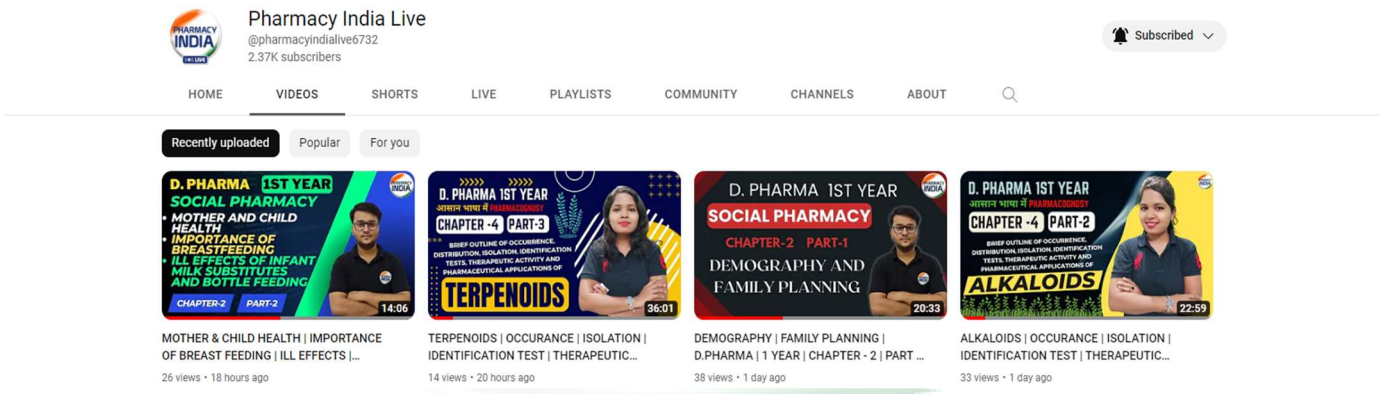
PHARMACOLOGY

MODEL PAPER – 3

Syllabus to be covered in this module are-

- ❖Chapter- 9 Drugs Acting on the Kidney
- ❖Chapter- 10 Hormones and Hormone Antagonists
- ❖Chapter- 11 Autacoids
- ❖Chapter- 12 Chemotherapeutics Agents



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Questions

Long Questions-

Ques.1 Discuss in detail about diuretics.

Ques.2 Explain in detail about sex hormones.

Ques.3 Write in detailed about anti-fungal agents.

Ques.4 Discuss anti-viral agents in detail.

Short Questions

Ques.1 What are anti-diuretics and give its mechanism of action?

Ques.2 Give the biosynthesis of thyroid hormones.

Ques.3 Write a short note on oral hypoglycaemic agents.

Ques.4 Write down about hormonal replacement therapy.

Ques.5 What are the adverse effects of corticosteroids.

Ques.6 Write a short note on oxytocin.

Ques.7 Give the pharmacological actions of prostaglandins.

Ques.8 Write a short note on serotonin.

Ques.9 Give the classification of anti-neoplastic agents.

Ques.10 Explain anthelmintic drugs.

Ques.11 Write a short note on DNA polymerase inhibitors.

Long Answers

Ques.1 Discuss in detail about diuretics.

Ans- DIURETICS

These are drugs which generally increase Na^+ excretion (natriuresis) in the kidney and the excreted Na is followed osmotically by water. They are used to decrease extracellular/plasma volume and so reduce oedema. They are important cardiovascular drugs used in the treatment of hypertension and chronic heart failure.

Classification

1. High efficacy diuretics (Inhibitors of Na^+ /K^+ /2Cl– cotransport): Furosemide, Bumetanide, Torasemide

2. Medium efficacy diuretics (Inhibitors of Na^+ /CI– symport)

(a) Benzothiadiazines (thiazides): Hydrochlorothiazide, Hydroflumethiazide, Clopamide

(b) Thiazide like (related heterocyclics): Chlorthalidone, Indapamide, Metolazone, Xipamide,

3. Weak or adjunctive diuretics

(a) Carbonic anhydrase inhibitors: Acetazolamide

(b) Potassium sparing diuretics:

(1) Aldosterone antagonist: Spironolactone

(ii) Inhibitors of renal epithelial Na channel: Triamterene, Amiloride.

(c) Osmotic diuretics: Mannitol, Isosorbide, Glycerol

1. Osmotic diuretics

e.g. mannitol

These are pharmacologically inert and freely filtered at Bowman's capsule. They increase osmolality of tubular fluid in proximal convoluted tubule and loop of Henle and so reduce passive reabsorption of H_2O. They are used in cerebral oedema as the increased osmolality removes fluid from the brain.

II. Loop diuretics

e.g. furosemide (frusemide), bumetanide

These are 'high-ceiling' diuretics which have a very powerful diuretic effect and can cause 15-25% of filtered Na to be excreted. They block Na^+ /2Cl– /K^+ symporter of the thick ascending limb of the loop of Henle. They reduce the ability of the loop of Henle to concentrate urine by preventing creation of a hypertonic interstitium in the medulla.

Adverse effects: Loop diuretics increase Na^+ delivery to distal convoluted tubule (DCT) which Promotes K^+ loss (leading to hypokalaemis). They decrease Na^+ entry into macula densa which promotes renin release and increases angiotensin II activity. Loss of transepithelial potential reduces sorption of divalent cations and causes the loss of Ca^{2+} and Mg^{2+} Postural hypotension (this may lead to falls) may arise due to volume depletion

Uses: Loop diuretics are used in chronic heart failure they reduce pulmonary oedema secondary to left ventricular failure and peripheral oedema. They are venodilators and have a rapid effect in acute left ventricular failure, also used in renal failure to improve diuresis.

III. Thiazides

e.g. bendroflumethiazide

Thiazides are moderately powerful diuretics which act on the DCT. They inhibit active Na reabsorption and accompanying CI This increases solute in tubular fluid and so decreases the gradient for water reabsorption.

Adverse effects: Hypokalaemia, Metabolic disturbances leading to impaired glucose control which may lead to diabetes, Postural hypotension due to volume depletion lead to falls.

Uses: First-line drugs in hypertension (for patients above 55 years), mild to moderate heart failure, Thiazides are renally excreted prior to acting on DCT and so are ineffective in moderate renal impairment.

HYPOKALAEMIA AND DIURETICS

Loop diuretics and thiazide cause K^+ loss which leads to hypokalaemia, causing more negative membrane potential (hyperpolarisation), predisposes to cardiac arrhythmias, potentiates the action of digoxin. Diuretics activate the renin-angiotensin-aldosterone system via. decreased Na^+ in extracellular fluid, loops block NaCl entry into macula densa, volume depletion.

