Case-Based Learning in PHARMACOLOGY

for Undergraduate Medical Students

As per the latest CBME Guideline | Competency based Undergraduate Curriculum for the Indian Medical Graduate

Snigdha Misra
Bhabagrahi Rath
Rajesh Kumar Suman

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Section

I

Disorders of the Gastrointestinal System

Chapter 1

Drugs for Peptic Ulcer and Gastroesophageal Reflux Disease

CASE 1: PEPTIC ULCER DISEASE (PUD)

A 35-year-old adult male RX, complains of intermittent pain in the upper abdomen. Pain aggravated at night after taking large meal. He was fond of fried and spicy food. He is a chronic smoker of cigarettes and an occasional drinker of alcohol. His grandmother had died of peptic ulcer disease. Haemoglobin values were normal and there was absence of blood in stool and vomiting.

The patient took ranitidine over the counter (OTC) for 3 times daily for a week for the relief of pain. Later after consultation with the physician ranitidine was changed to famotidine.

Qa. What are the factors which lead to peptic ulcer formation?

Imbalance between gastroduodenal mucosal defence forces and the aggressive forces lead to the pathogenesis of peptic ulcer. Thus, ***increase in acid-pepsin secretion and decrease in mucosal resistance*** appears to be the basic cause for peptic ulceration.

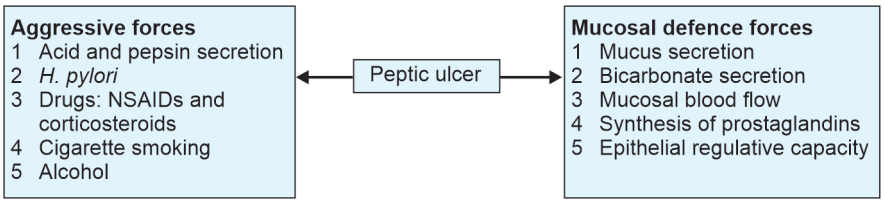


Fig. 1.1: Interplay of factors that contribute to pathogenesis of peptic ulcer

Qb. Explain the regulatory mechanisms for acid secretion from gastric parietal cells.

Neurologic, physical and hormonal stimuli release acetylcholine, gastrin and histamine which bind to their respective receptors on the basement membrane of the parietal cell. Through a cascade of events, increased intracellular calcium and raised cyclic AMP activates protein kinase A which stimulates the proton pump, the final common pathway which transports H^+ out in exchange for K^+. Chloride ions transported into the stomach lumen associate with H^+ ions to form hydrochloric acid (HCl).

