B.Pharm. SemesterVI

Subject Name: Pharmacology-III

Subject Code: BP602TP

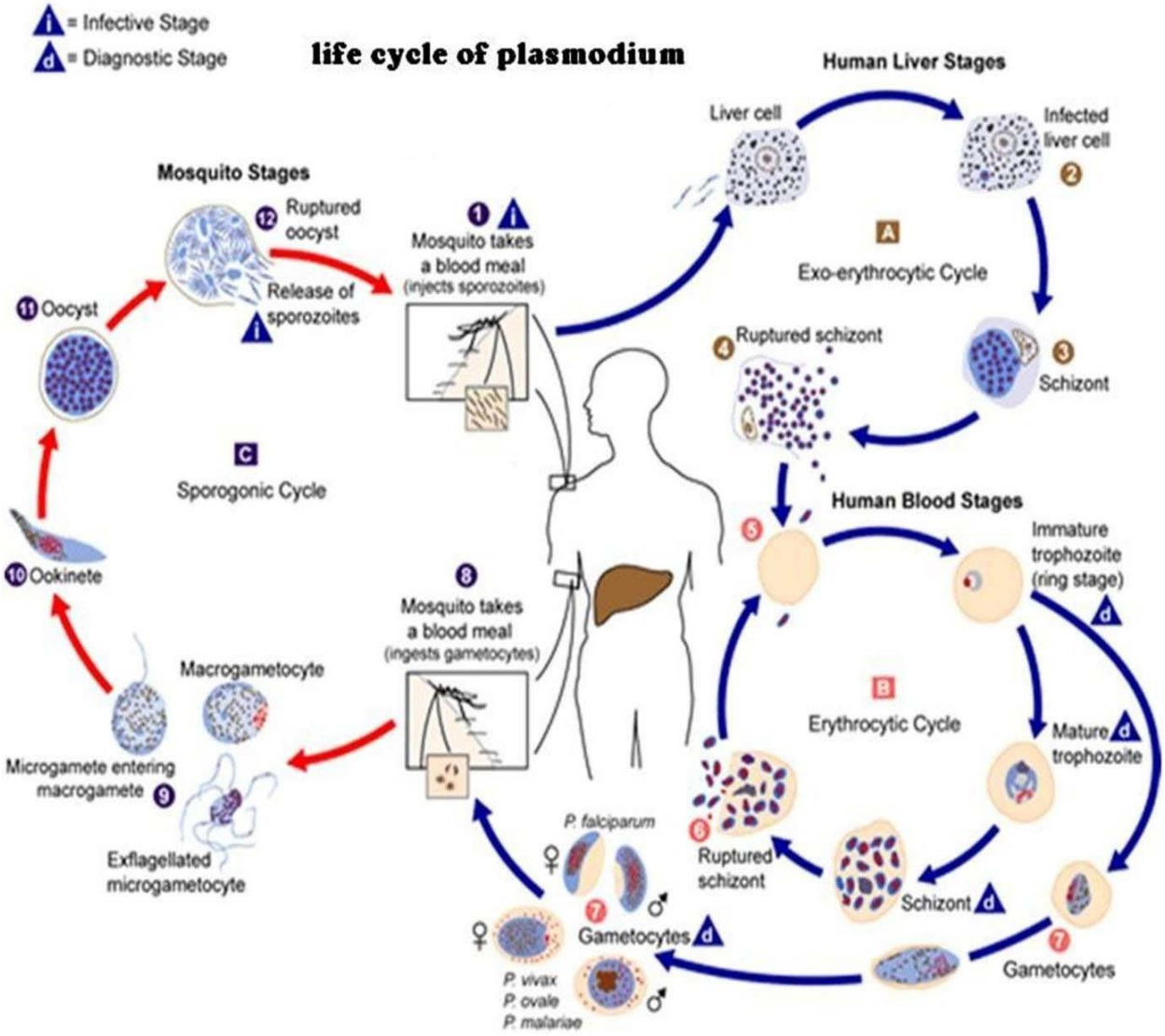
Sarswati Institute of Pharmaceutical Sciences

Malaria

Malaria is a protozoal disease caused by four species of genus plasmodium:

- *P. falciparum (mostfatal)*
- *P. vivax (lessfatal)*
- *Plasmodium malariae (leastfatal)*
- *P. ovale(rare)*

The plasmodium transmitted to human by the bite of an infected female anopheles mosquito.



History:-

- Maleria is probably older thanmankind.
- In the ancient time plant derivatives are used. Some of the plantsare
  - ✓ Artemisia annua(artemisinine)
  - ✓ Cinchona(Quinine)

➢ After second world war some synthetic drugs are introduced like Pamaquine, uinacrineetc.

➢ Among them 4-aminoquinoline moiety is the centre ofinvestigation.

➢ Along with quinolines certain sulpha drugs are also entertained for the antimalerial activity. e.g sulphapyrimidine.

➢ Then the pyrimidine ring simplified to open chain which also Shows good activity.e.gproguanil.

❖ **Classification:-**

1. Quinolines
   a. Cinchonaalkaloids
   b. 4-aminoquinolines
   c. 8-aminoquinolines
2. 9-aminoacridines
3. 2,4-diaminopyrimidines
4. Biguanides
5. Sulphones andsulphonamides
6. Miscellaneous agents
7. Neweragents

1. Quinolines:

Cinchona alkaloids
Quinine and Quinidine.
Quinidine is most potent anti- Malarial but it is more toxic.