Activation of the renin-angiotensin-aldosterone system stimulates the release of aldosterone Aldosterone induces the expression of Na^+ channels in the apical (luminal) membranes and Na pumps (aldosterone-induced proteins) in the basolateral membranes of DCT cells and the collecting duct. It is Na retaining at the expense of K^+.

IV. Potassium-sparing diuretics

These are weak diuretics that are used in combination with loop diuretics or thiazides to reduce the risk of hypokalaemia. They include:

Aldosterone (mineralocorticoid) receptor antagonists: e.g. spironolactone

Antagonise mineralocorticoid (MR) (or aldosterone) receptors. Prevent insertion of Na^+ and channels.

Sodium channel blockers: e.g., amiloride and triamterene

Block laminal Na^+ channels in DCT and collecting duct. Na^+ is no longer retained at expense of K^+.

Ques.2 Explain in detail about sex hormones.

Ans- Sex hormones produced by the gonads are necessary for conception, embryonic maturation and development of primary and secondary sexual characteristics at puberty, Sex hormones are used therapeutically in:

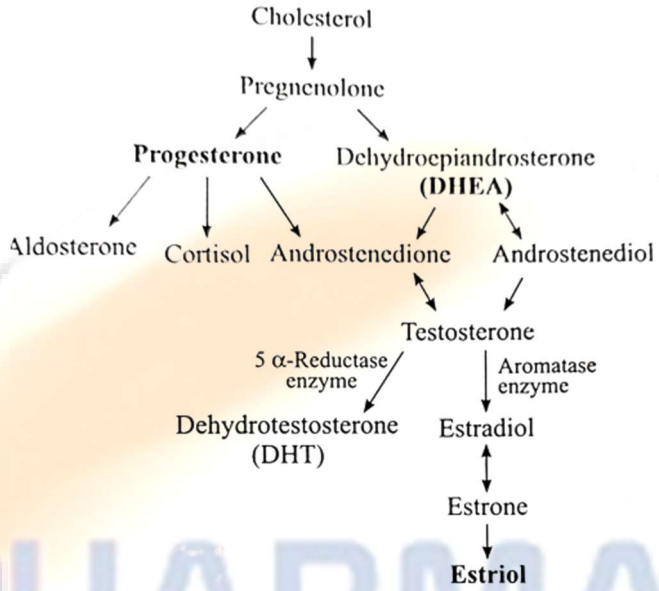
- Replacement therapy
- Contraception
- Management of menopausal symptoms
- Several gonadal hormones antagonists are effective in cancer chemotherapy

PHARMACOLOGY

Natural sex hormones are made by the gonads (ovaries or testes), adrenal gland or by conversion from one sex hormones in other Hormonal control of the reproductive systems in men and women involves

Sex steroids from the gonads, hypothalamic peptides (GnRH) and glycoprotein gonadotrophins from the anterior pituitary (FSH and LH)

Biosynthesis



ANDROGENS

Pharmacological Actions

1. Sex organs and secondary sex characters (Androgenic): Testosterone is responsible for all the changes that occur in a boy at puberty: Growth of genitals-penis, scrotum, seminal vesicles, prostate. Growth of hair-pubic, axillary, beard, moustache, body hair and male pattern of its distribution. Thickening of skin which becomes greasy due to proliferation and increased activity of sebaceous glands. Larynx grows and voice deepens, increases libido and aggressiveness.

2. Testes: Moderately large doses cause testicular atrophy by inhibiting Gin secretion from pituitary.

3. Skeleton and skeletal muscles (Anabolic): There is rapid bone growth, both in thickness as well as in length. After puberty, the epiphyses fuse and linear growth comes to a halt. Testosterone also promotes muscle building, especially if aided by exercise (↑protein synthesis and ↓se protein breakdown).

4. Erythropoiesis: Testosterone also accelerates erythropoiesis by increasing erythropoietin production and probably direct action on haem synthesis.

Testosterone is inactive orally due to high first pass metabolism in liver. Testosterone in circulation is 98% bound to sex hormone binding globulin (SHBG) and to albumin.

Side Effects

1. Virilization, excess body hair and menstrual irregularities in women; many effects, e.g. voice change may be permanent after prolonged therapy.

2. Acne: in males and females.

3. Frequent, sustained and often painful erections in males

4. Oligozoospermia, Precocious puberty and shortening of stature due to early closure of epiphysis.

5. Edema, Cholestatic jaundice, Hepatic carcinoma, Gynecomastia

6. Lowering of HDL and rise in LDL levels

7. Anabolic steroid abuse in sports.

Uses

1. Testicular failure

2. Hypopituitarism (HRT)

3. AIDS related muscle wasting

4. Hereditary angioneurotic edema

5. Ageing

6. Anabolic steroidal agents

7. Anaemia, osteoporosis and growth stimulator

ANABOLIC STEROIDS

These are synthetic androgens with supposedly higher anabolic and lower androgenic activity. Drugs are Nandrolone, Oxymetholone, Stanozolol and Methandienone. The anabolic androgenic ratio of testosterone is considered as 1. The anabolic selectivity of these steroids is modest with ratios between 1 to 3.

Side effects: Anabolic steroids were developed with the idea of avoiding the virilizing side effects of androgens while retaining the anabolic effects. But the same side effect profile applies to these compounds. The 17-alkyl substituted compounds oxymetholone, stanozolol, can produce jaundice and worsen lipid profile.

Uses

1. Catabolic states: Acute illness, severe trauma, major surgery, etc. are associated with negative N balance. Anabolic steroids can reduce N loss over short periods, but long-term benefits are questionable.

2. Renal insufficiency: Anabolic steroids reduce urea production-frequency of dialysis needed in renal failure can decrease.

3. Osteoporosis

4. Sub-optimal growth in boys

5. Hypoplastic, hemolytic and malignancy associated anaemia.

6. To enhance physical ability in athletes

HORMONAL REPLACEMENT THERAPY

Due to cessation of ovarian function at menopause, women suffer a number of physical, psychological and emotional consequences. The benefits and risks of HRT are considered below:

1 Post-menopausal HRT

a. Menopausal symptoms and atrophic changes: They are the primary indication for using HRT which improves general physical, mental and sexual well-being as well.

b. Osteoporosis and fractures: HRT restores Ca^{2+} balance: further bone loss is prevented and the excess fracture risk is nullified.

c. Cardiovascular events estrogens improve HDL: LDL ratio, retard atherogenesis, reduce arterial impedance, increase NO and PGI_2 production and prevent hyperinsulinemia, in postmenopausal women will have a protective cardiovascular influence.

d. Cognitive function and dementia

e. Cancer: That estrogens enhance the growth of breast cancer has been well recognized.

f. Gallstone, migraine: Estrogens slightly increase the risk of developing gallstones, while progestins may trigger migraine.

