AR-7516

M. Pharm. II SEMESTER

EXAMINATION, 2013

GENERAL PHARMACOLOGY & TOXICOLOGY (Paper first)

MODEL ANSWER

Time: Three Hours] [Max. *Marks: 80*

SECTION- A

Q1. i) Amrinone and milrinone work by inhibiting the phosphodiesterase enzyme and increase the concentration of cAMP

ii) Examples of class IB antiarrhythmic drugs- lidocaine, phenytoin, mexiletine, tocainide

iii) HDL transport cholesterol from extrahepatic tissues to liver for utilisation and thus helps in prevention of atheroma and xanthoma

iv) Alcohol may provoke the sexual desire but actually it significantly suppresses the sexual responsiveness. Further in men it causes reduction in plasma testosterone level, impotence, sterility and gynecomastia taking away the performance.

v) β-blockers increases the duration of exercise tolerance. Also by opposing the injurious effects of endogenous catecholamines reduces the risk of angina during emotional outburst.

vi) Antiarrhythmic drugs can cause arrhythmias particularly in long term prophylactic use and may be due to intraventriular slowing action of these drugs markedly get accentuated resulting in ventricular tachycardia and fibrillation.

vii) Bile acid sequestrants are basic ion exchange resins they are neither digested nor absorbed in the gut and enhance hepatic metabolism of Cholesterol and therefore are oldest and one of the safest hypolipidemic drug.

viii) Sumatryptan bind with $5HT_{1D}$ receptor, lead to the inhibition of release of substance P and prevent vasodilation. Therapeutic use: Used in migrane, cluster headache.

ix) Cotrimoxazole is the combination of suphamethoxazole and trimethoprim in 5: 1 ratio.

x) Nonselective beta blockers: propranolol, carvedilol, sotalol, nodalol, timolol.

xi) Disulfiram inhibit aldehyde dehydrogenase and get accumulated in body and produce very uncomfortable feeling, as a result patient out of panic for discomfort does not take alcohol.

xii) In causal prophylaxis drugs kills the malarial paracites while they are in preerythrocytic phase eg primaquine.

SECTION- B

STUDENTS ARE EXPECTED TO COVER THE POINTS GIVEN IN MODEL ANSWER AND USE THEIR OWN WORDS FOR ANSWERING THE QUESTION

Q2. Sedatives & Hypnotics: A sedative is a substance that induces sedation by reducing irritability or excitement. Hypnotics induce sleep. The sedatives at higher dose work as a hypnotic.

Molecular targets in the CNS: Sedatives and hypnotics like the benzodiazepines, the barbiturates, zolpidem, and many other drugs bind to the $GABA_A$ receptor in the central nervous system. The receptor, which is coupled with a chloride ion channel, is activated by the GABA.

The $GABA_A$ receptor has a pentameric structure assembled from five subunits 2 alpha, 2 beta and one gamma (Figure :1)

