

AS2523
MODEL ANSWER
B. PHARM. V SEMESTER EXAMINATION, 2013
PHARMACOLOGY –II

SECTION- A

- Q1. i) HDL transport cholesterol/lipids from extrahepatic tissues to liver for utilization. Thus prevent formation of atheroma and xanthoma.
- ii) A sensory perception of something that does not exist, arising from disorder of the nervous system, as in eg. LSD, tetrahydrocannabinol, phencyclidine.
- iii) Hematinics are the drugs that are used to treat anemia eg. iron, Vit B₁₂, folic acid, erythropoietin.
- iv) eg Hydralazine, minoxidil, sodium nitropruside, diazoxide.
- v) These are the drugs used for majority of epilepsies eg valproic acid,
- vi) Psychosis is an abnormal condition of the mind characterized by loss of contact with reality.
- vii) Examples of preanesthetic agents are: Atropine (antisecretory/anticholinergic agent), diazepam (antianxiety), morphine; pethidine (Opioid analgesic), ranitidine (H₂ blockers) etc
- viii) Captopril, enalapril, angiotensin receptor blocker (losartan), prazosin, amrinone, milrinone etc
- ix) There are three types of calcium channels, L, N and T. L is located on cardiac and smooth muscles, N is located on neurons and T is located on SA node & endocrine cells.
- x) White coat hypertension is a phenomenon in which patients exhibit rise in blood pressure in a clinical setting but not in other settings. This is due to the anxiety some people experience during a clinic visit. It does not require any drug treatment.
- xi) eg mephenesin, carisoprodol, chlorzoxazone, baclofen, diazepam, tizanidine etc
- xii) Disulfiram inhibit aldehyde dehydrogenase enzyme. When alcohol is ingested, due to disulfiram, the concentration of acetaldehyde increases in blood leading to flushing, perspiration, burning sensation, mental confusion, throbbing headache etc

SECTION- B

Q.2 a) Adrenaline constrict blood vessels, through its action on the adrenergic receptors found in the walls of blood vessels. There by slows down the absorption of local anaesthetics and thus slow its dispersal also. By this action it prolong the effect of lidocaine. When lidocaine and adrenaline are injected, they prevent pain signals passing from the area of injection to the brain and so numb the area. This means certain medical procedures or surgery, can be performed without causing pain. The numbness will gradually wear off after the procedure. Due to combination of these drugs the dose of lidocaine is reduced, thus toxicity is reduced and the local anaesthetic effect is prolonged.

Q2 b) Cardiac actions:

Effect on force of contraction:

Digitalis causes dose dependent increase in force of contraction of the heart (positive inotropic effect). Digitalis increases contraction of the cardiac sarcomere by increasing the free calcium concentration during systole. The increase in calcium concentration is the result of an increase of intracellular sodium concentration because of Na^+/K^+ *ATPase* inhibition; and due to reduction of calcium expulsion from the cell by the sodium-calcium exchanger caused by the increase in intracellular sodium. This effect is more pronounced in heart failure. The net result of the action at therapeutic concentrations of a digitalis is an increase in cardiac contractility. In isolated myocardial preparations, the rate of development of tension and of relaxation are both increased, with little or no change in time to peak tension. This effect occurs in both normal and failing myocardium, but in the intact animal or patient the responses are modified by cardiovascular reflexes and the pathophysiology of heart failure.

The more forceful contraction results in more complete ventricular emptying with a rise in stroke volume. It decreases the duration of systole that allows the greater time for both ventricular filling and heart rest.

Effect on heart rate:

In CHF the heart rate is decreased (negative chronotropic effect). At small doses the decrease in heart rate is due to vagal stimulation and at higher dose due to the direct action of digitalis on heart.

Effect on conduction velocity: Small doses increases the conduction velocity, larger doses decrease the conduction velocity.

Effect on Blood pressure:

In normal individuals digitalis increases the mean arterial pressure. In CHF patients systolic pressure may rise but diastolic pressure may fall.

Extracardiac actions: Digitalis produce diuretic effect, this effect is due to improved renal circulation of the blood. It affects all excitable tissues, including smooth muscle and the central nervous system. The gastrointestinal tract is the most common site of digitalis toxicity outside the heart. The effects include anorexia, nausea, vomiting, and diarrhea. Central nervous system effects include vagal and chemoreceptor trigger zone stimulation. Less often, disorientation and hallucinations especially in the elderly and visual disturbances are noted.

