine 150-200 mg produce a sense of well-being. Alertness, beats boredom, allays fatigue, and improves performance and increase the motor activity. Caffeine is more active than theophylline in producing these effects. Higher dose cause nervousness, restlessness, panic, insomnia, and excitements. Still higher dose cause tremors, delirium, and convulsions. Theophylline is more toxic than caffeine (stimulates medullary vagal, respiratory, and vasomotor centres).

CVS: Stimulates the heart and increases force of contraction. Increases the heart rate (direct action) but decrease it by vagal stimulation- net effect is variable.

All **smooth muscles** are relaxed; most prominent effect is exerted on bronchi, especially in asthmatics. Theophylline is more potent and slower, sustained dose related bronchodilation.

Kidney: Mild diuretics; inhibiting tubular reabsorption of Na^+ and water.

Skeletal muscles: Caffeine enhances contractile power. In high dose, it increases release of Ca^{2+} from sarcoplasmic reticulum by direct action.

Stomach: Enhances secretion of acid and pepsin; gastric irritation (more with theophylline). Increase BMR.

Mast cells and inflammatory cells: Theophylline inhibits the release of histamine and other mediators.

Absorbed orally, distributed in all tissues, metabolized in liver by demethylation and oxidation & excreted in urine. Primarily used to treat chronic obstructive lung disorders, asthma and apnea in premature infants. Adverse effects (narrow margin safety) observed are CVS and CNS stimulant,

GIT distress, rapid i.v. injection causes pre-cordial pain, syncope, and sudden death.

Anticholinergics

Parasympathetic activation or release of ACh causes bronchoconstriction and increases mucus secretion. Blocking the action of ACh by anticholinergic drugs produce bronchodilation and also reduce the volume of respiratory secretion. Less effective than sympathomimetic, Inhaled ipratropium/ tiotropium are choice of bronchodilator choice in COPD. Side effects are dry mouth, respiratory tract discomfort.

Leukotriene Antagonists

Block the cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4,). Alternative for inhaled glucocorticoids; prophylactic therapy for mild, moderate asthma; not used for terminating asthma. They are very safe drugs and ADRs are few (headache, rashes); eosinophilia and neuropathy are Mast Cell Stabilizers infrequent. Few cases Churg-Strauss syndrome (vasculitis with eosinophilia) have been reported.

Mast cell Stabilizers

Inhibits degranulation of mast cell by trigger stimuli and prevent the release of histamine. LTs, PAF interleukins etc. from mast cells. Inhibition of mediator release by cromolyn is through blockade of calcium influx in mast cells. Long time therapy reduces cellular inflammatory response. It is not histamine antagonist/bronchodilator- ineffective during asthmatic attack. Not absorbed orally, administered as an aerosol through metered dose inhaler, production of cough and bronchospasm because of particulate nature of the inhalation. Small fraction of the inhaled drug absorbed systemically and excreted unchanged form in urine and bile.

Used in bronchial asthma, allergic rhinitis; allergic conjunctivitis. Because of poor aqueous solubility, bronchospasm, throat irritation, cough, headache, arthralgia, rashes and dysuria occur

Corticosteroids

They are not bronchodilator; benefit by reducing bronchial hyper-reactivity, mucosal oedema and by suppressing inflammation. Inhaled glucocorticoids are partially absorbed and because of their systemic side effects, oral glucocorticoids are usually reserved for patients with severe persistent asthma. Systemic steroid therapy is used in severe chronic asthma not controlled by bronchodilator and inhaled steroids, status asthmaticus/acute asthma exacerbation. Inhaled steroids have high topical and low systemic activity (due to poor absorption/ first pass metabolism); not recommended for patient mild or episodic asthma. High dose inhaled are beneficial for advanced COPD with frequent exacerbations.

Anti-IgE Antibody

Recombinant DNA-derived monoclonal antibody, selectively binds to human immunoglobulin E (IgE) and decrease binding affinity of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils, reduce allergic response. Omalizumab may be particularly useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled with conventional therapy Due to the high

cost of the drug, limitations on dosage, and limited clinical trial data, it is not currently used as first line therapy.

Ques.5 Write in detailed about laxatives & purgatives.

Ans- LAXATIVES AND PURGATIVES

These are drugs that promote evacuation of bowels. A distinction is sometimes made according to the intensity of action.

(a) Laxative or aperient: milder action, elimination of soft but formed stools.