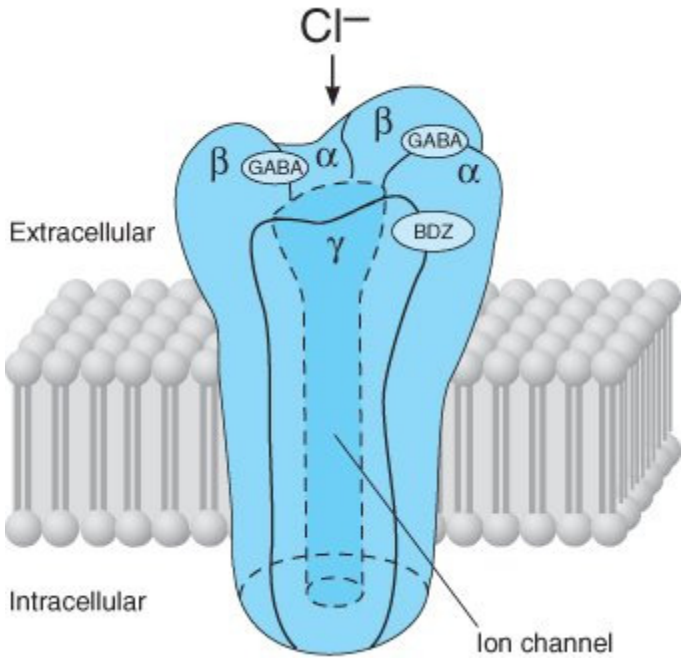


Figure: 1

The principal mechanism of action of barbiturates and BZD is through the modulation of $GABA_A$ receptor. Barbiturates bind to the $GABA_A$ receptor at the alpha or beta subunit. barbiturates potentiate the effect of GABA at this receptor. In addition to this GABA-ergic effect, barbiturates also block the AMPA receptor, a subtype of glutamate receptor. Glutamate is the principal excitatory neurotransmitter in the mammalian CNS. Taken together, the barbiturates potentiate inhibitory $GABA_A$ receptors and inhibit excitatory AMPA receptors and produce the CNS-depressant effects. At higher concentration, they inhibit the Ca^{2+}-dependent release of neurotransmitters. Barbiturates produce their pharmacological effects by increasing the duration of chloride ion channel opening at the $GABA_A$ receptor, whereas benzodiazepines increase the frequency of the chloride ion channel opening at the $GABA_A$ receptor by binding with beta subunit. Overall effect is hyperpolarisation which leads to sedative and hypnotic effect.

b) Effects of BZD's on EEG and Sleep stages:

Sleep disorders are common and often result from inadequate treatment of underlying medical conditions or psychiatric illness. Sleep is of two types REM and NREM. NREM sleep is divided in different stages:

While falling asleep person enters in different stages of sleep. Sleep stages are:

Stage 0: alpha waves are seen when eyes are closed and there is no mental activity.

Stage 1: alpha waves alongwith Θ waves

Stage 2: mainly Θ waves

Stage 3: shows Θ and ɗ waves

Stage 4: shows ɗ waves

Benzodiazepines hasten the onset of sleep and reduce intermittent awakening. Increase total sleep time. Time spent in stage 2 is increased while that in stage 3 and 4 is decreased. It also tend to shorten REM phase of sleep. Night terrors and body movements during sleep are also reduced. Most subject wake up with a feeling of refreshing. Benzodiazepines can cause a dose-dependent decrease in both REM and slow-wave sleep, though to a lesser extent than the barbiturates. The benzodiazepines depress REM sleep to a much smaller extent.

BZDS act preferably on midbrain ascending reticular formation and on limbic system. Muscle relaxation is produced by a primary medullary site of action.Only the alpha and beta subunits are

reuired for GABA action on GABA BZD receptor comples and most likely the binding site is located on beta subunit while alpaha/gamma subunit carries the BZD binding site.BZDs donot themselves increase chloride conduction. Have only GABA facilatatory action but no GABA mimetic action. BZDS are well tolerated and have wide margin of safety, therefore do not produce toxicity even at high doses. The specific antagonist of BZDS, flumazenil is available. If any accidental toxicity is seen the actions can be easily terminated by using flumazenil.

Zopiclone isa nonBZDS and effects are similar to that of BZDS but do not produce withdrawal symptoms. Used for short term treatment of insomnia.

Q3. i) General toxicity of neoplastic agents

Bone Marrow Toxicity

The alkylating agents alongwith most of the other anticancer drugs cause dose-limiting toxicity to bone marrow elements. Cyclophosphamide has lesser effects on peripheral blood platelet counts than do the other agents. Busulfan suppresses all blood elements, particularly stem cells, and may produce a prolonged and cumulative myelosuppression lasting months or even years.

Mucosal Toxicity :

Anticancer drugs are highly toxic to dividing mucosal cells, leading to oral mucosal ulceration and intestinal denudation. The mucosal effects are particularly significant in high-dose chemotherapy protocols associated with bone marrow reconstitution, as they predispose to bacterial sepsis arising from the gastrointestinal tract.

Neurotoxicity:

CNS toxicity is manifest in the form of nausea and vomiting, particularly after intravenous administration of nitrogen mustard. Ifosfamide is the most neurotoxic of this class of agents, producing altered mental status, coma, generalized seizures, and cerebellar ataxia.

Other Organ Toxicities:

All alkylating agents cause pulmonary fibrosis, usually several months after treatment. In high-dose regimens, vascular endothelial damage may precipitate veno-occlusive disease (VOD) of the liver. The nitrosoureas and ifosfamide, after multiple

cycles of therapy, may lead to renal failure. Cyclophosphamide and ifosfamide causes a severe hemorrhagic cystitis. Most of the drugs cause renal toxicity. Anticancer drugs also have toxic effects on the male and female reproductive systems, causing an often permanent amenorrhea, particularly in perimenopausal women, and an irreversible azoospermia in men.

ii)Urinary tract antiseptics

A urinary tract infection (UTI) is a condition where one or more parts of the urinary system (the kidneys, ureters, bladder, and urethra) become infected. UTIs are the most common of all bacterial infections and can occur at any time in the life of an individual. Almost 95% of cases of UTIs are caused by bacteria that typically multiply at the opening of the urethra and travel up to the bladder.