The most common cardiac manifestations of digitalis toxicity include atrioventricular junctional rhythm, premature ventricular depolarizations, bigeminal rhythm, and second-degree atrioventricular blockade.

Q3. Dysarrhythmia is an abnormal heart rate. The rhythm of the heart is disturbed.

Mechanisms of Arrhythmias

Many factors can precipitate or exacerbate arrhythmias: ischemia, hypoxia, acidosis or alkalosis, electrolyte abnormalities, excessive catecholamine exposure, autonomic influences, drug toxicity (eg, digitalis or antiarrhythmic drugs), overstretching of cardiac fibers, and the presence of diseased tissue.

The underlying cause may be

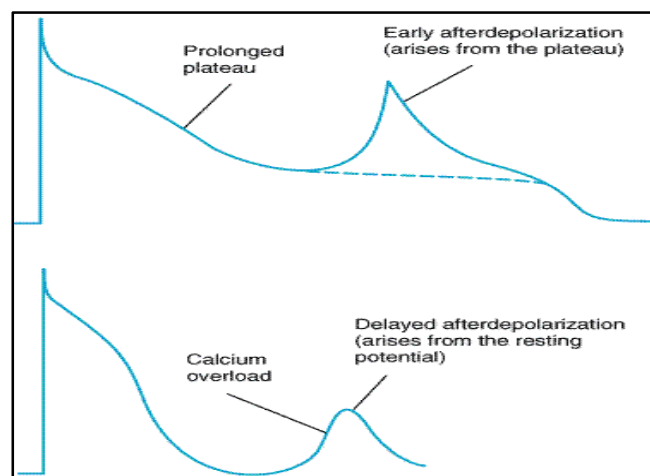
- 1) Disturbed impulse generation or
- 2) Disturbed impulse conduction or
- 3) Both disturbed impulse generation and conduction

Disturbances of Impulse generation:

Disturbance in impulse formation may be due to

- i) Depressed automaticity eg Sinus bradycardia
- ii) Increased automaticity eg Sinus tachycardia
- iii) Ectopic focus: In an abnormal cases impulse may originate from the part than SA node. This site is known as the ectopic focus/foci. Such sites are responsible for increase in heart rate.

Afterdepolarizations are depolarizations that interrupt phase 3 (early after depolarizations, EADs) or phase 4 (delayed afterdepolarizations, DADs). DADs, occur when intracellular calcium is increased. They are exacerbated by fast heart rates and are thought to be responsible for some arrhythmias related to digitalis excess, to catecholamines, and to myocardial ischemia. EADs are usually exacerbated at slow heart rates and are thought to contribute to the development of long QT related arrhythmias.

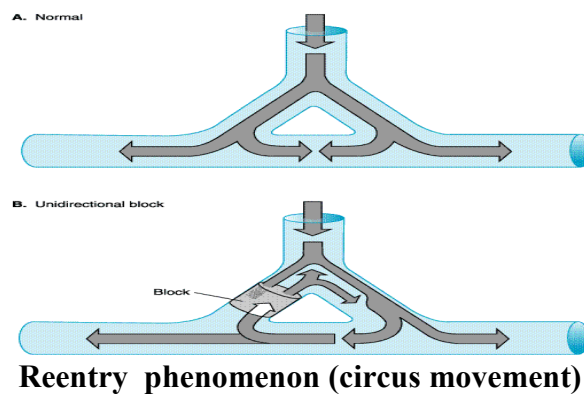


Afterdepolarisation

Disturbances of Impulse Conduction

Severely depressed conduction may result in simple block, eg, atrioventricular nodal block or bundle branch block. Because parasympathetic control of atrioventricular conduction is significant, partial

atrioventricular block is sometimes relieved by atropine. Another common abnormality of conduction is reentry (also known as circus movement), in which one impulse reenters and excites areas of the heart more than once. The path of the reentering impulse may be confined to very small areas, eg, within or near the atrioventricular node, or it may involve large portions of the atrial or ventricular walls. Some forms of reentry are strictly anatomically determined; for example, in the Wolff-Parkinson-White syndrome. In other cases e.g, atrial or ventricular fibrillation, multiple reentry circuits, determined by the properties of the cardiac tissue, may meander through the heart in apparently random paths. Furthermore, the circulating impulse often gives off "daughter impulses" that can spread to the rest of the heart. Depending on how many round trips through the pathway the impulse makes before dying out, the arrhythmia may be manifest as one or a few extra beats or as a sustained tachycardia.