(b) Purgative or cathartic: stronger action resulting in more fluid evacuation.

Many drugs in low doses act as laxative and in larger doses as purgative.

Classification

1. Bulk forming - Dietary fibre: Bran, Psyllium (Plantago) Ispaghula, Methylcellulose

2. Stool softener: Docusates (DOSS), Liquid paraffin

3. Stimulant purgatives:

(a) Diphenylmethanes: Phenolphthalein, Bisacodyl, Sodiumpicosulfate

(b) Anthraquinones (Emodins): Senna, Cascara sagrada

(c) 5-HT4 agonist: Tegaserod

(d) Fixed oil: Castor oil

4. Osmotic purgatives: Magnesium salts, sulfate, hydroxide; Sodium salts: sulfate, phosphate; Sodium Potassium Tartrate; Lactulose

Mechanism of Action

All purgatives increase the water content of faeces by:

(a) A hydrophilic or osmotic action, retaining water and electrolytes in lumen-increase volume of colonic content and make it easily propelled.

(b) Acting on intestinal mucosa, decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.

(c) Increasing propulsive activity as primary action-allowing less time for absorption of salt and water as a secondary effect.

Certain purgatives do increase motility through an action on the myenteric plexuses. Laxatives modify the fluid dynamics of the mucosal cell and may cause fluid accumulation in gut lumen by one or more of following mechanisms:

(a) Inhibiting Na^+ K^+ ATPase of villous cells impairing electrolyte and water absorption.

(b) Stimulating adenylyl cyclase in crypt cells increasing water and electrolyte secretion.

(c) Enhancing PG synthesis in mucosa which increases secretion.

(d) Structural injury to the absorbing intestinal mucosal cells.

BULK PURGATIVES

Dietary fibre: Bran Dietary fibre consists of unabsorbable cell wall and other constituents of vegetable food-cellulose, pectins, glycoproteins and other polysaccharides. Bran is a by-product of flour industry-consists of -40% dietary fibre. It absorbs water in the intestines, swells, increases water content of faeces, softens it and facilitates colonic transit. Osmotically active products may be formed in the colon by bacterial degradation of pectins, etc. which act to retain water Dietary fibre supports bacterial growth in colon which contribute to the faecal mass. Certain dietary fibres (gums, lignins, pectins) bind bile acids and promote their excretion in faeces→ degradation of cholesterol in liver is enhanced plasma LDL cholesterol is lowered. Increased intake of dietary fibres is the most appropriate method for prevention of functional constipation. It is the first line approach for most patients of simple constipation.

Drawbacks: Bran is generally safe, but it is unpalatable, large quantity (20-40 g/day) needs to be ingested. It has been included in some breakfast cereals. Full effect requires daily intake for at least 3-4 days. It does not soften faeces already present in colon or rectum. As such, bran is useful for prevention of constipation, but not for treating already constipated subjects. Flatulence may occur.

Psyllium (Plantago) and Ispaghula: They contain natural colloidal mucilage which forms a gelatinous mass by absorbing water; 3-12 g of refined husk freshly mixed with water or milk and taken daily-acts in 1-3 days. It should not be swallowed dry (may cause esophageal impaction).

Methylcellulose: A semi-synthetic, colloidal, hydrophilic derivative of cellulose, 4-6 g/ day is satisfactory in most individuals. Generous amounts of water must be taken with all bulk forming agents. The choice among different bulking agents is a matter of personal preferences.

STOOL SOFTENER

Drugs Acting on the Gastro-intestinal Tract 131

Docusates (Dioctyl sodium sulfosuccinate: DOSS) It is an anionic detergent, softens the stools by net water accumulation in the lumen by an action on the intestinal mucosa It emulsifies the colonic contents and increases penetration of water into faeces. By a detergent action, it can disrupt the mucosal barrier and enhance absorption of many non-absorbable drugs, e.g. liquid paraffin should not be combined with it. It is a mild laxative; especially indicated when straining at stools must be avoided.

Cramps and abdominal pain can occur It is bitter; liquid preparations may cause nausea. Hepatotoxicity is feared on prolonged use.

Liquid paraffin: It is a viscous liquid, a mixture of petroleum hydrocarbons and pharmacologically inert. Taken for 2-3 days, it softens stools and is said to lubricate hard seybali by coating them.