Types of UTIs: UTIs are generally classified as:

- Uncomplicated or complicated, depending on the factors that trigger the infections
- Primary or recurrent, depending on whether the infection is occurring for the first time or is a repeat event

Uncomplicated Urinary Tract Infections (UTIs)

Uncomplicated UTIs are due to a bacterial infection, most often *E. coli*. They affect women much more often than men.

Cystitis: Cystitis (bladder infection) is the most common urinary tract infection. It occurs in the lower urinary tract and nearly always in women. In most cases, the infection is brief and acute and only the surface of the bladder is infected. Deeper layers of the bladder may be harmed if the infection becomes persistent, or chronic, or if the urinary tract is structurally abnormal.

Complicated Urinary Tract Infections: Complicated infections, which occur in men and women of any age, are also caused by bacteria but they tend to be more severe, more difficult to treat, and recurrent. They are often the result of:

- Some anatomical or structural abnormality of the urinary tract.

- Catheter use in the hospital setting or chronic indwelling catheter in the outpatient setting,
- Bladder and kidney dysfunction, or kidney transplant.

Recurrences occur in up to 50 - 60% of patients with complicated UTI.

Recurrent Urinary Tract Infections

Most women who have had an uncomplicated UTI have occasional recurrences. About 25 - 50% of these women can expect another infection within a year of the previous one. Recurrence may be due to reinfection or relapse:

Drugs commonly recommended for simple UTIs include:

- Cotrimoxazole (Sulfamethoxazole-trimethoprim)
- Amoxicillin
- Nitrofurantoin
- Ampicillin
- Ciprofloxacin
- Levofloxacin and other fluoroquinolones

Usually, symptoms clear up within a few days of treatment. But you may need to continue antibiotics for a week or more.

iii) Preanaesthetic medication

A general anesthetic is rarely given as the sole agent. Rather, anesthetic adjuvants are usually are used to augment specific components of anesthesia, permitting lower doses of general anesthetics with fewer side effects.

Benzodiazepines

While benzodiazepines can produce anesthesia similar to that of barbiturates, they are more commonly used for sedation rather than general anesthesia because prolonged amnesia and sedation may result from anesthetizing doses. As adjuncts, benzodiazepines are used for anxiolysis, amnesia, and sedation prior to induction of anesthesia or for sedation during procedures not requiring general anesthesia.

αAdrenergic Agonists. Dexmedetomidine is an imidazole derivative that is highly selective for the α_2 adrenergic receptor. Activation of the α_{2A} adrenergic receptor by dexmedetomidine produces both sedation and analgesia, but does not reliably provide general anesthesia, even at maximal doses.

Dexmedetomidine has the very useful property of producing sedation and analgesia with minimal respiratory depression thus, it is particularly valuable in sedation of patients who are not endotracheally intubated and mechanically ventilated.

Analgesics

With the exception of ketamine, neither parenteral nor currently available inhalational anesthetics are effective analgesics. Thus, analgesics typically are administered with general anesthetics to reduce anesthetic requirement and minimize hemodynamic changes produced by painful stimuli. Nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, or acetaminophen sometimes provide adequate analgesia for minor surgical procedures. However, because of the rapid and profound analgesia produced, opioids are the primary analgesics used during the perioperative period. Fentanyl, sufentanil, alfentanil, remifentanil, meperidine and morphine are the major parenteral opioids used in the perioperative period.

Neuromuscular Blocking Agents:

Depolarizing (*e.g., succinylcholine*) and nondepolarizing muscle relaxants (*e.g., pancuronium*) often are administered during the induction of anesthesia to relax muscles of the jaw, neck, and airway and thereby facilitate laryngoscopy and endotracheal intubation. Following induction, continued muscle relaxation is desirable for many procedures to aid surgical exposure and to provide additional insurance of immobility.

Q.4 Hypertensions: Hypertension refers to high Blood pressure. Hypertension is amongst the major health disorder as it does not have any symptoms and in most cases it is not detected. Hypertension is a serious condition as it increases the risk of heart disease and other medical problems. If left untreated it may lead to atherosclerosis, Myocardial Infarction, stroke, Kidney damage.