Strategies for treatment:

Main aim in the treatment is to restore cardiac function. The normal pacemaking and conduction of impulses is disturbed. Normal pacemaking and conduction require normal action potential which is dependent on Na^+ , Ca^{++} and K^+ channel activity. Antiarrhythmic drugs act on one or more of these currents or on the second messenger system that modulate these currents.

Classification of antiarrhythmic drugs: Antiarrhythmic agents are classified as under:

- **Class I** : Membrane stabilizing agents (interfere with the Na^+ channel).
 - Class I a:** Prolong action potential duration eg Quinidine, procainamide, disopyramid.
 - Class I b:** Shorten Phase 3 of repolarisation and decrease duration of action potential.eg Lignocaine, phenytoin, tocainide
 - Class I c:** Moderately slow phase '0' of depolarisation eg flecainide, propafenone.
- **Class II:** These are beta blockers which suppresses the phase 4 and prolong phase 3 of repolarisation.eg propranolol, metoprolol.
- **Class III** : These agents are K^+ blockers which prolong phase 3 of repolarisation. Also prolong ERP. eg Amiodarone, bretylium tosylate
- **Class IV:** These agents are Ca^{++} blockers which decline Phase II of repolarization.eg verapamil, diltiazem, nifedipine.

Q. 4. I) Glyceryl trinitrate:

Organic nitrates have been used in the therapy of angina pectoris routinely for more than 140 years, and their use is increasingly favored in a variety of cardiac conditions. Glyceryl trinitrate is an organic nitrate, also called as nitroglycerin.

Mechanism of action: The mechanism of action of glyceryl trinitrate involves an interaction with nitrate receptors that are present in vascular smooth muscles. The nitrate receptor possesses sulfhydryl groups, which reduce nitrate to inorganic nitrite and nitric oxide (NO). The formation of free NO, stimulate intracellular soluble guanylate cyclase, which leads to an increase in intracellular cyclic guanosine monophosphate (GMP) formation. The increase in GMP results in vascular smooth muscle relaxation, possibly through inhibition of calcium entry via L-type calcium channels, decreased calcium release from the sarcoplasmic reticulum, or via an increase in calcium extrusion.

Absorption, Metabolism and Excretion

Glyceryl trinitrate is a lipid-soluble substance that is rapidly absorbed across the sublingual or buccal mucosa. Its onset of action occurs within 2 to 5 minutes, with maximal effects observed at 3 to 10 minutes. The plasma half-life of nitroglycerin, given sublingually or by spray, is estimated to be 1 to 3 minutes. Glyceryl trinitrate undergo extensive first pass hepatic metabolism and are rapidly metabolized by the enzyme glutathione organic nitrate reductase. It is readily excreted by the kidney.

Pharmacological Actions

It dilates both peripheral capacitance and resistant vessels, the effect on the venous capacitance system predominates. Dilation of the capacitance vessels leads to pooling of blood in the veins and to diminished venous return to the heart (decreased preload). This reduces ventricular diastolic volume and pressure and shifts blood from the central to the peripheral compartments of the cardiovascular system. These effects of glyceryl trinitrate relieve acute anginal attacks by decreasing circulating blood volume.

Q. 4. ii) Cough

Cough is a natural reflex expulsive defense mechanism of the body, for clearing excess secretions or mucous or inhaled irritants/toxins/foreign substance in the respiratory tract. Coughing protects the respiratory system by clearing respiratory tract. As long as cough is helpful in getting rid of infectious material with the help of mucous from the airway, it should not be stopped. The cough usually manifests in common cold, but it may be the initial manifestation of serious illness such as pulmonary hypertension, pneumonia, tuberculosis or asthma. In such cases, the cough has a pathological character and it is necessary to use cough-suppressing agents.

Cough is of two types productive (produce phlegm) and nonproductive (dry cough)

Drugs Used for Treatment of Cough

Productive coughs are treated with expectorants that loosen mucus from the respiratory tract. Nonproductive coughs are treated with antitussives (cough suppressants) that suppress the urge to cough. Following are the drugs used for treatment of various types of cough:

1) Pharyngeal demulcents: These soothe the throat and reduce afferent impulses from inflamed/irritated pharyngeal mucosa. Examples are lozenges, cough drops and linctu, glycerin and liquorice.

2) Expectorants: These are drugs which increase bronchial secretion or reduce its viscosity thus facilitating its removal by coughing.