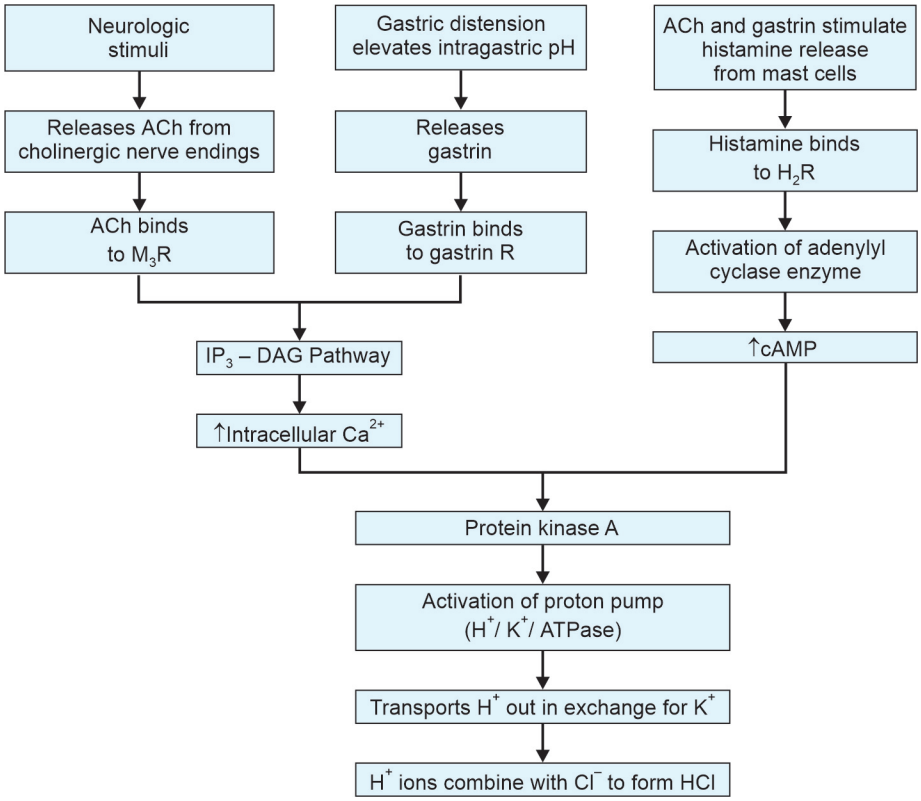


Fig. 1.2: Regulation of gastric acid secretion from the parietal cell

Qc. Which drugs are used for reducing acid secretion in peptic ulcer disease?

Drugs that reduce gastric acid secretion	
H2-receptor antagonists	Cimetidine, ranitidine, famotidine, nizatidine
Proton pump inhibitors	Omeprazole, rabeprazole, pantoprazole
Antimuscarinic agents	Pirenzepine, telenzepine
Prostaglandins	Misoprostol, enprostil, rioprostil

Qd. How is ranitidine or famotidine superior to cimetidine which is the prototypic H2- blocker in the treatment of dyspepsia?

Ranitidine and famotidine are superior to cimetidine in the following ways:

1. Both ranitidine and famotidine have greater potency and longer duration of action than cimetidine. This provides a longer duration of acid suppression.
2. Cimetidine crosses the blood–brain barrier and may induce mental confusion, headache and delirium. Ranitidine and famotidine have less penetration into the central nervous system, thereby producing less central adverse effects.
3. Cimetidine is antiandrogenic and increases prolactin levels, thereby leading to gynecomastia, galactorrhea, impotence and reduced sperm count in males. Hormonal side effects are minimal with ranitidine and famotidine.

4. Cimetidine inhibits CYP1A2, 2C9, 2D6 enzymes. Therefore, plasma levels of drugs metabolized by these enzymes may increase leading to toxicity. Ranitidine and famotidine have minimal or no action on hepatic CYP enzymes and decreased incidence of drug interactions.

Comparison of various H2-receptor antagonists			
Parameters	*Cimetidine*	*Ranitidine*	*Famotidine*
Bioavailability	80	50	40
Relative potency	1	5–10	32
Half-life (hrs)	1.5–2.3	1.6–2.4	2.5–4
Duration of action (hrs)	6	8	12
Inhibition of CYP450	1	0.1	0
Dose mg (bd)	400	150	20

Qe. Mr RX, wishes to take a H2-antagonist before he takes alcohol to avoid gastric irritation. He consults you. Which H2-antagonist will you ask him to take?

Mr RX was recommended famotidine and nizatidine because these have minimal effect on hepatic cytochrome P450 enzymes and hence do not affect the metabolism of alcohol unlike other H2-blockers which act as inhibitors of cytochrome P450 and thus inhibit the gastric first pass metabolism of ethanol increasing the concentration of alcohol in the blood producing undesirable effects.

Case Continued

Mr RX experienced pain more frequently and periods of remission decreased. Endoscopic examination revealed active duodenal ulcer. Mucosal biopsy suggested *H. pylori*. A case of duodenal ulcer associated with *H. pylori* was confirmed.

Qa. Mention the treatment regimen you would recommend for *H. pylori* eradication in peptic ulcer disease in case of RX.

Proton pump inhibitor (PPI) based standard tripple therapy (PPI-clarithromycin-amoxicillin) is an acceptable first line management strategy for RX because he has not received clarithromycin previously and has no known allergy to penicillin. Amoxicillin is usually preferred initially because it is associated with a little or no bacterial resistance, has fewer adverse effects, and leaves metronidazole as an option for second-line therapies.