Primary hypertension:

Primary Hypertension also known as Essential hypertension/ Idiopathic hypertension is most common and is found in more than 90 % of the hypertensive population. The exact underlying cause is not known.

Secondary hypertension:

Secondary hypertension has an identifiable definite causes and is is found in about 10 % of the hypertensive population. eg. Pheochromocytoma, aldosteroism.

WHO has classified the hypertension in following classes based on diastolic blood pressure

Borderline hypertension: BP is about 85-89 mm Hg

Mild hypertension: BP is about 90 -104mm Hg

Moderate hypertension: BP is about 105-114 mm Hg

Severe hypertension: BP is above 115 mm Hg and above

Hypertension treatment: In order to reduce the risk stroke, heart attack, and kidney failure the detection and treatment of hypertension at an early stage is necessary. Depending on the severity and seriousness of the disease, the treatment for hypertension in the initial stages is associated with lifestyle improvement and diet improvement. If the lifestyle changes are ineffective or the presenting blood pressure is critical, then drug therapy is initiated, often requiring more than one agent to effectively lower hypertension.

ANTI-HYPERTENSIVES: Following class of drugs are used for the treatment of Hypertension

1. **Diuretics:**

   Diuretics specially thiazide diuretics are used as the first line treatment for Hypertension. These prevent the binding and transport of chloride ions into the distal tubular epithelial cell, thereby inhibiting the cotransport of sodium. Thiazides are the most commonly used diuretics for treating hypertension, in part because their diuretic effect is accompanied by a reduction in peripheral resistance after prolonged administration that further reduces blood pressure. eg Hydrochlorthiazide, furosemide, spironolactone etc

2. **ACE Inhibitors:** ACE inhibitors act by inhibiting the Angiotensin Converting Enzyme. ACE converts Angitensin I (inactive) to its active form Angiotensin II, this active form of Angiotensin causes vasoconstriction. Thus by inhibiting the Angitensin Converting Enzyme, ACE Inhibitors result in vasodilation and thereby reducing the blood pressure. This leads to decreased work-load of the heart. ACE inhibitors also reduce blood pressure in the kidneys, slowing the progression of kidney disease due to high blood pressure or diabetes. eg: Captopril, Enalapril, Ramipril
3. **Angiotensin II receptor antagonist:** Angiotensin II is the active form of angiotensin I which by interaction with its receptors causes vasoconstriction. Angiotensin II receptor Antagonism leads to vasodilation and hence lowering of blood pressure and decreased work-load of the heart eg. Losartan, Valsartan
4. **Calcium Channel Blockers (CCBs):** Calcium is required by the heart and arteries muscle cells for causing Contraction. Calcium Channel Blockers inhibit the movement of calcium in the muscle cells of the heart and the arteries. Thus CCBS act by lowering blood pressure by decreasing the cardiac contraction and relaxing the muscle cells in the walls of the arteries eg. Verapamil, Diltiazem, Amlodipine, Nefidipine,
5. **Alpha Receptor blockers:** Alpha-blockers lower blood pressure by blocking alpha-receptors in the smooth muscle of peripheral arteries throughout the tissues of the body. The alpha-receptors are part of the sympathetic nervous system and serve to cause peripheral vasoconstriction and blocking these receptors lead to vasodilation and lower blood pressure. eg. Prazocin, terazocin, tamsulosin or alfuzosin are alpha-blockers that work well in combination with other anti-hypertensive medications.
6. **Beta adrenergic blockers:** Beta blockers are mild antihypertensive used only for mild to moderate cases of hypertension. Hypotension develop only after 1-3 weeks treatment.These are contraindicated in cardiac, pulmonary and peripheral vascular disorder eg Propranolol, metoprolol, atenolol.

7. **Beta adrenergic blockers:** These drug reduce total peripheral resistance faster than pure beta blockers and are used particularly to reduce BP in cheese reaction and clonidine withdrawal eg Labetalol, carvedilol.
8. **Centrally acting drugs:** Alpha2 agonists stimulates alpha2 receptor thereby decrease sympathetic outflow and reduce BP - produce bradycardia. Side effects with alpha 2 agonists are common and therefore used seldomly.
9. **Vasodilators:** Hydralazine, minoxidil are used in moderate to severe hypertension not controlled by the first line drugs. Usually low doses are added to the diuretics and beta blockers already being administered.