(i) Mucokinetics: Increase bronchial secretion e.g. sodium potassium citrate, potassium iodide, squill and guaiphenesin etc.

(ii) Mucolytics: These reduce viscosity of phlegm. e.g. bromhexine and cysteine

3) Antitussives: These are drugs that act in the CNS to raise the threshold of cough center or act peripherally in the respiratory tract to reduce tussal reflexes (impulses) or both these actions. The aim is to control rather than eliminate cough. Antitussives should be used only for dry unproductive cough or if cough is unduly tiring, disturb sleep or is hazardous. e.g. noscapine, benzonatate, codeine and dextromethorphan. Codeine is more selective for cough centre and is used as the standard antitussive

4) Adjuvant antitussives: These include bronchodilators like salbutamol that dilates respiratory tract and helps in clearing the tract and proper breathing.

Q.5 i) Hematinics:

Hematinics are substances required in the formation of blood and are useful in the treatment of anemia.

Iron: Iron deficiency is the most common cause of chronic anemia. Iron forms the nucleus of the iron-porphyrin heme ring, which together with globin chains forms hemoglobin. Hemoglobin reversibly binds oxygen and provides the critical mechanism for oxygen delivery from the lungs to other tissues. In the absence of adequate iron, small erythrocytes with insufficient hemoglobin are formed, giving rise to microcytic hypochromic anemia. Iron is transported in the plasma bound to transferrin. Increased erythropoiesis is associated with an increase in the number of transferrin receptors on developing erythroid cells. Iron store depletion and iron deficiency anemia are associated with an increased concentration of serum transferrin.

Vitamin B₁₂: Vitamin B₁₂ serves as a cofactor for several essential biochemical reactions. Deficiency of vitamin B₁₂ leads to anemia, gastrointestinal symptoms and neurologic abnormalities. Although deficiency of vitamin B₁₂ due to an inadequate supply in the diet is unusual, deficiency of B₁₂ in adults especially older adults due to inadequate absorption of dietary vitamin B₁₂ is a relatively common and easily treated disorder.

Erythropoietin

Erythropoietin stimulates erythroid proliferation and differentiation by interacting with specific erythropoietin receptors. Erythropoietin also induces release of reticulocytes from the bone marrow. Endogenous erythropoietin is primarily produced in the kidney. In response to tissue hypoxia, more erythropoietin is produced through an increased rate of transcription of the erythropoietin gene. This results in correction of the anemia, provided that the bone marrow response is not impaired.

Q.5 ii) Antidepressants

These are the drugs which can elevate mood in depressive illness. Most antidepressants exert important actions on the metabolism of monoamine neurotransmitters and their receptors, particularly norepinephrine and serotonin. The primary clinical manifestations of major depression are significant depression of mood and impairment of function. Major depression is characterized by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, lack of pleasure, self-deprecation and agitation. These include insomnia or hypersomnia; altered eating patterns, with anorexia and weight loss or sometimes overeating; decreased energy and libido; and disruption of the normal circadian rhythms of activity, body temperature, and many endocrine functions.

Antidepressants and sedative-anxiety agents are commonly used to treat anxiety disorder.

Monoamine Oxidase (MAO) Inhibitors. MAO inhibitors inhibit the metabolism of dopamine, norepinephrine and serotonin in neuronal tissues. Early MAO inhibitors result in irreversible and nonselective blockade of both MAO-A and MAO-B. Now a days selective MAO-A and MAO-B are available. The nonselective MAO inhibitors elevate the mood of depressed patients but may cause hypomania and mania eg tranylcypromine. These have anticholinergic, sedative, cognitive, cardiovascular adverse effects and is not safe at higher doses.

Selective MAO-A inhibitors: These drugs selectively bind to MAO-A and produce good antidepressant activity. These lack anticholinergic, sedative, cognitive, cardiovascular adverse effects and safer in higher doses. Adverse effects are nausea, vomiting, dizziness, insomnia etc. eg Moclobemide

Tricyclic Antidepressants : These drugs inhibit noradrenaline and serotonin transporter at neuronal membrane. These drugs inhibit monoamine reuptake and interact with muscarinic, alpha adrenergic, histamine, 5HT, dopamine D₂ receptors. eg amitriptyline, doxepin, and imipramine. In depressed patients elevate the mood. The mood is gradually improved after 2-3 weeks. Patient start taking interest in self and surroundings.