2. Senile vaginitis

3. Delayed puberty in girls

4. Dysmenorrhoea

5. Acne

6. Dysfunctional uterine bleeding

7. Carcinoma prostate

ESTROGENS

Classification

Natural estrogens: Estradiol

Synthetic estrogens: Natural estrogens are inactive orally and have a short duration of action due to rapid metabolism in liver. To overcome this, synthetic compounds have been produced:

- Steroidal: Ethinylestradiol, Mestranol, Tibolone.
- Non-steroidal Diethylstilbesterol (stilbestrol), Hexestrol, Dienestrol

Pharmacological Actions

1. Sex organs: The estrogens bring about pubertal changes in the female including growth of uterus, fallopian tubes and vagina. Vaginal epithelium gets thickened, stratified and cornified.

2. Secondary sex characters: Estrogens produced at puberty cause growth of breasts-proliferation of ducts and stroma, accumulation of fat. The pubic and axillary hair appear, feminine body contours and behaviour are influenced.

3. Metabolic effects: Estrogens are anabolic, like but weaker than testosterone. Estrogen is important in maintaining bone mass primarily by retarding bone resorption.

Mechanism of Action

Estrogens bind to specific nuclear receptors in target cells and produce effects by regulating protein synthesis. Two ERs designated ER alpha and ER beta have been identified, cloned and structurally characterized.

Adverse Effects

1. Suppression of libido, gynaecomastia and feminization when given to males.

2. Fusion of epiphyses and reduction of adult stature when given to children.

3 Stilbestrol given to pregnant women, especially during first trimester (as test of pregnancy or otherwise) increased the incidence of vaginal and cervical carcinoma in the female offspring in childhood or early adulthood.

4. In postmenopausal women, estrogens can increase the risk of irregular bleeding and endometrial carcinoma (5-15-fold).

5. Estrogens can accelerate the growth of existing breast cancer, but low-dose estrogen only HRT does not appear to increase the risk of developing new breast cancer.

6. Long-term estrogen therapy doubles the incidence of gallstones. Benign hepatomas are more common in women taking estrogens in their teens and twenties.

7. Migraine, epilepsy and endometriosis may be worsened by estrogens.

Uses: Currently, the two most common uses of estrogens are as contraceptives and for hormone replacement therapy in postmenopausal women, but there are some other indications as well.

Ques.3 Write in detailed about anti-fungal agents.

Ans- ANTI-FUNGAL AGENTS

Classification Based on Mechanism of Action

1. Fungal cell wall synthesis inhibition: Caspofungin

2. Bind to fungal

cell membrane ergosterol: Amphoterein-B, Nystatin

3. Inhibition of ergosterol+lanosterol synthesis: Terbinafine, Naftifine, Butenafine

4. Inhibition of ergosterol synthesis: Azoles (Ketoconazole, clotrimazole, miconazole, Fluconazole, itraconazole, voriconazole)

5. Inhibition of nucleic acid synthesis: 5-Flucytosine

6. Disruption of mitotic spindle and inhibition of fungal mitosis: Griseofulvin

7. Miscellaneous: Ciclopirox, Tolnaftate, Topical azoles

I. ANTI-FUNGAL DRUGS FOR SYSTEMIC FUNGAL INFECTIONS

Caspofungin

It is water soluble, lipopeptide derived from fermentation of Glarea lozayensis.

Mechanism of Action: Inhibit the enzyme β-1, 3-glucan synthase (unique component of the fungal cell wall) →→ disturbing the integrity of the fungal cell wall→→ Weakening of the cell wall→ leads to osmotic susceptibility- →death of fungal cell.

Pharmacokinetics: Not absorbed orally: given intravenously well distributed in tissues, not in CSF Metabolized by the liver (hydrolysis and N-acetylation) and excreted in urine as well as faeces.

Uses: Approved for deep and invasive candidiasis, esophageal candidiasis, and salvage therapy of non-responsive invasive aspergillosis

Adverse Drug Reactions: acute febrile reaction, vomiting, dyspnea, hypokalemia and joint pain may occur.

AMPHOTERICIN-B

Amphotericin-B is an amphiphilic polyene antibiotic.

Mechanism of action: Bind to ergosterol in membrane of fungal cells & alters permeability by formation of "pores" in the membrane. Leaking of small molecules (mainly K^+, Na^+, Mg^{2+}, H^+) from the cells pores leads to fungicidal or fungistatic activity depending on the organism and drug concentration.

Pharmacokinetics: AMB is not absorbed orally, given orally for intestinal candidiasis / adm. as iv infusion. Widely distributed, but penetration in CSF is poor. Binds to sterols in tissues and to lipoproteins in plasma and stays in the body for long periods (15 days). About 60% of AMB is metabolized in the liver. Excretion occurs slowly both in urine and bile.

Interactions: Flucytosine has supra-additive action with AMB (AMB increases the penetration of 5-FC into the fungus), Rifampin and minocycline, potentiate AMB action. Anti-fungal spectrum: AMB is active against a wide range of yeasts and fungi.

Uses: topically for oral, vaginal and cutaneous candidiasis and otomycosis; or various types of systemic mycoses.

Adverse effects:

- Acute reaction chills, fever, aches and pain all-over, nausea, vomiting and dyspnoea lasting for 2-5 hours, probably due to release of cytokines (IL, TNFα). Thrombophlebitis of the injected vein
- Long-term toxicity: Nephrotoxicity (dose-related: manifestations are azotaemia, reduced g.fr. acidosis, hypokalaemia, and inability to concentrate urine).
- Anaemia: bone marrow depression; reversible.
- CNS toxicity occurs only on intrathecal injection-headache, vomiting, nerve palsies, etc.

AZOLE GROUP OF ANTIFUNGAL DRUGS: KETOCONAZOLE

Pharmacokinetics: Variable oral absorption, dependent on pH (low); $t_{1/2}$: 7-10 hours; Protein binding>99%; Hepatic, bile, and kidney elimination.

Mechanism of action: They bind to14-α demethylase enzyme responsible for demethylation of lanosterol to ergosterol (Acetyl CoA → Squalene → Lanosterol → Ergosterol), results in leaky fungal cell membrane. Also inhibit fungal respiration under aerobic conditions (respiratory chain electron transport blockade).