Q. 5 a) Angiotensin receptor blockers:

Angiotensin II can bind to two distinct receptors, termed the angiotensin type 1 (AT1) and the angiotensin type 2 (AT2) receptor. These receptors belong to a superfamily of G protein–coupled receptor. The AT1 and AT2 receptors have distinct signal transduction pathways, and are not necessarily found on the same cell type or tissue. Most of the physiological effects of angiotensin II are mediated through effects at the AT1 receptor.

Losartan is the first AT1 receptor antagonist developed and is a selective competitive antagonist to angiotensin II. Other AT1 receptor antagonists are valsartan, irbesartan, candesartan cilexetil, telmisartan and eprosartan. These antagonists share some pharmacological characteristics, including a high affinity for the AT1 receptor, little to no affinity for the AT2 receptor, high protein binding, and the ability to produce an almost insurmountable blockade of the AT1 receptor. The administration of an AT1 receptor antagonist results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload). All of the physiological effects of angiotensin II, including stimulation of the release of aldosterone, are antagonized in the presence of an AT1 receptor antagonist. Reductions in blood pressure occur independently of the status of the renin–angiotensin system, making these drugs effective antihypertensives even in patients with normal to low activity of the renin–angiotensin system. Following the chronic administration of an AT1 receptor antagonist, plasma renin activity increases as a result of removal of the angiotensin II negative feedback. Clinically AT1 receptor antagonists are effective as monotherapy in the treatment of hypertension.

b) Third generation cephalosporins:

Third-generation agents include cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetil, cefdinir, cefditoren pivoxil, ceftibuten, and moxalactam.

Antimicrobial Activity: Compared with second-generation agents, these drugs have expanded gram-negative coverage, and some are able to cross the blood-brain barrier. Third-generation drugs are active against citrobacter, *S marcescens,* and providencia. They are also effective against beta-lactamase-producing strains of haemophilus and neisseria. Ceftazidime and cefoperazone are the only two drugs with useful activity against *P aeruginosa.* Like the second-generation drugs, third-generation cephalosporins are hydrolyzable by constitutively produced AmpC beta lactamase, and they are not reliably active against enterobacter species. Ceftizoxime and moxalactam are active against *B fragilis.* Cefixime, cefdinir, ceftibuten, and cefpodoxime proxetil are oral agents possessing similar activity except that cefixime and ceftibuten are much less active against pneumococci and have poor activity against *S. aureus.*

Pharmacokinetics: Cephalosporins penetrate body fluids and tissues well and, with the exception of cefoperazone and all oral cephalosorins, achieve levels in the cerebrospinal fluid sufficient to inhibit most pathogens, including gram-negative rods, except pseudomonas.

Uses: Third-generation cephalosporins are used to treat a wide variety of serious infections caused by organisms that are resistant to most other drugs. Strains expressing extended-spectrum β-lactamases, however, are not susceptible. Third-generation cephalosporins should be avoided in treatment of enterobacter infections even if the clinical isolate appears

susceptible in vitro-because of emergence of resistance. Ceftriaxone and cefotaxime are approved for treatment of meningitis, including meningitis caused by pneumococci, meningococci, *H influenzae,* and susceptible enteric gram-negative rods, but not by *L monocytogenes.* Ceftriaxone and cefotaxime are the most active cephalosporins against penicillin-resistant strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by these strains.

c) Antileprotic drugs:

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae.* Host defenses are crucial in determining the patient's response to the disease, the clinical presentation, and the bacillary load. Current recommendations for the treatment of leprosy suggest multidrug regimens rather than monotherapy because such a regimen is more effective, delays the emergence of resistance, prevents relapse, and shortens the duration of therapy. Established agents used in the treatment of leprosy are dapsone, clofazimine, and rifampin.Treatment of tuberculoid leprosy is continued for at least 1 to 2 years, while patients with lepromatous leprosy are generally treated for 5 years. In addition to chemotherapy, patients with leprosy need psychosocial support, rehabilitation, and surgical repair of any disfiguration.

Dapsone and Sulfones

The sulfones are structural analogues of PABA and are competitive inhibitors of folic acid synthesis. Sulfones are bacteriostatic and are used only in the treatment of sulfone for the long-term therapy of leprosy. Although the sulfones are highly effective against most strains of *M. leprae,* a small number of organisms, especially those found in lepromatous leprosy patients, are less susceptible and can persist for many years, resulting in relapse Sulfones, such as dapsone and sulfoxone, are well absorbed orally and are widely distributed throughout body fluids and tissues. Dapsone, combined with other antileprosy agents like rifampin and clofazimine, is used in the treatment of both multibacillary and paucibacillary *M. leprae* infections

Acedapsone is a derivative of dapsone that has little activity against *M. leprae* but is converted to an active dapsone metabolite. It is a long-acting intramuscular repository form of dapsone with a half-life of 46 days. It may prove useful in leprosy patients who cannot

tolerate long-term oral dapsone therapy. The sulfones can produce nonhemolytic anemia, methemoglobinemia, and sometimes acute hemolytic anemia in persons with a glucose-6-phosphate dehydrogenase deficiency.