STIMULANT PURGATIVES

They irritate the intestinal mucosa and thus stimulate motor activity; primarily increase motility by acting on myenteric plexuses; accumulation of water and electrolytes in the lumen by altering absorptive and secretory activity of the mucosal cell. They inhibit Na^+ K^+ ATPase at the basolateral membrane of villous cells-transport of Na" and accompanying water into the interstitium is reduced.

Larger doses of stimulant purgatives can cause excess purgation fluid and electrolyte imbalance. Hypokalaemia can occur on regular use. Routine and long-term use must be discouraged, produces colonic atony.

Diphenylmethanes

Phenolphthalein is an indicator and is in use as purgative; it turns urine pink if alkaline.

Bisacodyl is partly absorbed and re-excreted inbile: enterohepatic circulation is more important in phenolphthalein which can produce protracted action. Bisacodyl is activated in the intestine by deacetylation. Their primary site of action is in the colon: irritate the mucosa, produce mild inflammation and secretion.

Anthraquinones

Senna is obtained from leaves and pod of certain Cassia sp., while Cascara sagrada is the powdered bark of the buck-thorn tree called emodins. Unabsorbed in the small intestine, they are passed to the colon where bacteria liberate the active anthrol form, which either acts locally or is absorbed into circulation-excreted in bile to act on small intestine. Thus, they take 6-8 hours to produce action. Taken at bed time-a single, soft but formed evacuation generally occurs in the morning.

Cramps and excessive purging occur in some cases. The active principle acts on the myenteric plexus to increase peristalsis and decrease segmentation. They also promote secretion and inhibit salt and water absorption in the colon. Skin rashes, fixed drug eruption is seen occasionally.

Tegaserod

It is a new selective 5-HT_4 receptor partial agonist with no action on other receptors. By activating prejunctional 5-HT_4 receptors on intrinsic enteric afferents, tegaserod enhances release of excitatory transmitters ACh and calcitonin gene related peptide (CGRP) which promote peristaltic reflex and colonic secretion (by enhancing CAMP mediated C1 efflux). Only a small fraction of tegaserod is absorbed. It is mainly excreted unchanged in faeces. Side effects reported are loose motions, flatulence, and headache.

Castor oil

It is one of the oldest purgatives. Castor oil is a bland vegetable oil obtained from the seeds of *Ricinus communnis;* mainly contains triglyceride of ricinoleic acid which is a polar long chain fatty acid. Castor oil is hydrolysed in the ileum by lipase to ricinoleic acid and glycerol. Ricinoleic acid being polar, is poorly absorbed, irritate the mucosa and stimulate intestinal contractions. The decrease in intestinal absorption of water and electrolytes, and enhanced secretion by a detergent like action on the mucosa. Due to its unpalatability, frequent cramping, a rather violent action, possibility of dehydration and after constipation (due to complete evacuation of colon), it is no longer a favoured purgative.

OSMOTIC PURGATIVES

Solutes that are not absorbed in the intestine retain water osmotically and distend the bowel-increasing peristalsis indirectly. Magnesium ions release cholecystokinin which may aid purgative action of Magnesium salts. All inorganic salts used as osmotic (saline) purgatives have similar action-differ only in dose, palatability, and risk of systemic toxicity.

1 Mag. sulfate (Epsom salt): 5-15 g; bitter in taste.

2. Mag. hydroxide (as 8% W/W suspension milk of magnesia) 30 ml, bland in taste, also used as antacid.

3. Sod sulfate (Glauber's salt): 10-15 g, bad in taste.

4. Sod phosphate: 6-12 g, taste not unpleasant.

5. Sod. pot. tartrate (Rochelle salt): 8-15 g, relatively pleasant tasting.

The salts in above mentioned doses, dissolved in 150-200 ml of water, produce 1-2 fluid evacuations within 1-3 hours with mild cramping, cause nearly complete emptying of bowels. Smaller doses may have a milder laxative action.

Lactulose: It is a semi-synthetic disaccharide of fructose and lactose which is neither digested nor absorbed in the small intestine-retains water. Further, it is broken down in the colon by bacteria to osmotically more active products. In a dose of 10 g BD taken with plenty of water, it produces soft formed stools in 1-3 days. Flatulence and flatus are common, cramps occur in few Some patients feel nauseated by its peculiar sweet taste.

Short Answers

Ques.1 Give the classification of anti-hypertensive agents.

Ans- Classification

1. DIURETICS

(a) Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide

(b) High ceiling: Furosemide, Torsemide, ethacrynic acid.