If RX had a documented allergy to penicillin, metronidazole can be used instead of amoxicillin in the PPI-based three-drug regimen.

Bismuth-based quadruple therapy containing a bismuth salt, metronidazole, tetracycline, and either a PPI or H2-receptor antagonist has been frequently used as second line therapy.

Qb. What is the reasonable treatment period of eradication therapy for *H. pylori* infections with treatment regimens?

A 10–14-day-regimen is superior to shorter treatment regimens and is less likely to be associated with antimicrobial resistance. A treatment duration of less than 7 days is not recommended and is associated with unacceptable eradication rates.

Section

II

Disorders of the Respiratory System

2. Drugs for Bronchial Asthma

Chapter 2

Drugs for Bronchial Asthma

CASE 1: MODERATE PERSISTENT ASTHMA

RY, a 7-year-old girl, presents to the clinic with a history of asthma and seasonal allergic rhinitis (hay fever) each spring but not the rest of the year. She complains of shortness of breath and frequent night-time awakenings.

On enquiry, she revealed that her symptoms get worsened during spring season but over last 6 months she gives a history of three similar attacks which were of lesser intensity. The attacks were apparently spontaneous and occurred at an interval of around 1.5 to 2 months.

Medication history: **The attacks of bronchial asthma were well controlled previously with 2 puffs of salbutamol metered dose inhaler (MDI) taken as and when needed. However, the present attack did not subside in spite of 8 puffs of salbutamol MDI taken as 2 puffs every 10 minutes. She has been taking leukotriene receptor antagonist for allergic rhinitis.**

On examination: **Pulse is found to be 110/min and respiratory rate is 23/min. Examination of respiratory system reveals bilateral expiratory rhonchi with prolonged expiration. Rest of the systemic examination is normal.**

Past history: **Eczema and hay fever since she was 4 years old. There is no history suggestive of any cardiac cause of breathlessness or history suggestive of any abdominal or CNS problem.**

Your diagnosis: **Moderate persistent asthma.**

Qa. What could be the predisposing factor for bronchial asthma in case of RY?

Presence of allergic rhinitis and history of eczema and hay fever are important risk factors for asthma development. Patients with allergic rhinitis have threefold greater chance of developing asthma.

Qb. Describe the underlying pathophysiology of bronchial asthma that causes signs and symptoms as described in the case of RY.