Adverse effects:

- Nausea and vomiting (drug with meals)
- loss of appetite, headache, paraesthesia, rashes and hair loss.
- ↓ androgen & oestradiol production (Gynaecomastia & Menstrual irregularities)

Drug Interaction:

- ↑ plasma levels of oral anticoagulants, oral hypoglycemic, phenytoin, cyclosporine.
- Enhanced arrhythmogenic effect of antihistamine, astemizole and terfenadine.
- Cimetidine increases gastric pH thereby interfere with absorption of ketoconazole (↓ plasma level).
- Rifampin increases hepatic metabolism of the azole (↓ plasma level).

TERBINAFINE

A highly lipophilic, keratophilic drug. Effective orally against dermatophytes and candida Useful in fungal infections of nails (6-12 weeks).

Adverse effects: Gastric upset, rashes and taste disturbances; Rarely hepatotoxicity Mechanism of action: They inhibit squalene-2, 3 epoxidase enzymes responsible for conversion of squalene to lanosterol (Acetyl CoA → Squalene → Lanosterol→ Ergosterol), results in decreased ergosterol production which affects fungal cell membrane integrity and function.

GRISEOFULVIN

Very insoluble, oral absorption (better with small particle size: Absorption promoted by fatty mealy, deposited in newly forming skin where it binds to keratin precursor cells, protecting the skin from new infection. Biliary excretion and a potent enzyme inducer.

Mechanism of Action: Disrupts mitotic spindle during metaphase by interacting with fungal microtubules → decreases fungal mitosis (metaphase arrest), sufficient to inhibit growth of fungi (static), preventing them from invading.

Adverse actions: GI disturbances, Allergic reactions, Photosensitivity, Angioedema, Peripheral neuritis, Being an antimitotic bone marrow suppression, leukopenia, neutropenia.

FLUCYTOSINE (5-FC)

Water soluble pyrimidine analogue related to chemotherapeutic agent fluorouracil.

Pharmacokinetics: Given orally, well absorbed. Poor protein binding; wide distribution including CNS. Eliminated by glomerular filtration. Half-life 3-4 h and TDM is important in renal insufficiency (50-100 mg/ml).

Adverse effects:

- Toxic effects due to fluorouracil formation (by gut flora); Toxic enterocolitis
- Bone marrow depression, anaemia, leukopenia, thrombocytopenia
- Liver enzymes abnormalities & Narrow therapeutic window.

Ques.4 Discuss anti-viral agents in detail.

Ans- ANTI-VIRAL AGENTS

Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cells. Antiviral agents must either block viral entry into or exit from the cell or he active inside the host cell. Anti-viral agents are most active, when viruses are replicating. The earlier the treatment is given, the better the result.

CLASSIFICATION OF VIRUSES

A DNA Viruses

1. Adenoviruses (Upper respiratory tract and eye infection)

2. Hepadnaviruses (Hepatitis-B)

3. Herpes Virus:

(a) Herpes Simplex Virus Type-1 (Oral and Ocular Herpes and Herpes keratitis)

(b) Herpes Simplex Virus Type-2 (Genital Herpes)

(c) Varicella Zoster Virus (Chicken Pox)

(d) Cytomegalo Virus (CMV: Infectious mononucleosis)

(e) Epstein-Barr Virus (EBV; B-cell Lymphoma)

4. Papilloma Virus (Warts)

5. Poxviruses (Small Pox)

6. Parvoviruses (aplastic anaemia)

B. RNA Viruses

1. Picornaviruses (Polio virus causing Polio and Hepatoviral causing Hepatitis-A)

2. Orthomyxoviruses (Influenza virus A, B, C-H_1, B_1, virus causes Swine Flu)

3. Paramyxoviruses:

(a) Rubella virus (Mumps)

(b) Morbillivirus (Measles)

(c) Respiratory Syncytial virus (lower respiratory tract infection)

4. Rhabdoviruses (Rabies)

5. Arboviruses (arthropod-borne viruses):

(a) Toga virus (Chikungunya and Encephalitis)

(b) Flavivirus (Dengue and Yellow Fever)

(c) Bunyavirus (Encephalitis)

6. Rotavirus (Gastroenteritis in children)

7. Retrovirus:

(a) Human Immunodeficiency virus (AIDS)

(b) Human T-cell leukaemia virus (T-cell leukaemia)

8. Arenavirus (viral meningitis)

9. Coronavirus (Upper Respiratory tract infection)

Classification of Anti-Viral Agents

PHARMACOLOGY

1. Anti-Herpes virus:

Purine analogues: Acyclovir, Valacyclovir, Famciclovir, Ganciclovir,

Pyrimidine analogues: Idoxuridine, Trifluridine

Non-nucleosides: Foscarnet

2. m-RNA Synthesis inhibitor: Ribavirin, Fomivirsen

3. Anti-Influenza virus (Inhibition of viral Penetration and Uncoating): Amantadine, Rimantadine

4. Neuraminidase inhibitors: Zanamivir, Oseltamivir, Peramivir

5. Immunomodulators: Interferon α, Palivizumab, Imiquimod

DNA POLYMERASE INHIBITORS

Pharmacokinetics: The bioavailability of oral acyclovir is 15-20% and is unaffected by food. Acyclovir is cleared primarily by glomerular filtration and tubular secretion. Acyclovir diffuses into most tissues and body fluids Mechanism of Action:

Resistance: Resistance to acyclovir through alteration in either the viral thymidine kinase or the DNA polymerase. Agents such as Foscarnet, cidofovir, and trifluridine do not require activation by viral thymidine kinase and thus have preserved activity.

Adverse effects: Acyclovir is generally well tolerated with Nausea, diarrhoea, and headache. i.v. infusion may be associated with reversible renal dysfunction due to crystalline nephropathy or neurologic toxicity (e.g., tremors, delirium, seizures).

Anti-viral Spectrum and Clinical Use

Acyclovir: is highly effective against HSV-1 which causes **Herpes labialis** (Cold Sores), Hepes esophagitis, Herpes keratitis, Herpes encephalitis and ocular Herpes.

Ganciclovir: Parenteral Ganciclovir is used for the treatment of serious and vision threatening retinitis due to cytomegalovirus in immune-compromised cases (AIDS).

Adefovir: Used in Chronic Hepatitis-B viral infections (HBV) and effective in Lamivudine resistant strains of HBV.

Entacavir: Used for treating Chronic Hepatitis-B in adults with or without AIDS.

Telbivudine: Used to treat Chronic Hepatitis-B.

m-RNA Synthesis Inhibitors (Ribavirin)

Broad-spectrum antiviral activity (DNA and RNA viruses).