Q.6 Tuberculosis is a common infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected.

Tuberculosis remains the most important communicable disease in the world. The WHO estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis.* The ability of the tubercle bacillus to remain dormant but viable and capable of causing disease is a major therapeutic challenge. It remains alive even in highly adverse condition and when the conditions become favorable they grow and produce infection. The mycobacteria are slow growing intracellular organisms, therefore difficult to treat that require the administration of a combination of drugs for extended periods to achieve effective therapy and to prevent the emergence of resistance.

Drugs used in the treatment of tuberculosis can be divided into two major categories. "First-line" agents combine the greatest level of efficacy with an acceptable degree of toxicity; these include *isoniazid, rifampin, ethambutol, streptomycin*, and *pyrazinamide*. The large majority of patients with tuberculosis can be treated successfully with these drugs. Excellent results for patients with non-drug-resistant tuberculosis can be obtained with a 6-month course of treatment; for the first 2 months, isoniazid, rifampin, ethambutol, and pyrazinamide are given, followed by isoniazid and rifampin for the remaining 4 months. Administration of rifampin in combination with isoniazid for 9 months also is effective therapy for all forms of disease caused by strains of *Mycobacterium tuberculosis*

susceptible to both agents. Occasionally, because of microbial resistance, it may be necessary to resort to "second-line" drugs in addition; thus, treatment may be initiated with 5 to 6 drugs. This category of agents includes moxifloxacin or gatifloxacin, ethionamide, para aminosalicylic acid, cycloserine, amikacin, kanamycin, capreomycin, and linezolid. In HIV-infected patients receiving protease inhibitors and/or nonnucleoside reverse transcriptase inhibitors, drug interactions with the rifamycins (rifampin, *rifapentine, rifabutin*) are an important concern. Directly observed therapy, in which a health care worker actually witnesses the ingestion of medications, improves the outcome of tuberculosis treatment regimens. Isoniazid is ineffective in the treatment of leprosy or *M. avium* complex infection.

Isoniazid: Isoniazid is bacteriostatic for "resting" bacilli, but is bactericidal for rapidly dividing microorganisms. Isoniazid penetrates cells with ease and is just as effective against bacilli growing within cells as it is against those growing in culture media. A primary action of isoniazid is to inhibit the biosynthesis of mycolic acids. Mycolic acids are unique to mycobacteria, explaining the high degree of selectivity of the antimicrobial activity of isoniazid. which may increase the likelihood of damage to the mycobacteria from reactive oxygen species and H_2O_2. Exposure to isoniazid leads to a loss of acid-fastness and a decrease in the quantity of methanol-extractable lipids in the microorganisms.

Rifampin: The rifampin, rifabutin, rifapentine are a group of structurally similar, complex macrocyclic antibiotics produced by *Amycolatopsis mediterranei*. Rifampin inhibits DNA-dependent RNA polymerase of mycobacteria and other microorganisms by forming a stable drug-enzyme complex, leading to suppression of initiation of chain formation (but not chain elongation) in RNA synthesis. Rifampin is bactericidal for both intracellular and extracellular microorganisms. Rifampin for oral administration is available alone and as a fixed-dose combination with isoniazid. Rifampin and isoniazid are the most effective drugs available for the treatment of tuberculosis.

The dose of rifampin for treatment of tuberculosis in adults is 600 mg, given once daily, either 1 hour before or 2 hours after a meal. Rifampin, like isoniazid, should never be used alone for the treatment of tuberculosis because of the rapidity with which resistance may

develop. Despite the long list of untoward effects from rifampin, their incidence is low, and treatment seldom has to be interrupted.

Ethambutol: Ethambutol has been used with notable success in the therapy of tuberculosis of various forms when given concurrently with isoniazid. Because of a lower incidence of toxic effects and better acceptance by patients, ethambutol has essentially replaced aminosalicylic acid. Ethambutol is not recommended for children under 5 years of age.