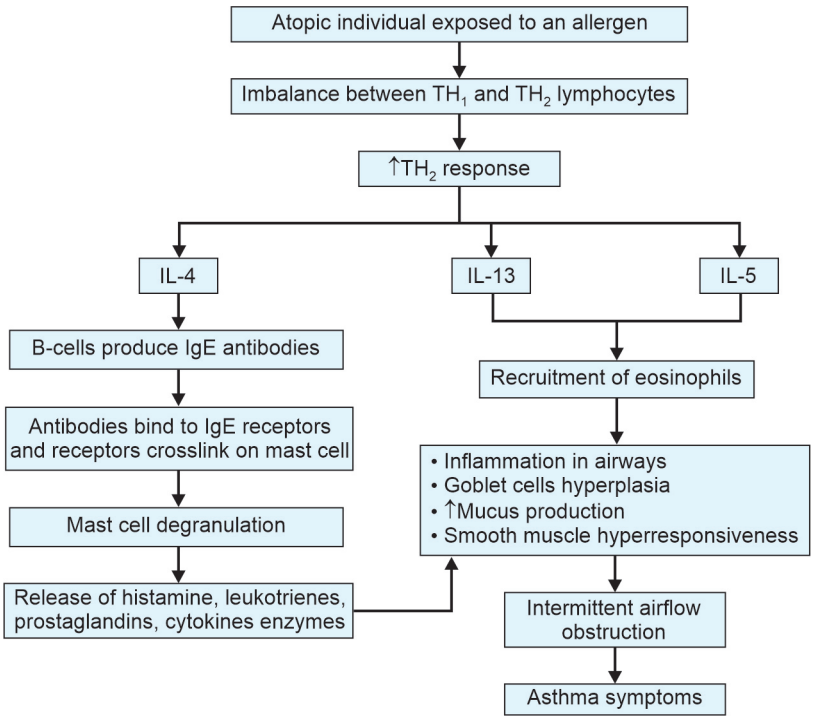


Fig. 2.1: Pathophysiology of asthma

Asthma is a disease of chronic airway inflammation in which allergen-specific T-helper-2 cells play a central role. There is increased production of T-helper-2-associated cytokines, such as interleukin (IL)-4, IL-13, and IL-5.

Interleukin-4 is a key cytokine in the development of allergic inflammation. It is associated with the secretion of IgE by B lymphocytes. Interleukin-4 also has the ability to upregulate IgE-receptors on the surface of mast cells. IgE-mediated activation of mast cell leads to degranulation and release of histamine and leukotrienes that promote cellular inflammation and lung remodelling in chronic asthma.

Interleukin-13 is implicated as a central regulator of eosinophilic inlammation, mucus hypersecretion, airway hyper-responsiveness and fibrosis.

Interleukin-5 is a powerful proinflammatory cytokine that is responsible for maturation, proliferation, activation and migration of eosinophils from bloodstream to the airways.

Qc. Which drugs are available for the management of bronchial asthma?

Bronchodilators

1. Selective β2-agonist: Salbutamol, terbutaline, salmeterol, formoterol
2. Non-selective sympathomimetics: Epinephrine, ephedrine, isoprenaline
3. Anticholinergics: Ipratropium bromide, tiotropium bromide
4. Methyxanthines: Theophylline, aminophylline

Corticosteroids

1. Oral: Prednisone, prednisolone and methylprednisolone
2. Parenteral: Methylprednisolone, hydrocortisone, sodium succinate
3. Inhalational: Beclomethasone, fluticasone, budesonide, flunisolide and ciclesonide

Mast Cell Stabilisers

Sodium chromoglycate and nedocromil sodium

Leukotriene Modulators

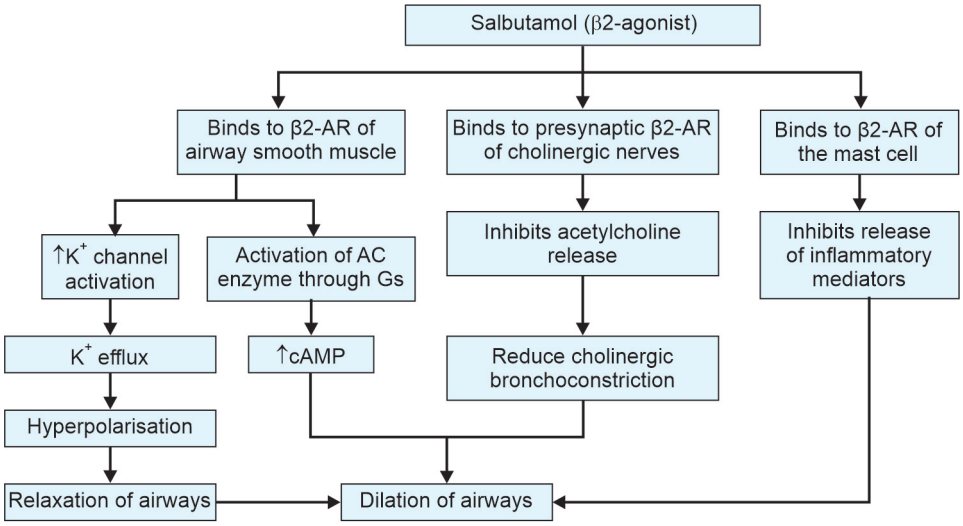
1. 5-Lipoxygenase inhibitor: Zileuton
2. Leukotriene receptor antagonists: Zafirlukast, montelukast, pranlukast

Biologicals

Monoclonal anti-IgE antibody: Omalizumab

Interleukin-5 (IL-5) pathway inhibitors: Mepolizumab, benralizumab

Qd. How does salbutamol relieve symptoms of asthma?