(c) K^+ Sparing: Spironolactone, Amiloride

2. βACE INHIBITORS: Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril

3. β+α ANGIOTENSIN (AT_1 RECEPTOR) BLOCKERS: Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan

4. CALCIUM CHANNEL BLOCKERS: Verapamil, Diltiazem, Nifedipine, Amlodipine, Nitrendipine, Lacidipine

5. BADRENERGIC BLOCKERS: Propranolol, Metoprolol, Atenolol, etc.

6. β + α ADRENERGIC BLOCKERS: Labetalol, Carvedilol

7. α ADRENERGIC BLOCKERS: Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine

8. CENTRAL SYMPATHOLYTICS: Clonidine, Methyldopa

9. VASODILATORS:

(a) Arteriolar: Hydralazine, Minoxidil, Diazoxide

(b) Arteriolar+ venous: Sodium nitroprusside

10. DIRECT RENIN INHIBITOR: Alis Kiren

11. OTHERS: Adrenergic neurone blockers (Reserpine, Guanethidine); **Ganglion blockers** (Pentolinium)

Ques.2 Give the complete classification of anti-arrhythmic agents.

Ans- Classification

1. Class I: Membrane Active Drugs

(a) IA: Quinidine, Procainamide, Disopyramide, Moricizine

(b) IB: Lidocaine, Mexiletine, Tocainide, Phenytoin

(c) IC: Flecainide and propafenone

2. Class II: Beta Adrenergic Antagonist: Propranolol, Esmolol, Acebutolol, Timolol Metoprolol

3. Class III: Prolong Duration of Action Potential and Refractoriness: Amiodarone, Sotalol, Bretylium, Ibutilide, dofetilide.

4. Class IV: Calcium Channel Antagonists: Verapamil and Diltiazem

5. Unclassified: Digoxin, Adenosine

Class IA

Quinidine is D-isomer of quinine obtained from cinchona bark. It blocks sodium channels to decrease automaticity, conduction velocity and prolongs repolarization, decreases phase 0 depolarization, increases action potential duration (APD) & effective refractory period (ERP) Also decreases blood pressure (a block) and skeletal muscle relaxation. Used for atrial and ventricular arrhythmias. Adverse effects are arrhythmias and heart block, hypotension, QT prolongation, thrombocytopenia, hepatitis, idiosyncratic reactions, high dose causes cinchonism like quinine.

Procainamide: Derivative of procaine with no vagolytic or a-blocking action unlike quinidine and better tolerated. Adverse effects are nausea, vomiting and hypersensitivity reactions: Higher doses can cause hypotension, heart block and QT prolongation.

Disopyramide has significant anticholinergic properties: dry mouth, blurred vision, constipation, urinary retention.

Class 1B

Lignocaine is a local anaesthetic which raises threshold for action potential, decreases automaticity, suppresses electrical activity of arrhythmogenic tissues, normal tissues less effected. High first pass metabolism so given parenterally and used for ventricular arrhythmias. Adverse effects are drowsiness, hypotension, blurred vision, confusion, and convulsions.

Phenytoin: Antiepileptic is also useful in ventricular arrhythmias (not preferred) and digitalis induced arrhythmias.

Mexiletine: Can be used orally causes dose related neurological adverse events like tremors and blurred vision; nausea is common. Used as alternative to lignocaine in ventricular arrhythmias.

Class IC

Encainide, Flecainide, Propafenone have minimal effect on repolarization; most potent sodium channel blockers. Risk of cardiac arrest & sudden death so not used commonly. May be used in evere ventricular arrhythmias.

Class II Drugs

Suppress adrenergically mediated ectopic activity; antiarrhythmic action due to of β blockade depress myocardial contractility, automaticity, and conduction velocity.

Propranolol is used for the treatment & prevention of supraventricular arrhythmias especially associated with exercise, emotion, or hyperthyroidism.

Esmolol is i.v. short acting can be used to treat arrhythmias during surgery, following MI & other emergencies.

Class III Drugs

Amiodarone is iodine containing long-acting drug that prolongs APD by blocking K^+ channels, Mocks inactivated sodium channels, β blocking action and blocks Ca^{2+} channels. This leads to decrease conduction and ectopic automaticity. It has variable absorption 35-65% with slow onset Le two days to several weeks. Used for both supraventricular and ventricular tachycardia. Adverse effects are heart

block, QT prolongation, bradycardia, cardiac failure, hypotension, pneumonitis leading to pulmonary fibrosis, bluish discoloration of skin, GIT disturbances, hepatotoxicity, blocks peripheral conversion of T_4 to T_3 can cause hypothyroidism or hyperthyroidism.