Mechanism of action: Its mono- and triphosphate derivatives generated intracellularly inhibit GTP & viral RNA polymerase→→ inhibit viral m-RNA and DNA synthesis.

Pharmacokinetics: Oral bioavailability ~50%; increased with fatty meal. Partly metabolized and eliminated. Accumulates on daily dosing and persists months after discontinuation

Adverse effects: Anaemia, bone marrow depression, haemolysis; Teratogenic, Aerosol can cause bronchospasm and irritation of mucosae.

Uses: Reduce mortality in Lassa fever (arenavirus infection), effective against Influenza-A and Influenza-B viruses, Ribavarin +s.c. Interferon alpha-2b in treatment of Chronic Hepatitis-C virus infections.

Inhibitors of Viral Penetration & uncoating (amantadine)

Inhibits uncoating of viral RNA within infected host cells and replication of Influenza-A

Mechanism of action: Inhibition of M^2 protein→→ prevention of H^+ mediated dissociation of ribonucleoprotein core segment (a prerequisite for viral replication).

Pharmacokinetics: Well absorbed orally, excreted unchanged in urine over 2-3 days, Half-life is 16 hours

Side effects: Nausea, Anorexia, insomnia, dizziness, nightmares, lack of mental conc., hallucinations, postural hypotension, ankle oedema. Contraindicated in Epilepsy & other CNS disorders, gastric ulcer, pregnancy.

Uses: Prevention and treatment of Influenza virus-A infections and in the therapy of Parkinson's disease.

Neuraminidase Inhibitors (Zanamivir & Oseltamivir)

Mechanism of action: Interfere with the release of progeny influenza virus from infected-new host cells (Neuraminidase enzyme required for release)

Side effects: Nausea and abdominal pain (gastric irritation), Bronchospasm, reversible decrease in pulmonary function & transient nasal & throat discomfort (zanamivir), Aggravation of diabetes (Oseltamivir).

Uses: Acute uncomplicated influenza-A virus (H_1, N_1, swine Flu virus) or Influenza-B virus.

Immunomodulators

Interferons: Three types of human IFNs (α, β and γ) are known to have anti-viral activity.

Mechanism of action: Interferon receptors (JAK-STAT tyrosine protein kinase receptors) activation phosphorylates cellular proteins. These further migrate to nucleus & induce transcription of "interferon-induced-proteins to show anti-viral effects (inhibit viral RNA translation degradation of viral mRNA and tRNA).

Pharmacokinetics: Not active orally; administered s.c. or i.v., high cellular uptake and metabolism by the liver and kidney: less plasma level, negligible renal elimination occurs.

Adverse effects: Flu-like symptoms, anorexia, nausea, taste, and visual disturbances develop few hours after each injection; Neurotoxicity: numbness, neuropathy, altered behaviour, mental depression, tremor, sleepiness, rarely convulsions; Myelosuppression: dose dependent neutropenia, Thrombocytopenia; Thyroid dysfunction (hypo as well as hyper); Hypotension, transient arrhythmias, alopecia and liver dysfunction.

Drug interaction: Toxic accumulations of theophylline, Potentiate the myelosuppression caused by other bone marrow depressing agents.

Clinical Uses: IFN alpha-2a: Chronic Hepatitis-B, Chronic Hepatitis-C and Hairy cell leukemia: IFN alpha-2b: Hepatitis-C, Hepatitis-B and Non-Hodgkin's lymphoma; complex of Polyethylene Glycol with IFNs in Chronic Hepatitis-B and Hepatitis-C infections.

Short Answers

Ques.1 What are anti-diuretics and give its mechanism of action?

Ans- ANTI-DIURETICS

These are drugs that reduce urine volume, particularly in diabetes insipidus. An antidiuretic is an agent or drug that, administered to an organism, helps control body water balance by reducing urination, opposing diuresis. Drugs are:

1. Anti-diuretic hormone (ADH, Vasopressin), Desmopressin, Lypressin, Terlipressin

2. Thiazide diuretics, Amiloride

3. Miscellaneous: Indomethacin, Chlorpropamide, Carbamazepine

ADH/Vasopressin: A hormone secreted by the posterior lobe of the pituitary gland that constricts blood vessels, raises blood pressure, and reduces excretion of urine. Also called anti-diuretic hormone.

MECHANISM OF ACTION

The V2 subtypes of ADH receptors are present on the basolateral side of CD cell membrane. Activation of these receptors increases cAMP formation intracellularly → activation of CAMP dependent protein kinase A → phosphorylation of relevant proteins which promote exocytosis of 'aquaporin-2' water channel containing vesicles (WCVs) through the apical membrane → more aqueous channels get inserted into the apical membrane. The rate of endocytosis and degradation of WCVs is concurrently reduced. The water permeability of CD cells is increased in proportion to the population of aquaporin-2 channels in the apical membrane at any given time. Continued V2 receptor simulation (during chronic water deprivation) in addition upregulates aquaporin-2 synthesis through CAMP response element of the gene encoding aquaporin-2.

Desmopressin is a synthetic replacement for the hormone vasopressin, the hormone which reduces the urine production. It may be taken nasally, iv form or as a tablet. Doctors usually prescribe Desmopressin most frequently for the treatment of diabetes insipidus or nocturnal enuresis.

Ques.2 Give the biosynthesis of thyroid hormones.

Ans- Biosynthesis

1. Uptake: Iodide is taken up in the gland by a follicle cell basement membrane protein called sodium/iodide symporter (NIS). The NIS is also controlled by an auto-regulatory mechanism whereby decreased thyroid iodine stores increase uptake due to TSH mediated stimulation of NIS and vice versa i.e., increased intrathyroidal iodine decreasing NIS protein expression.

2. Oxidation and iodination: Iodide thus taken up is oxidized by thyroidal peroxidase (TPO) to iodinium ions or hypoiodous acid or enzyme linked hypoiodate in the presence of hydrogen peroxide. These forms which form iodinate tyrosine residues in thyroglobulin molecule to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) by the process of iodide organification. TPO is blocked transiently by high intrathyroidal iodide and persistently by thioamide drugs.

3. Coupling and Release: Two molecules of DIT combine within the thyroglobulin molecule to form T_4 (1-thyroxine). One molecule of MIT and one molecule of DIT combine to form T_3 (liothyronine), T_4, T_3,

MIT and DIT are released from thyroglobulin by endocytosis and proteolysis of thyroglobulin at the apical border of follicular cells. T_4 and $T_3$are released into the circulation while MIT and DIT are deiodinase within the gland and the iodine is reutilized. The process of proteolysis is also blocked by high levels of intrathyroidal iodide.