AR: Adrenergic receptor, AC: Adenylyl cyclase, Gs: Stimulatory G protein

Fig. 2.2: Mechanism of action of salbutamol

Salbutamol acts as a bronchodilator due to its stimulatory effect on β2-adrenergic receptors at various sites:

1. Stimulation of β2-adrenergic receptors in the airway smooth muscle activates adenylyl cyclase (AC) and causes cyclic AMP mediated relaxation of airways. β2-agonists open large conductance calcium activated potassium channels causing potassium efflux and hyperpolarization of airway smooth muscle cells. Decreased intracellular calcium concentration together with increased membrane potassium conductance leads to smooth muscle relaxation and bronchodilation.
2. Stimulation of β2-adrenergic receptors at the presynaptic cholinergic nerve endings has an inhibitory effect on the release of acetylcholine and reduced cholinergic bronchoconstriction.

3. Stimulation of β2-adrenergic receptors on the mast cells inhibit the release of inflammatory mediators such as histamine and leukotrienes which are potent bronchoconstrictors.

Qe. Why is salbutamol preferred over isoproterenol and adrenaline in the management of acute symptoms of asthma?

Isoproterenol is a β1- and β2-adrenergic receptor agonist. Although it causes β2-mediated relaxation of the airways, the β1-stimulatory action on the heart increases the risk for tachycardia and arrhythmias.

Adrenaline is a non-selective adrenergic agonist that stimulates α, β1- and β2-receptors. Acting via α-receptors it causes peripheral vasoconstriction leading to rise in blood pressure and through β1-agonistic action causes cardiac effects like tachycardia and arrhythmias.

Salbutamol unlike adrenaline and isoproterenol, has selective β2-agonistic action. There is relaxation of airway smooth muscle reducing airflow obstruction and this provides relief of acute symptoms of asthma. Therefore, the beneficial effects of salbutamol can be achieved while cardiac side effects can be avoided.

Qf. What are the likely side effects of salbutamol use in bronchial asthma?

The side effects of salbutamol are more prominent with systemic administration and at higher dosages. They are the following:

1. Tremor or shakiness may be attributed to the stimulation of β2-receptor of the skeletal muscle.
2. Palpitation may be experienced by the patient due to β2-mediated vasodilation-induced reflex tachycardia. Cardiac effects are more common with non-specific agonists due to their additional β1-stimulatory action on heart.
3. Decrease in potassium concentration may occur due to β2-adrenergic activation of the Na^+-K^+-pump leading to transport of potassium intracellularly. A β2-adrenergic-mediated increase in glucose and insulin secretion also can contribute to the intracellular shift of potassium causing hypokalemia.

Qg. Aerosolized salbutamol is preferred over oral or parenteral administration in the management of acute asthma. Why?

It has been documented that inhaled route of salbutamol administration exerts as great or greater beneficial effect on pulmonary function tests with fewer systemic side effects than either the parenteral or oral routes. It has a rapid onset of action (15–30 min), a peak effect at 30–60 min and duration of action of approximately 4 to 6 hours. This time course of drug action makes salbutamol a suitable drug for quick relief of acute symptoms of asthma and is therefore frequently used as rescue treatment for all asthma patients. Salbutamol should not be administered orally to treat acute episode of severe asthma because of slow onset of action, lower efficacy and erratic absorption.

Qh. What could be the reason for lack of response to therapy with multiple doses of salbutamol in patient RY? What are the drawbacks of using salbutamol frequently, as monotherapy on long-term basis to control asthma?