Selective Serotonin Reuptake Inhibitors: To overcome the shortcomings of tricyclic antidepressants SSRIs are developed. These are safe and better acceptable and become first line antidepressants. These

drugs produce little or no sedation and lack alpha blocking action. eg fluoxetine and fluvoxamine were the first widely used selective serotonin reuptake inhibitors (SSRIs).

Atypical antidepressants: These drugs differ in mechanism of action as compared to conventional antidepressants. Those patients who do not tolerate TCAs are treated with these drugs eg trazodone, mianserin, mirtazapine etc.

Q. 6 a) Parkinson's disease :

It was discovered by James Parkinson in 1817, this movement disorder is known as Parkinson's disease or parkinsonism. It generally affects the elderly and is estimated to afflict more than 1% of individuals over the age of 65.

The onset of symptoms of Parkinson's disease is usually gradual. The most prominent features of parkinsonism are tremor, rigidity and bradykinesia/akinesia. The absence of facial expression (masklike face) results from loss of facial muscle function. Inability to swallow leads to drooling, while bradykinesia of the muscles in the larynx results in changes in voice quality. Orthostatic hypotension may also be observed and may complicate therapy. Cognitive dysfunction and dementia are also seen in a small percentage of Parkinson's disease patients, especially the elderly. The most prominent pathological findings in Parkinson's disease are degeneration of dopamine neurons in the substantia nigra, loss of dopamine in the neostriatum and the presence of intracellular inclusion bodies known as Lewy bodies.

Pharmacotherapy of Parkinsonism

Since there is no cure for parkinsonism, the aim of pharmacotherapy is to provide symptomatic relief.

Levodopa and Carbidopa

Levodopa (*L-DOPA*), the most reliable and effective drug used in the treatment of parkinsonism, can be considered a form of replacement therapy. Levodopa is the biochemical precursor of dopamine. It is used to elevate dopamine levels in the neostriatum of parkinsonian patients. Dopamine itself does not cross the blood-brain barrier and therefore has no CNS effects. However, levodopa, as an amino acid, is transported into the brain by amino acid transport systems, where it is converted to dopamine by the enzyme L-aromatic amino acid decarboxylase. If levodopa is administered alone, it is extensively metabolized by L-aromatic amino acid decarboxylase in the liver, kidney, and gastrointestinal tract. To prevent this peripheral metabolism, levodopa is coadministered with carbidopa, a peripheral decarboxylase inhibitor. The combination of levodopa with carbidopa lowers the necessary dose of levodopa and reduces peripheral side effects associated with its administration.

Dopamine Agonists

Bromocriptine, an ergot derivative, is an agonist at the D₂ receptors and a partial D₁ antagonist. Pergolide, also an ergot derivative, is an agonist at both D₁ receptor subtypes. Postural hypotension, nausea and fatigue are common adverse effects of bromocriptine and pergolide therapy and can limit the use of these drugs. Tolerance to the adverse effects develops over weeks or months therapy.

Selegiline

It is an irreversible inhibitor of MAO-B, blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors. Selegiline, as monotherapy, may be effective in the newly diagnosed patient with parkinsonism.

Anticholinergic Drugs

Central anticholinergic agents like trihexyphenidyl, biperiden, procyclidine are useful in most types of parkinsonism. The efficacy of anticholinergic drugs in parkinsonism is likely due to the ability to block muscarinic receptors in the striatum.

Amantadine

Amantadine is an antiviral drug, work by releasing dopamine.

Q. 6 b) Antipsychotic: Antipsychotics (neuroleptics or major tranquilizers) are used to manage psychosis (including delusions, hallucinations), particularly in schizophrenia and bipolar disorder. Schizophrenia is a particular kind of psychosis characterized mainly by a clear sensorium but a marked thinking disturbance. The pathogenesis of schizophrenia is unknown. At least one gene that encoding neuregulin 1 is associated with schizophrenia in northern European populations. Based on the efficacy of antipsychotic drugs, efforts continue to link the disorder with abnormalities of dopamine. The antipsychotic which are developed are mainly D₂ antagonists.

Classification:

A number of chemical structures have been associated with antipsychotic properties. The drugs can be classified as:

Phenothiazine derivatives:

Three subfamilies of phenothiazines, based primarily on the side chain of the molecule, were once the most widely used of the antipsychotics. Aliphatic derivatives (eg, chlorpromazine) and piperidine derivatives (eg, thioridazine) are the least potent. Piperazine derivatives (eg, Fluphenazine) are more potent (effective in lower doses) but not necessarily more efficacious. The piperazine derivatives are also more selective in their pharmacologic effects.