4. Conversion of T_4 to T_3 in periphery: Almost 80% of the T_1 is derived from the sequential mono deiodination of thyroxine in the peripheral tissues, primarily liver by the enzyme iodothyronine 5' deiodinase. Iodothyronine 5 'deiodinase exists in two forms, type I is present in the liver and is responsible for circulating T_3 while type II is found primarily in brain and pituitary and is responsible for local production of T 3 in these tissues. Most tissues utilize the circulatory T_1 except brain and pituitary where local generation of T_3 is the major source of intracellular hormone. The recommended daily intake of iodide is about is 100-150 micro grams.

Ques.3 Write a short note on oral hypoglycaemic agents.

Ans- ORAL HYPOGLYCEMIC AGENTS

Pancreas as an endocrine gland produces the peptide hormones insulin, glucagon, and somatostatin and as an exocrine gland produces digestive enzymes. The peptide hormones are secreted from cells located in the islets of Langerhans (β cells produce insulin, α cells produce glucagon, and δ cells produce somatostatin). These hormones play an important role in regulating the metabolic activities of the body, particularly the homeostasis of blood glucose. Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.

- Hyperglycaemia, glycosuria, hyperlipidaemia, hyperuricemia
- Fasting plasma glucose >7.0 mmo1/1 (126 mg/dL) & Two-hour plasma glucose ≥ 11.1 mM (200 mg/dL), HbA1c ≥ 6.5%

Signs & Symptoms

- Insulin deficiency causes hyperglycaemia leading to glycosuria
- Increased catabolism: increased lipolysis (in adipose tissue), increased fatty acids (in plasma) & oxidation (in liver) leading to ketoacidosis.
- Decreased anabolism: Osmotic diuresis, Dehydration & loss of electrolytes produces diabetic coma.

Long Term Complications of Diabetes

- Vascular changes: Microvascular (atherosclerosis, Infarcts & gangrene in extremities);

Macrovascular (Neuropathy, nephropathy & retinopathy).

- Metabolic changes: Protein Glycosylation (neuropathy, retinopathy & nephropathy), Lesions in aorta, eye lens, kidneys, and nerves.
- Immune changes: Infections like TB, UTI, pneumonia, fungal infections & bacterial infections

Types

1. Type I: Immune β-cell destruction or idiopathic, leading to absolute insulin deficiency

2. Type II: Insulin resistance with relative insulin deficiency or insulin secretory defect with insulin resistance,

3. Gestational Diabetes: Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes.

4. Specific types of diabetes due to other causes: Neonatal diabetes, maturity-onset diabetes of the young [MODY], diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation).

Ques.4 Write down about hormonal replacement therapy.

Ans- HORMONAL REPLACEMENT THERAPY

Due to cessation of ovarian function at menopause, women suffer a number of physical, psychological and emotional consequences. The benefits and risks of HRT are considered below:

1 Post-menopausal HRT

a. Menopausal symptoms and atrophic changes: They are the primary indication for using HRT which improves general physical, mental and sexual well-being as well.

b. Osteoporosis and fractures: HRT restores Ca^{2+} balance: further bone loss is prevented and the excess fracture risk is nullified.

c. Cardiovascular events estrogens improve HDL: LDL ratio, retard atherogenesis, reduce arterial impedance, increase NO and PGI_2 production and prevent hyperinsulinemia, in postmenopausal women will have a protective cardiovascular influence.

d. Cognitive function and dementia

e. Cancer: That estrogens enhance the growth of breast cancer has been well recognized.

f. Gallstone, migraine: Estrogens slightly increase the risk of developing gallstones, while progestins may trigger migraine.

2. Senile vaginitis

3. Delayed puberty in girls

4. Dysmenorrhoea

5. Acne

6. Dysfunctional uterine bleeding

7. Carcinoma prostate

Ques.5 What are the adverse effects of corticosteroids.

Ans- Adverse Effects

A. Mineralocorticoid: Sodium and water retention, oedema, hypokalaemia alkalosis and a progressive rise in BP. These are now rare due to availability of highly selective glucocorticoids. Gradual rise in BP occurs due to excess glucocorticoid action as well.

B. Glucocorticoid:

1. Cushing's habitus: characteristic appearance with rounded face, narrow mouth, supraclavicular hump, obesity of trunk with relatively thin limbs.

2. Fragile skin, purple striae-typically on thighs and lower abdomen, easy bruising, hirsutism, Cutaneous atrophy occurs with topical use also.

3. Hyperglycaemia, may be glycosuria, precipitation of diabetes.

4. Muscular weakness: proximal (shoulder, arm, pelvis, thigh) myopathy occurs occasionally- withdraw corticoids.

5. Susceptibility to infection,

6. Delayed healing: of wounds and surgical incisions.

7. Peptic ulceration

8. Osteoporosis

9. Posterior subcapsular cataract may develop after several years of use, especially in children.

10. Glaucoma: may develop in susceptible individuals after prolonged topical therapy

11. Growth retardation in children occurs even with small doses if given for long periods.

12 Foetal abnormalities: Cleft palate and other defects like risk of abortion, stillbirth or neonatal death is not increased, but intrauterine growth retardation can occur.

13. Psychiatric disturbances

14. Suppression of hypothalamo-pituitaryadrenal (HPA) axis

Ques.6 Write a short note on oxytocin.

Ans- OXYTOCIN

Oxytocin (Pitocin, Syntocinon) is a cyclic 8-amino acid peptide that is synthesized in the paraventricular nucleus of the hypothalamus and transported within hypothalamic neurons (in association with neurophysin) to the posterior pituitary for storage. Its mechanism of action involves the direct stimulation of oxytocin receptors found on the myometrial cells. Oxytocin circulates unbound in the plasma, where it has a half-life of approximately 15 minutes. It is primarily inactivated in the kidneys and liver.

Pharmacological Actions

1. Uterus: Oxytocin increases the force and frequency of uterine contractions. With low doses, full relaxation occurs in between contractions; basal tone increases only with high doses.

Mechanism of action: Action of oxytocin on myometrium is independent of innervation. There are specific G-protein coupled oxytocin receptors which mediate the response mainly by depolarization of muscle fibres and influx of Ca^{2+} ions as well as through phosphoinositide hydrolysis and IP's mediated

intracellular release of Ca^{2+} ions. The number of oxytocin receptors increases markedly during later part of pregnancy. Oxytocin increases PG synthesis and release by the endometrium which may contribute to the contractile response. Distinct subtypes of oxytocin receptors have been shown on the myometrium and the endometrium.