Salbutamol has a short duration of action which is inadequate for control of nocturnal symptoms. Lack of response to therapy with multiple doses of salbutamol may be attributed to severity of airway obstruction with inflammation playing an important part

Chapter

4

Drug Therapy for Angina Pectoris

CASE 1: DRUG THERAPY OF CHRONIC STABLE ANGINA

A 55-year-old female RY, body weight 78 kg, presents to her family physician for evaluation of chest pain. She complains of occasional crushing type of chest pain and discomfort located on the left side of the chest, associated with physical exertion such as climbing stairs or lifting heavyweights. The pain does not occur at rest and is not associated with intake of meals. On examination blood pressure is 138/88 mmHg.

Medication history: **She is hypertensive for past 7 years and diabetic for 2 years. Her treatment consists of telmisartan and metformin for hypertension and diabetes respectively. There is no history of bronchial asthma.**

Personal history: **She is a smoker and an occasional drinker.**

Family history: **Father died of ischemic heart disease.**

Laboratory investigations indicate slightly abnormal lipid profile. ECG is normal.

Probable diagnosis: **Stable angina.**

Treatment Advised

- **Lifestyle modification**
- **Patient was educated to take sublingual nitroglycerin during acute attack.**
- **Tablet metoprolol succinate (beta-blocker) 50 mg orally twice a day was prescribed for prevention of angina episodes.**
- **Tab aspirin 100 mg/day**

Qa. What is 'angina'? How would you differentiate various types of angina on the basis of their clinical presentation and pathophysiology?

Angina is not a disease, it is primarily a symptom of ischemic heart disease which occurs due to imbalance between *myocardial oxygen supply and myocardial oxygen demand*.

Angina is of three different types:

- Stable angina
- Unstable angina
- Vasospastic angina

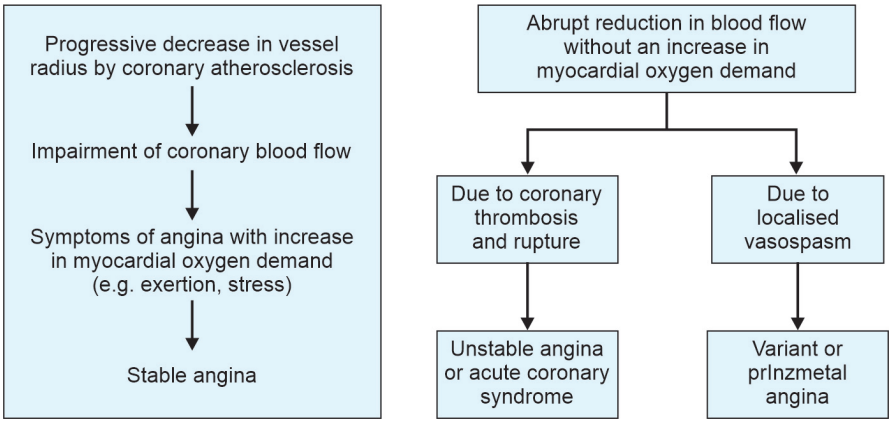


Fig. 4.1: Types of angina

Stable angina, also known as typical angina or angina pectoris, is characterized by chest discomfort that is provoked with exertion and alleviated at rest or with nitroglycerin. The mechanism behind stable angina is the result of supply–demand mismatch. The myocardial oxygen demand transiently exceeds the myocardial oxygen supply, which often leads to manifestations of symptoms.

Unstable angina or sometimes referred to as acute coronary syndrome, differs from stable angina in that the discomfort is usually more intense and easily provoked, and ST-segment depression or elevation on ECG may occur. With unstable angina, symptoms may occur at rest, become more frequent, severe or prolonged than the usual pattern of angina, change from the usual pattern of angina or not respond to rest or nitroglycerin.

Prinzmetal angina (vasospastic angina or variant angina) is characterized by chest discomfort or pain at rest with transient electrocardiographic changes in the ST segment, and with a prompt response to nitrates. These symptoms occur due to sudden coronary artery spasm reducing blood flow to the heart.

Qb. What are the determinants of myocardial oxygen supply and demand that can result in chest pain or angina?