Bretylium: Adrenergic neuron blocker used in resistant ventricular arrhythmias

Sotalol: Beta blocker & **Dofetilide:** Selective K channel blocker, less adverse events.

Calcium Channel Blockers (Class IV)

Inhibit the inward movement of calcium ions and reduce contractility, automaticity and AV conduction. Used to control ventricular rate in atrial flutter or fibrillation.

Other Anti-arrhythmic

Adenosine is purine nucleotide having short and rapid action i.e. acetylcholine sensitive K channels and causes membrane hyperpolarization through interaction with A_1 type of adenosine GPCRs on SA node; suppresses automaticity, AV conduction and dilates coronaries. Adverse events like nausea, dyspnoea, flushing, headache is observed.

Atropine: Used in sinus bradycardia.

Digitalis: Atrial fibrillation and atrial flutter

Magnesium SO_4: digitalis induced arrhythmias

Ques.3 What are the pharmacological actions of CHF?

Ans- Pharmacological Actions

All digitalis glycosides have qualitatively similar action; there are only quantitative & pharmacokinetic differences. Digoxin is described as prototype.

1. Heart:

(a) Force of contraction: It increases force of contraction of heart, a positive inotropic. In normal individual, it constricts blood vessels of arteries & veins. In CCF there is decrease force of contraction of heart, this result in decrease cardiac output & decrease stroke volume

(b) Tone: Maximum length of fibre at a given filling pressure or resting tension in the muscle fibre. This is not affected by therapeutic doses of digitalis.

(c) Rate: Heart rate is decreased by digitalis (-ve chronotropic), Bradycardia is more marked in CHF patients; improved circulation (due to ve inotropic action) restores the diminished vagal tone & abolishes sympathetic over activity. Vagal tone is increased by direct stimulation of vagal centre & sensitization of SA node to Ach.

(d) Conduction velocity & refractory period: smaller doses produce increase in conduction velocity due to vagal action whereas; larger doses of digitalis produce decrease in conduction velocity because of direct action. The decrease in conduction in AV node is therapeutically useful in conditions of atrial flutter & fibrillation. The refractory period in atria is shortened in lower doses whereas, in larger doses digitalis prolongs the refractory period. The refractory period of AV node is prolonged by vagal impulse & also by direct action of digitalis.

(e) Electrocardiogram (ECG): Digitalis produces depression of ST segment (at high dose), innervations of T wave (decreased amplitude), increased P-R interval (slowing of A-v conduction), A-V block at toxic doses shortening of QT interval. ST segment (due to interference with repolarization).

2. Blood Vessels: Blood vessels Digitalis has mild direct vasoconstrictor action peripheral resistance is decreased in normal individuals. Digitalis has no prominent effect on BP, systolic BP may increase & diastolic may fall in CHF patients pulse pressure increases. Hypertension is no contraindication to the use of digitalis.

3. Kidney: In CCF there is decrease in renal blood flow resulting in sodium retention & oedema. Digitalis by improving renal circulation & decreasing venous pressure increases the formation of urine. This results into increased excretion of Na^+ & decrease in oedema and produces a prominent diuretic effect.

4. CNS: Digitalis has little apparent CNS effect in therapeutic dose. Higher doses cause CTZ activation-nausea, vomiting. Still higher doses produce mental confusion, visual disturbance, diarrhoea, central sympathetic stimulation hyperpnoea, disorientation.

Ques.4 Give the pharmacokinetics of calcium channel blockers.

Ans- Pharmacokinetics

All are 90-100% absorbed orally, peak occurring at 1-3 hour (except amlodipine 6-9 hour). The oral bioavailability of Ca^{2+} channel blockers is incomplete with marked inter and intraindividual variations; due to high first pass metabolism (modest and less variable for amlodipine). All are highly plasma protein bound, metabolized in liver, and excreted in urine.

Verapamil dilates arterioles and decreases total peripheral resistance. It slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand. It also has some β adrenergic blocking activity. Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator. Verapamil should not be given with β blockers, digoxin, cardiac depressants like quinidine and disopyramide.