2. Breast: Oxytocin contracts myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids-milk ejection reflex (milk let down in cattle) is initiated by suckling so that it may be easily sucked by the infant

3. Cardio Vascular System: Conventional doses used in obstetrics have no effect on BP but higher doses cause vasodilatation brief fall in BP, reflex tachycardia and flushing.

4. Kidney: Oxytocin in high doses exerts an ADH-like action-urine output is decreased pulmonary oedema can occur if large amounts of i.v. fluids and oxytocin are infused together. Conventional doses are without any effect.

Physiological Role

1. Labour: Oxytocin is released during labour and the uterus is highly sensitive to it currently.

2. Milk ejection reflex: It is mediated by oxytocin. The myoepithelial cells in breast are more sensitive than myometrium to oxytocin, milk ejection reflex is absent in the hypophysectomised.

3. Neuro transmission: Oxytocin appears to function as a peptide neuro transmitter in the hypothalamus and brainstem to regulate autonomic neurones.

Adverse effects: Inappropriate use of oxytocin can lead to uterine rupture, anaphylactoid and other allergic reactions, and possibly maternal death. Prolonged stimulation of uterine can result in the following foetal adverse reactions: persistent uteroplacental insufficiency sinus bradycardia, premature ventricular contractions, other arrhythmias, and foetal death. Prolonged use of oxytocin can lead to water intoxication secondary to the antidiuretic hormone-like effects of oxytocin. Maternal and foetal cardiovascular parameters should be monitored during oxytocin administration.

Ques.7 Give the pharmacological actions of prostaglandins.

Ans- PHARMACOLOGICAL ACTIONS

1. Regulation of blood pressure: PGE, PGA & PGI_2 are vasodilator in function; results in increased blood flow and decreased peripheral resistance to lower the blood pressure.

2. Inflammation: PGEI & PGE2 induce the symptoms of inflammation (redness, swelling. oedema etc.) due to arteriolar vasodilation. e.g., rheumatoid arthritis, psoriasis, conjunctivitis etc.

3. Reproduction: PGs increase tone as well as amplitude of uterine contractions; causes dysmenorrhea in most women.

4. Pain and fever: Pyrogens (fever producing agents) promote prostaglandin synthesis leading to the formation of PGE_2 in hypothalamus-regulation of body temperature, PGE_2 along with histamine & bradykinin cause pain.

5. Regulation of gastric secretion: PGE inhibits gastric secretion. PGs stimulate pancreatic secretion & increase the motility of intestine which often causes diarrhoea.

6. Influence on immune system: Macrophages secrete PGE which decreases the immunological functions of B- & T-lymphocytes.

7. Effects on respiratory function: PGE is a bronchodilator whereas PGF acts as a constrictor of bronchial smooth muscles.

8. Influence on renal functions: PGE increases glomerular filtration rate & promotes urine output. Effects on metabolism: through the mediation of cAMP. PGE decrease lipolysis, increases glycogen formation & promotes calcium mobilization.

9. Platelet aggregation & thrombosis: PGI_2 inhibits platelet aggregation whereas TXA, &PGE, promote platelet aggregation & blood clotting that might lead to thrombosis.

Ques.8 Write a short note on serotonin.

Ans- SEROTONIN

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter. Primarily found in GI tract, blood platelets and CNS of animals, including humans. It is popularly thought to be a contributor to feelings of well-being and happiness. Formed from tryptophan by hydroxylation followed by decarboxylation. After synthesis, the free amine is either stored or rapidly inactivated by monoamine oxidase (MAO) to 5-hydroxyindolacetic acid (a diagnostic test for carcinoid tumor). Actions are mediated through many cell membrane receptors, 7 families of receptors ($5\text{-}HT_{1\text{-}7}$) with various subtypes. Six of them are G-protein coupled, and one ($5HT_3$) a ligand-gated ion channel

PHARMACOLOGICAL EFFECTS OF SEROTONIN

1. Acts as a neurotransmitter in CNS (pineal gland) as a precursor of melatonin involved in sleep-wake behaviour.

2. 5-HT, receptors in the GIT and in the vomiting, centre is involved in the vomiting reflex. (Cancer chemotherapy).

3. It is a potent stimulant of pain and itch sensory nerve endings responsible for the symptoms produced by insect and plant stings.

4. It activates $5\text{-}HT_3$ receptors in vagal afferents (chemo-sensitive endings) in the coronary vascular bed causing bradycardia and hypotension.

5. Mild bronchoconstriction ($5\text{-}HT_{2A}$ receptors); facilitates acetylcholine release from bronchial vagal nerve endings.

6. Platelet aggregation by activating surface SHT, receptors,

7. Stimulation of GI smooth muscle, increasing tone and facilitating peristalsis ($5\text{-}HT_2$ receptors)

SEROTONIN & ITS AGONISTS

Serotonin has no clinical applications as a drug.

1. Buspirone ($5\text{-}HT_{1A}$) Anxiolytic.

2. Dexfenfluramine ($5\text{-}HT_{2C}$) Appetite suppression (very toxic)

3. Lorcaserin, $5\text{-}HT_{2C}$ agonist, has recently been approved by the FDA for use as a weight-loss.

4. Sumatriptan (5-HT $_{1D}$ & 5-HT$_{1B}$) Acute migraine and cluster headache (vascular headaches).

5. Tegaserod (5-HT$_4$): irritable bowel syndrome with constipation,

6. SSRIs (fluoxetine): Depression.

Ques.9 Give the classification of anti-neoplastic agents.

Ans- CLASSIFICATION

A. Drugs Acting Directly on Cells (Cytotoxic Drugs)

1. Alkylating agents

(a) Nitrogen mustards: Mechlorethamine (Mustine HC1), Cyclophosphamide, Ifosfamide, Chlorambucil,

Melphalan

(b) Ethylenimine: Thio-TEPA

(c) Alkyl sulfonate: Busulfan

(d) Nitrosoureas: Carmustine (BCNU), Lomustine (CCNU)

(e) Triazine: Dacarbazine (DTIC)

2. Anti-metabolites.

(a) Folate antagonist: Methotrexate (Mtx)

(b) Purine antagonist: 6-Mercaptopurine (6-MP), 6-Thioguanine (6-TG), Azathioprine, Fludarabine

(c) Pyrimidine antagonist: 5-Fluorouracil (5-FU), Cytarabine (cytosine arabinoside)

3. Vinca alkaloids: Vincristine (Oncovin), Vinblastine

4. Taxanes: Paclitaxel, Docetaxel

5. Epipodophyllotoxin: Etoposide

6. Camptothecin analogues: Topotecan, Irinotecan

7. Antibiotics: Actinomycin D (Dactinomycin), Doxorubicin, Daunorubicin (Rubidomycin), Mitoxantrone, Bleomycins, Mitomycin C

8. Miscellaneous: Hydroxyurea, Procarbazine, L-Asparaginase, Cisplatin, Carboplatin, Imatinib

B. Drugs Altering Hormonal Milieu

1. Glucocorticoids: Prednisolone and others

2. Estrogens: Fosfestrol, Ethinylestradiol

3. Selective estrogen receptor modulators: Tamoxifen, Toremifene

4. Selective estrogen receptor down regulators: Fulvestrant

5. Aromatase inhibitors: Letrozole, Anastrozole, Exemestane

6. Anti-androgen: Flutamide, Bicalutamide

7. 5-a reductase inhibitor: Finasteride, Dutasteride

8. GnRH analogues: Nafarelin, Triptorelin

9. Progestins: Hydroxy progesterone acetate, etc.

Ques.10 Explain anthelmintic drugs.