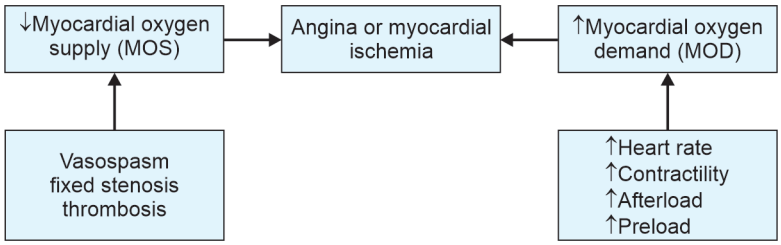


Fig. 4.2: Determinants of myocardial oxygen supply and myocardial oxygen demand contributing to angina

Factors which decrease myocardial oxygen supply due to reduced blood flow are:

- Focal or diffuse coronary spasm (variant angina)
- Fixed atherosclerotic narrowing of an epicardial coronary artery (stable angina)
- Rupture of an atherosclerotic plaque with platelet aggregation and thrombus formation (unstable angina or myocardial infarction)

Factors which increase myocardial oxygen demand:

- *Increase in heart rate and contractility:* Increases the workload on the heart with greater oxygen consumption and myocardial oxygen demand.
- *Increased afterload:* Resulting from increased peripheral vascular resistance leading to increased myocardial oxygen consumption and myocardial oxygen demand.
- *Increased preload:* Increases end-diastolic volume and pressure which increases diastolic ventricular wall stress. This increases end-diastolic fibre length and increased force of contraction (Frank-Starling law) and energy consumption.

Qc. Mention various formulations of nitroglycerin that are available.

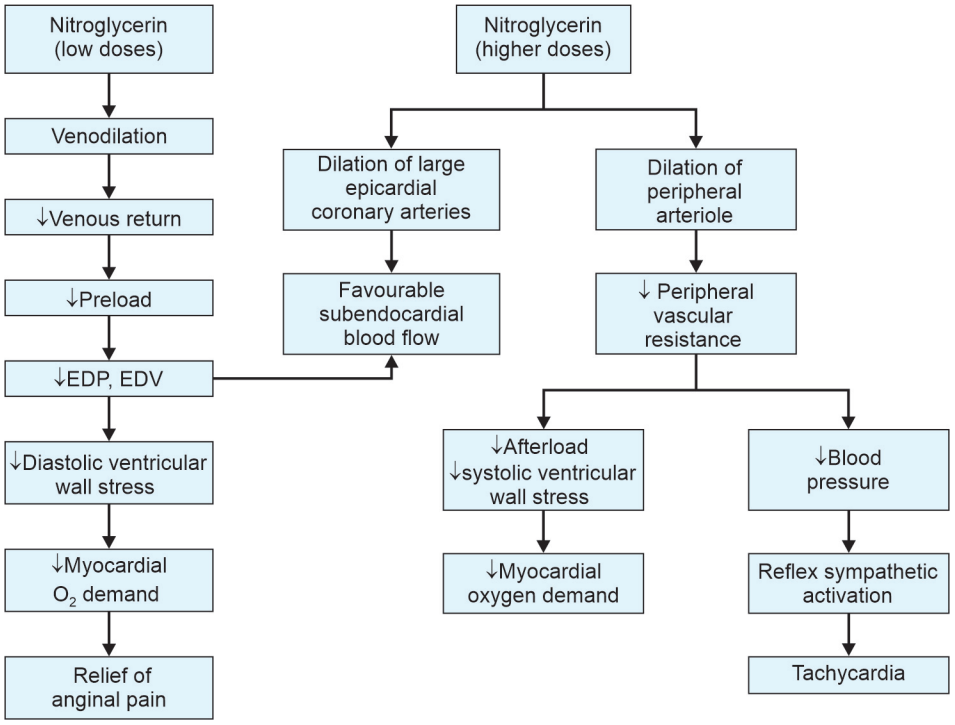
Sublingual nitroglycerin and nitroglycerin spray are referred to as shortacting preparations and used to treat acute anginal attacks.