Diltiazem also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator. Diltiazem can relieve coronary artery spasm and is particularly useful in patients with variant angina. It is somewhat less potent vasodilator than nifedipine and verapamil, and has modest direct negative inotropic action, but direct depression of SA node and A-V conduction are equivalent to verapamil.

Nifedipine is the prototype DHP with a rapid onset and short duration of action. It causes arteriolar dilatation and decreases total peripheral resistance. Nifedipine is usually administered as an extended-release oral formulation. It causes direct depressant action on heart in higher dose. Frequent side effects are palpitation, flushing, ankle oedema, hypotension, headache, drowsiness, and nausea. Nifedipine has paradoxically increased the frequency of angina in some patients.

Calcium channel blockers can be safely given to patients with obstructive lung disease and peripheral vascular disease (as ß blockers are contraindicated). CCB are used for the treatment of angina pectoris, hypertension, cardiac arrhythmias & hypertrophic cardiomyopathy.

Potassium Channel Openers (Nicorandil): Antianginal action of nicorandil is mediated through ATP sensitive K^+ channels thereby hyperpolarizing vascular smooth muscle. Nicorandil is well absorbed orally, nearly completely metabolized in liver, and is excreted in urine. Administered i.v. during

angioplasty for acute MI, it is believed to improve outcome. Side effects are flushing, palpitation, weakness, headache, dizziness, nausea and vomiting.

Ques.5 Write a short note on anti-platelet agents.

Ans- ANTI-PLATELET AGENTS

Platelet aggregation inhibitors decrease the formation or the action of chemical signals that promote platelet aggregation. These agents have proven beneficial in the prevention and treatment of occlusive cardiovascular diseases, the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombolytic therapy in myocardial infarction.

Aspirin: Aspirin blocks thromboxane A_2 synthesis from arachidonic acid in platelets by irreversible acetylation and inhibition of cyclooxygenase, a key enzyme in prostaglandin and thromboxane A_2 synthesis. The inhibitory effect is rapid, apparently occurring in the portal circulation. The aspirin-induced suppression of thromboxane A_2 synthetase and the resulting suppression of platelet aggregation last for the life of the platelet-approximately 7 to 10 days. Aspirin is currently employed in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent myocardial infarction and to decrease mortality in post myocardial infarction patients. Currently, a single loading dose of 200 to 300 mg of aspirin followed by a daily dose of 75 to 100 mg is recommended. Bleeding time is prolonged, causing complications that include an increased incidence of haemorrhagic stroke as well as gastro-intestinal bleeding, especially at higher doses of the drug.

Ticlopidine: Ticlopidine also acts as an inhibitor of platelet aggregation but by a mechanism other than that of aspirin. The drug inhibits the ADP pathway involved in the binding of platelets to fibrinogen and to each other. Ticlopidine has been shown to decrease the incidence of thrombotic stroke. After oral ingestion it is extensively bound to plasma proteins and undergoes hepatic metabolism. The drug can cause prolonged bleeding; its most serious adverse effect is neutropenia. Therefore, it is reserved for patients, who cannot tolerate aspirin.

Ques.6 What are expectorants and mucolytic agents?

Ans- EXPECTORANTS

Expectorants (Mucokinetics) are drugs believed to increase bronchial secretion or reduce in viscosity, facilitating its removal by coughing. They are classified as

(a) Bronchial secretion enhancers: Sodium or Potassium citrate, Potassium iodide Guaiphenesin (Glyceryl guaiacol ate), balsam of Tolu, Vasaka, Ammonium chloride.

(b) Mucolytics: Bromhexine, Ambroxol, Acetylcysteine, Carbocisteine

Sodium and potassium citrate are considered to increase bronchial secretion by salt action Potassium iodide is secreted by bronchial glands and can irritate the airway mucosa; rarely used now Guaiphenesin, vasaka, tolu balsam are plant products which are supposed to enhance bronchial secretion and muco-ciliary function while being secreted by tracheobronchial glands. Ammonium salts are nauseating-reflexly increase respiratory secretions,

Mucolytic Agents

Bromhexine is a derivative of the alkaloid vasicine obtained from *Adhatodavasica* (Vasaka), capable of inducing thin copious bronchial secretion. It depolymerizes mucopolysaccharides directly as well as by liberating lysosomal enzymes network of fibers in tenacious sputum is broken. Side effects are rhinorrhoea and lacrimation; gastric irritation, hypersensitivity Ambroxol metabolite of bromhexine having similar mucolytic action, uses and side effects.