Ans- ANTHELMINTIC DRUGS

Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths. Helminthiasis is more common in developing countries with poorer personal and environmental hygiene. In the human body, g.i.t is the abode of many helminths, but some also live in tissues, or their larvae migrate into tissues. They harm the host by depriving him of food, causing blood loss injury to organs, intestinal or lymphatic obstruction and by secreting toxins. Helminthiasis is rarely fatal but is a major cause of ill health.

Classification

Anthelmintics are classified based upon their chemical structures.

(i) Piperazines: Diethylcarbamazine citrate, Piperazine citrate

(ii) Benzimidazoles: Albendazole, Mebendazole, Thiabendazole

(iii) Heterocyclics: Oxamniquine, Praziquantel

(iv) Natural products: Ivermectin, Avermectin

(v) Vinyl pyrimidines: Pyrantel, Oxantel

(vi) Amide: Niclosamide

(vii) Nitro derivative: Niridazole

(viii) Imidazothiazole: Levamisole

Mebendazole

It is a synthetic benzimidazole that has a wide spectrum of anthelmintic activity and a low incidence of adverse effects. It is a drug of choice in the treatment of infections by whipworm eggs pinworm, hookworms, and roundworm.

Mechanism of action: Mebendazole probably acts by inhibiting microtubule synthesis. It binds with parasite β-tubulin' and inhibits its polymerization. In addition, mebendazole probably blocks glucose uptake in parasite and depletes its glycogen stores. Efficacy of the drug vanes with gastrointestinal transit time, with intensity of infection, and perhaps with the strain of pare.

Pharmacokinetics: Absorption of mebendazole from intestines is minimal. Less than 10% of orally administered mebendazole is absorbed. The absorbed drug is protein-bound (>90%), rapidly converted to inactive metabolites (primarily during its first pass in the liver) and has a half – life of 2-6 hours 75 - 90% of oral dose passed in the faeces.

Dose: 100 mg chewable tablet, 100 mg/5 ml suspension 100 mg tablet. Mebendazole is one of the preferred drugs for treatment of multiple infestations and is more effective than albendazole in trichuriasis.

Adverse effects: Well tolerated even by patient in poor health. Mild nausea, vomiting, diarrhoea and abdominal pain have been reported infrequently. Rare side effects, usually with high-dose therapy, are hypersensitivity reactions (rash, urticaria), agranulocytosis, alopecia, and elevation of liver enzymes. Mebendazole is contraindicated in pregnancy & should be used with caution in children younger than 2 years of age.

Ques.11 Write a short note on DNA polymerase inhibitors.

Ans- DNA POLYMERASE INHIBITORS

Pharmacokinetics: The bioavailability of oral acyclovir is 15-20% and is unaffected by food. Acyclovir is cleared primarily by glomerular filtration and tubular secretion. Acyclovir diffuses into most tissues and body fluids Mechanism of Action:

Resistance: Resistance to acyclovir through alteration in either the viral thymidine kinase or the DNA polymerase. Agents such as Foscarnet, cidofovir, and trifluridine do not require activation by viral thymidine kinase and thus have preserved activity.

Adverse effects: Acyclovir is generally well tolerated with Nausea, diarrhoea, and headache. i.v. infusion may be associated with reversible renal dysfunction due to crystalline nephropathy or neurologic toxicity (e.g., tremors, delirium, seizures).

Anti-viral Spectrum and Clinical Use

Acyclovir: is highly effective against HSV-1 which causes **Herpes labialis** (Cold Sores), Herpes esophagitis, Herpes keratitis, Herpes encephalitis and ocular Herpes.

Ganciclovir: Parenteral Ganciclovir is used for the treatment of serious and vision threatening retinitis due to cytomegalovirus in immune-compromised cases (AIDS).

Adefovir: Used in Chronic Hepatitis-B viral infections (HBV) and effective in Lamivudine resistant strains of HBV.

Entacavir: Used for treating Chronic Hepatitis-B in adults with or without AIDS.

Telbivudine: Used to treat Chronic Hepatitis-B.

m-RNA Synthesis Inhibitors (Ribavirin)

Broad-spectrum antiviral activity (DNA and RNA viruses).

Mechanism of action: Its mono- and triphosphate derivatives generated intracellularly inhibit GTP & viral RNA polymerase→→ inhibit viral m-RNA and DNA synthesis.

Pharmacokinetics: Oral bioavailability ~50%; increased with fatty meal. Partly metabolized and eliminated. Accumulates on daily dosing and persists months after discontinuation

Adverse effects: Anaemia, bone marrow depression, haemolysis; Teratogenic, Aerosol can cause bronchospasm and irritation of mucosae.

Uses: Reduce mortality in Lassa fever (arenavirus infection), effective against Influenza-A and Influenza-B viruses, Ribavarin +s.c. Interferon alpha-2b in treatment of Chronic Hepatitis-C virus infections.

Inhibitors of Viral Penetration & uncoating (amantadine)

Inhibits uncoating of viral RNA within infected host cells and replication of Influenza-A

Mechanism of action: Inhibition of M^2 protein→→ prevention of H^+ mediated dissociation of ribonucleoprotein core segment (a prerequisite for viral replication).

Pharmacokinetics: Well absorbed orally, excreted unchanged in urine over 2-3 days, Half-life is 16 hours

Side effects: Nausea, Anorexia, insomnia, dizziness, nightmares, lack of mental conc., hallucinations, postural hypotension, ankle oedema. Contraindicated in Epilepsy & other CNS disorders, gastric ulcer, pregnancy.

Uses: Prevention and treatment of Influenza virus-A infections and in the therapy of Parkinson's disease.