Streptomycin: Streptomycin is bactericidal for the tubercle bacillus *in vitro.* Streptomycin does not readily enter living cells and thus cannot kill intracellular microbes. Since other effective agents have become available, the use of streptomycin for the treatment of pulmonary tuberculosis has been sharply reduced.

Pyrazinamide : Pyrazinamide exhibits bactericidal activity *in vitro* only at a slightly acidic pH. The target of pyrazinamide appears to be the mycobacterial fatty acid synthase I gene involved in mycolic acid biosynthesis Pyrazinamide has become an important component of short-term (6-month) multiple-drug therapy of tuberculosis. Pyrazinamide has been safe and effective when administered twice or thrice weekly.

Quinolones: The fluoroquinolones, are highly active against *M. tuberculosis* as well as nontuberculous mycobacteria and are important components of treatment regimens of multidrug-resistant tuberculosis. The C-8-methoxy-fluoroquinolones, such as gatifloxacin and moxifloxacin, are the most active and therefore least likely to result in the development of quinolone resistance. Unfortunately, when resistance develops to one fluoroquinolone in mycobacteria, cross-resistance develops within this entire class of antibiotics.

Ethionamide: It acts on both extra and intracellular organism. Resistance develops rapidly. It has a short duration of action. It is seldom used only in case of resistance to better tolerated drugs.

Para Aminosalicylic acid: Para amino salicylic acid (PAS) is bacteriostatic and one of the least active drugs. Resistance develops slowly. Patients' acceptability to it is poor and therefore rarely used.

Cycloserine: It inhibits cell wall synthesis and is bacteriostatic. Resistance develops slowly. It is rarely used in the cases not responding to the usual therapy.

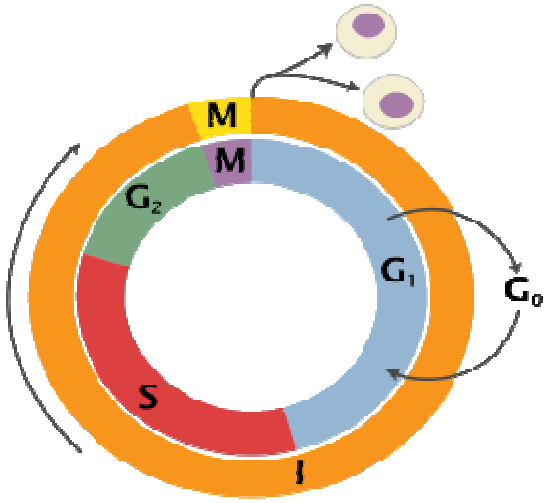
Amikacin, kanamycin and capreomycin: These are more toxic antibiotics used as reserve therapy in rare cases not responding to the usual therapy.

Q.7 Carcinoma: A carcinoma is tumor tissue derived from putative epithelial cells whose genome has become altered or damaged to such an extent that the cells become transformed, and begin to exhibit abnormal malignant properties.

Sarcoma: Malignant tumor originating in connective tissues. A sarcoma is a cancer that arises from transformed cells of mesenchymal origin. Thus, malignant tumors made of cancerous bone, cartilage, fat, muscle, vascular, or hematopoietic tissues are considered sarcomas.

Common malignancies, such as breast, colon, and lung cancer, are almost always carcinoma.

Cell cycle:



The cell cycle consists of four distinct phases: G_1 phase (Gap1), S phase (synthesis), G_2 phase (Gap2) and M phase (mitosis). M phase is mitosis, in which the cell's chromosomes are divided between the two sister cells. Cytoplasm divides in half forming distinct cells. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called G_0 phase. After cell division, each of the daughter cells begin the interphase of a new cycle.

G_0 phase : The term "post-mitotic" is sometimes used to refer to both quiescent and senescent cells. Nonproliferative cells in multicellular eukaryotes generally enter the quiescent G_0 state from G_1 and may remain quiescent for long periods of time.

Interphase: Before a cell can enter cell division, it needs to take in nutrients. All of the preparations are done during the interphase. Interphase proceeds in three stages, G_1, S, and G_2. Cell division operates in a cycle. Therefore, interphase is preceded by the previous cycle of mitosis and cytokinesis.

G_1 phase: The first phase within interphase, from the end of the previous M phase until the beginning of DNA synthesis is called G_1. It is also called the growth phase. During this phase the biosynthetic activities of the cell, which had been considerably slowed down during M phase, resume at a high rate.

S phase: The ensuring S phase starts when DNA replication commences; when it is complete, all of the chromosomes have been replicated.