Acetylcysteine opens disulfide bonds in mucoproteins present in sputum-makes it less viscid but must bead ministered directly into the respiratory tract.

Carbo cysteine liquefies viscid sputum in the same way as acetylcysteine and is administered orally. Side effects are g.i.t. irritation and rashes.

Ques.7 Explain nasal decongestants.

Ans- NASAL DECONGESTANTS

Nasal decongestants are drugs used to treat the common cold and allergic rhinitis, conditions the collectively cause more discomfort and lost work time than all other known illnesses combine Nasal decongestants may be used in treating nasal congestion associated with sinusitis, middle infections, and upper respiratory infections.

Nasal congestion results from dilation of nasal blood vessels due to infection, inflammation, allergy. With dilation there's transudation of fluid into tissue spaces causing swelling of the nasal cavity. Nasal decongestants are administered topically, by inhalation, or orally.

Classification

1. Adrenaline releasing Phenylpropanolamine HCL agents: Phenylpropanolamine, Pseudoephedrine

Phenylpropanolamine HCL

2. α-Adrenergic receptor agonists: Naphazoline HCL, Oxymetolazone

3. Corticosteroids: Beclomethasone, Budesonide, Dexamethasone, fluticasone

4. Miscellaneous: Saline (water and sodium chloride solution)

Decongestants (sympathomimetic amines) stimulate alpha-adrenergic receptor causing vasoconstriction of capillaries within nasal mucosa and shrinking of the nasal mucus membranes & reduction in fluid secretion (runny nose). Use in congestion due to common cold, hay fever, upper respiratory allergies, sinusitis. Side effects like jittery, nervous, restlessness, increase in BP & blood sugar Frequent use, esp. nasal spray, can result in tolerance & rebound nasal congestion due irritation of nasal mucosa.

Corticosteroids decrease the inflammation locally in the nose. Used for perennial or seas allergic rhinitis (sneezing, runny nose). May be used alone or with anti-histaminic. Side effect rare, but with continuous use dryness of the nasal mucosa may occur.

Ques.8 Write a short note on proton pump inhibitors & ulcer protectives.

Ans- PROTON PUMP INHIBITORS (PPIS)

Omeprazole is inactive at neutral pH, but at pH <5 rearranges to two charged cationic forms (a sulphonic acid and a sulphonamide configuration) that react covalently with SH groups of the H^+K^+ ATPase enzyme and inactivate it irreversibly, especially when two molecules of omeprazole react with one molecule of the enzyme. After diffusing into the parietal cell from blood, it gets concentrated in the acidic pH of the canaliculi because the charged forms generated there are unable to diffuse back. It also inhibits gastric mucosal carbonic anhydrase.

Pharmacokinetics

The oral absorption of omeprazole is -50%, because of instability at acidic pH. Bioavailability of all PPIs is reduced by food, they should be taken in empty stomach, followed 1 hour later by a meal to activate the HK ATPase and make it more susceptible to the PPI. Omeprazole is highly plasma protein bound, rapidly metabolised in liver, and excreted in urine.

Adverse effects

Nausea, loose stools, headache, abdominal pain, muscle and joint pain, dizziness is complained by 3-5%. Rashes (1.5% incidence), leukopenia and hepatic dysfunction are infrequent. On prolonged treatment, atrophic gastritis has been reported occasionally.

ULCER PROTECTIVES

Sucralfate is a basic aluminium salt of sulphated sucrose; a drug of its own kind. Sucralfate polymerizes at pH < 4 by cross linking of molecules, assuming a sticky gel-like consistency It preferentially and

strongly adheres to ulcer base, especially duodenal ulcer; to remain there for-6 hours. It precipitates surface proteins at ulcer base and acts as a physical barrier preventing acid, pepsin, and bile from coming in contact with the ulcer base. Dietary proteins get deposited on this coat, forming another layer. Sucralfate has no acid neutralizing action, but delays gastric emptying-its own stay in stomach is prolonged.

Sucralfate is minimally absorbed after oral administration; action is entirely local. It promotes healing of both duodenal and gastric ulcers; efficacy has been found similar to cimetidine at 4 weeks. Antacids should not be taken with sucralfate because its polymerization is dependent on acid Ph.

Side effects are few, constipation, hypophosphatemia by binding phosphate ions in the intestine. Dry mouth and nausea are infrequent.