Thioxanthene derivatives:

In general, these compounds are slightly less potent than their phenothiazine analogs eg thiothixene.

Butyrophenone derivatives:

This group, of which haloperidol is the most widely used. The butyrophenones and congeners tend to be more potent and to have fewer autonomic effects but greater extrapyramidal effects.

Miscellaneous structures:

The newer drugs have a variety of structures and include pimozide, molindone, loxapine, clozapine, olanzapine, quetiapine, risperidone, ziprasidone and aripiprazole

Side effects: Most common side effects associated with antipsychotics are drowsiness, lethargy, mental confusion. It also produces postural hypotension, palpitation, inhibition of ejaculation, dryness of mouth. The most prominent side effects are extrapyramidal symptoms, similar to parkinsonism.

Q7. Opioids: The opioids represent all compounds with morphine-like activity and include morphine, morphine derivatives and peptides. These drugs are frequently referred to as narcotics.

Opioid Receptors: Opioid receptors have been classified as μ , κ , δ and σ . The σ receptor, once thought to be an opioid receptor, is a nonopioid receptor and is no longer considered an opioid receptor. The opioid receptors are members of the large superfamily of G protein-coupled receptors. Subtypes of the receptors have been proposed. It has been shown that μ receptors mediate the analgesic and euphoric effects of the opioids and physical dependence on them, whereas κ receptors mediate the bradycardiac and respiratory depressant effects. μ Receptors, of which at least two subtypes have been identified pharmacologically, mediate spinal analgesic effects and have been implicated in the modulation of tolerance to opioids. High levels of opioid binding have been found in the ascending pathways for nociceptive transmission, including the dorsal horn of the spinal cord and in particular the substantia gelatinosa lamina II. Other ascending tracts with high levels of binding include the spinothalamic tracts to the subcortical regions and limbic areas of the brain responsible for the discriminative and sensory aspects of pain and the euphoric effects of the drugs. Limbic areas, including cortical sites and the amygdala, are involved in the anxiolytic effects of the drugs. Binding in the hypothalamus is linked to the modulation of hormone release and to thermoregulation by the opioids and opioid peptides. Some descending pathways possess high levels of opioid receptors believed to be linked to the analgesic effects of the drugs.

Mechanisms of Action

Opioid receptors are members of the G protein superfamily of receptors. Drug-induced interaction with these receptors is associated with a decrease in activation of the enzyme adenylyl cyclase and a subsequent decrease in cyclic adenosine monophosphate (cAMP) levels in the cell. Binding of opioids to their receptors produces a decrease in calcium entry to cells by decreasing the phosphorylation of the voltage operating calcium channels and allows for increased time for the channels to remain closed. In addition, activation of opioid receptors leads to potassium efflux, and the resultant hyperpolarization limits the entry of calcium to the cell by increasing the negative charge of the membrane to levels at which these calcium channels fail to activate. The net result of the cellular decrease in calcium is a decrease in the release of dopamine, serotonin, and nociceptive peptides, such as substance P, resulting in blockage of nociceptive transmission.

Morphine

Morphine remains the standard by which other analgesic drugs are compared. The predominant effects of morphine are at the μ opioid receptor, although it interacts with other opioid receptors as well. Morphine is indicated for the treatment of moderate to severe and chronic pain. It is useful as preanaesthetic medication for sedation, anxiolytic effects and to reduce the dose of anesthetics. Morphine is the drug of choice for the treatment of myocardial infarction because of its bradycardiac and vasodilatory effects. In addition, morphine is the most commonly used drug for the treatment of dyspnea associated with pulmonary edema. It is thought that morphine reduces the anxiety associated with shortness of breath in these patients along with the cardiac preload and afterload. The morphine undergoes first-pass metabolism.

Patients can develop respiratory depression, nausea and itching because of histamine release.

Adverse Effects and Contraindications

The opioids generally have a high level of safety when used in therapeutic dosages. However, morphine and other opioids are contraindicated in patients with hypersensitivity reactions to the opioids. In addition, morphine should not be used in patients with acute bronchial asthma and should not be given as the drug of first choice in patients with pulmonary disease, because it has antitussive effects that prevent the patient from clearing any buildup of mucus in the lungs. Opioids with less antitussive effect such as meperidine, are better for such situations.