G_2 phase: During the gap between DNA synthesis and mitosis, the cell will continue to grow. The G2 checkpoint control mechanism ensures that everything is ready to enter the M (mitosis) phase and divides.

Mitosis (M phase): The relatively brief *M phase* consists of nuclear division. Mitosis and cytokinesis together define the mitotic (M) phase of the cell cycle - the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell. This accounts for approximately 10% of the cell cycle. Mitosis occurs exclusively in eukaryotic cells, but occurs in different ways in different species. The process of mitosis is complex and highly regulated.

Information on cell and population kinetics of cancer cells explains the limited effectiveness of most available anticancer drugs. Based on the cell cycle anticancer drugs are classified into **cell cycle specific** and **cell cycle nonspecific** drugs.

Cell cycle specific drugs: These drugs kills only actively dividing cells. Their toxicity is expressed in S phase. Examples of drugs acting on different phases are:

G_1-: Vinblastine

S- Methotrexate, cytarabine, 6 mercaptopurine, 5 fluorouracil etc

G_2- Daunorubicin, bleomycin, etoposide.

M-Vincristine, vinblastine, pacilitaxel

Cell cycle nonspecific drugs: These kills resting as well as dividing cells eg. nitrogen mustard, cyclophosphamide, chorambucil, busulphan etc

The anticancer drugs belonging to different categorie are listed in the table below

Cell Cycle Specific Agents	Cell Cycle Nonspecific Agents
Antimetabolites	**Alkylating agents**
Cytarabine	Busulfan
Fludarabine	Carmustine
5-Fluorouracil	Cyclophosphamide
Gemcitabine	Lomustine
6-Mercaptopurine	Mechlorethamine
Methotrexate	Melphalan
6-Thioguanine	Thiotepa
Epipodophyllotoxins	**Anthracyclines**
Etoposide	Daunorubicin
Antitumor antibiotic	Doxorubicin
Bleomycin	**Antitumor antibiotics**
Taxanes	Dactinomycin
Paclitaxel	Mitomycin
Docetaxel	**Platinum analogs**
Vinca alkaloids	Carboplatin
Vinblastine	Cisplatin
Vincristine	

b) Methotrexate:

Methotrexate, is an inhibitor of dihydrofolate reductase, also directly inhibits the folate-dependent enzymes of *de novo* purine and thymidylate synthesis. Methotrexate also has been used with benefit in the therapy of psoriasis Additionally,

methotrexate inhibits cell-mediated immune reactions and is employed as an immunosuppressive agent to suppress graft-*versus*-host disease in allogenic bone marrow and organ transplantation and for the treatment of dermatomyositis, rheumatoid arthritis.

The primary target of methotrexate is the enzyme dihydrofolate reductase (DHFR). Inhibition of DHFR leads to partial depletion of the tetrahydrofolate cofactors required for the respective synthesis of thymidylate and purines. Because folic acid and many of its analogs are polar, they cross the blood-brain barrier poorly and require specific transport mechanisms to enter mammalian cells.

Absorption, Fate, and Excretion. Methotrexate is readily absorbed from the gastrointestinal tract but larger doses are absorbed incompletely and are routinely administered intravenously. After intravenous administration, the drug disappears from plasma in a triphasic fashion. The rapid distribution phase is followed by a second phase, which reflects renal clearance (half-life of about 2 to 3 hours). A third phase has a half-life of approximately 8 to 10 hours. This terminal phase of disappearance, may be prolonged in renal failure, may be responsible for major toxic effects of the drug on the marrow, GI epithelium, and skin. Distribution of methotrexate into body spaces, such as the pleural or peritoneal cavity, occurs slowly.

Approximately 50% of methotrexate is bound to plasma proteins and may be displaced from plasma albumin by a number of drugs, including sulfonamides, salicylates, *tetracycline*, *chloramphenicol*, and phenytoin. Up to 90% of a given dose is excreted unchanged in the urine within 48 hours, mostly within the first 8 to 12 hours. A small amount of methotrexate also is excreted in the stool. Metabolism of methotrexate in humans is usually minimal. Methotrexate is of limited value in the types of leukemia seen in adults, except for treatment and prevention of leukemic meningitis. The intrathecal administration of methotrexate has been employed for treatment or prophylaxis of meningeal leukemia or lymphoma and for treatment of meningeal carcinomatosis. Methotrexate is of established value in choriocarcinoma and related trophoblastic tumors of women.