Transdermal nitroglycerin, nitroglycerin ointment and capsules are long-acting nitrates and do not act rapidly enough to be used for acute anginal attacks. They are used to prevent episodes of angina in people who have coronary artery disease.

Qd. What are the benefits of sublingual nitroglycerin for the management of acute attack of angina?

Sublingual nitroglycerin has rapid onset of action in 1 to 2 minutes and relief of pain occurs in 5 minutes. The drug is rapidly absorbed through the oral mucus membrane, transported through the facial vein and internal jugular vein into the systemic circulation bypassing the first pass metabolism and producing immediate pain relief. Hence sublingual nitroglycerin is commonly used in the management of acute anginal pain.

Qe. How does nitroglycerin relieve anginal pain and prevent myocardial ischaemia?



EDV: End diastolic volume; EDP: End diastolic pressure

Fig. 4.3: Effects of nitroglycerin use in the management of ischaemic heart disease

Decrease in myocardial oxygen demand is the key mechanism through which nitroglycerin (NTG) relieves anginal pain rather than increase in myocardial oxygen supply. At low doses, nitrates preferentially dilate the veins, increasing the venous capacitance and causing venous pooling. This decreases preload, diastolic ventricular wall stress and myocardial oxygen demand. At higher doses, it decreases peripheral arteriolar resistance which reduces afterload and systolic ventricular stress.

Nitroglycerin improves subendocardial perfusion due to reduction in diastolic ventricular wall stress which helps to increase the blood flow through the subendocardial blood vessels during diastole and thus reduces subendocardial crunch.

Nitroglycerin selectively dilates large epicardial coronary arteries (> 200 µm) without altering the tone of small to medium arterioles (resistance vessels). This increases the blood flow in the coronary arteries distal to the narrowing and in the collateral blood vessels and further facilitates the blood flow to the ischaemic subendocardium through the autoregulatory mechanism.

Antiplatelet effect of nitroglycerin due to increased cGMP in the platelet, improves blood flow to the ischaemic regions due to inhibition of platelet aggregation.

Qf. During an acute attack of angina, if 3 to 5 tabs of nitroglycerin fails to provide pain relief and the patient takes high doses of nitroglycerin, will it produce beneficial action? Explain with reasons.

Nitroglycerin has a rapid onset of action and pain relief is achieved immediately. If 3 tabs of nitroglycerin 0.5 mg each over a 15 minute period do not relieve anginal pain it may be myocardial infarction or unstable angina or other causes of pain. The patient should be transported to the emergency department of the hospital for further evaluation of chest pain.

High doses of nitrates do not produce much beneficial action. At high doses, there is more venous pooling and pronounced decrease in systemic vascular resistance causing marked reduction in cardiac output and blood pressure. Severe hypotension can produce large decrease in coronary perfusion leading to aggravation of angina and producing symptoms of fatigue, weakness and dizziness.

Due to significant fall in blood pressure, there is increased activation of sympathetic reflexes increasing the adrenergic tone and tachycardia. This offsets the decrease in preload and afterload actions of nitroglycerin and overrides the beneficial actions of nitroglycerin and can aggravate ischaemia.

Qg. What is the danger associated with the use of nitrates in a patient with coexisting autonomic dysfunction?

At normal therapeutic doses of nitrates, fall in blood pressure is compensated by activation of sympathetic system which helps to normalise the blood pressure.

In patients with autonomic dysfunction there is inability to increase sympathetic outflow and hence fall in blood pressure cannot be compensated. This can lead to life-threatening hypotension and even aggravation of ischaemia.

Qh. How does nitroglycerin act to dilate the blood vessels?

Nitroglycerin is denitrated by mitochondrial aldehyde dehydrogenase (mALDH) in smooth muscle and other cells. This results in the release of nitrite ion, which is then converted to nitric oxide. Nitric oxide that is released stimulates guanylate cyclase in smooth muscle, producing an increase in cGMP which causes vasodilation.