➢ **Mechanism ofaction:**

Inhibits DNA strand separation.
Increases pH of the lysosomes in theparasite,so preventits utilization of erythrocytehemoglobin.

Uses:

- Chloroquine-resistant *P. falciparum*(orally).
- Cerebralmalaria

A/E:

- Cinchonism i.e. headache, dizziness, &tinnitus.
- Inhibits cardiac conductivity, hemolysis in G-6-P Dandblack water fever (intravascularhemolysis).

- **<u>Quinidine:</u>**

It is the dextro-isomer of quinine.
It is used when quinine is not available

- Its **mechanism of action** isunknown.
- *Uses:*
- Treatment & prophylaxis of chloroquine-resistant P.falciparum.

A/E:

GIT upset, headache, dizziness, syncope, extrasystoles & seizures.

- **4-aminoquinolines:-**

Mechanism of action:

- Inhibits synthesis of DNA and RNA in theplasmodium.
- Increases pH of the vacuoles in theparasite,so preventits utilization of erythrocytehemoglobin.

Uses:

- ✓ For treatment of most types ofmalaria.
- ✓ Also as a immunosuppressant in certain autoimmunediseases.
- ✓ Amebic liver abscess (as chloroquine is concentrated in theliver).
- ✓ **A/E:**
- ✓ GIT upset, rash, headache, peripheral neuritis, cardiac depressant, retinal damage, toxic psychosis andprecipitates
- ❖ porphyria.
- ❖ aminoquinolines

Primaquine: N^4-(6-metoxy-8-quinolyl)-1,4-pentane-diamine

- It is a tissue schizonticide.
- It has a cellular oxidant activity and possibly interferes with mitochondria function. Gametoside, so inhibits infection transmission bymosquito.

Mechanism of action:-

- ✓ It acts by disrupting the mitochondria of the parasite and blocks entry of the parasites inerythrosites.
- ✓ Narrow spectrum ofaction.

Uses:

- Eradicationofliverstages(hypnozoites)of*P.vivax*&*P. ovale*, after standard chloroquine therapy to preventrelapse.
- It should not be given if there is risk ofreinfection.

A/E:

- ❖ GIT upset, pruritis, headache, methemoglobinemia, hemolysis especially in G-6-PD.

ii) **Pamaquine**: 8-(4-diethylamino-1-methylbutylamino)-6-methoxy quinoline

2) 9-aminoacridines

- Now a day these classes of drugs are not usedclinically.

3) 2,4-diaminopyrimidines

- Mainly two drugs areemployed:

Pyrimethamine: 2,4-diamino-5-(p-chlorophenyl)-4-ethyl pyrimidine

- ✓ These drugs are designed on the basis of biochemical difference between host andparasite.
- ✓ Other drugs designed on these concept are biguanides, dihydrotriazines and sulphonamides.

Mechanism of action:

- Inhibit dihydrofolate reductase, so inhibit tetrahydrofolate (folinic acid) synthesis.
- They are effective against both theexo-erythrocyticand erythrocytic phases of the disease.

❖ **Use**

- Very effective in the chemoprophylexisandtreatment of chloroquine resistance falciparummaleria.

ii) Trimethoprim : 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine

- These class of drug usually used in combination with long acting sulpha drugs e.gSulphadoxine
- So combination gives supra-additiveeffect.
- Therefore minimum chances ofresistance.

- Combinations are i) Pyrimethamine +sulphadoxine

  ii) Pyrimethamine +Dapsone

4) Biguanides:

❖ **Mechanism ofaction:**

- Inhibits dihydrofolate reductase, so inhibit tetra- hydrofolate (folinic acid) synthesis.
- It causes damage to gametocytes and fails to carryoutlife cycle in mosquito.

5) Sulphones andSulphonamides

❖ **Mechanism ofaction:**

- Sulfonamide inhibits dihydropteroate synthetase, soinhibits folic acid synthesis.
- These drugs are used in combination withbiguanides and 2,4- diaminopyrimidines.

❖ **A/E:**

- Rashes, kidney damage, hemolysis & GITupset.

6) Miscellaneous drugs

Halofantrine:

- Unknown mechanism ofaction.
- Used only by oral route in P. falciparum cerebralmalaria.

Sesquiterpenes (artemisinin)

- It is obtained from the plant artemisiaannua.

Mechanism of action:

- It acts by Oxidativemechanism.
- The peroxide linkage breaks and formation of oxygen centered free radicals..

- It causes denaturation of plasmodium cellmembrane.

Other derivatives are

✓ Artether	Lipophillic
✓Artemether	
✓Artesunate	Hydrophillic
✓Artelinate	

- It is a blood schizonticide against all types of malaria including chloroquine-resistant p.falciparum.

Uses:

- P. falciparum cerebral malaria (oral &parenteral).

Atovaquone:

- 1,4-napthaquinonederivative.
- Unknown mechanism ofaction.
- Used alone for treatment of pneumocytosis andtoxoplasmosis
- in patients withAIDS.
- Atovaquone + proguanil (malarone) for treatment& prophylaxis of chloroquine-resistant *P.falciparum*.
- ***A/E*:**
- Fever, rashes, cough, nausea, vomiting, diarrhea, headache &insomnia.

ANTIFUNGAL AGENTS

- An **antifungal drug** is amedicationused to treatfungalinfectionssuch as athlete's foot,ringworm,candidiasis(thrush), serious systemic infections such ascryptococcalmeningitis, andothers.
- Fungal infections are caused primarily by various yeasts &molds.
- Yeast such as *Candida albicans* and Baker'syeast.
- Molds such as *Trichophytonrubrum.*

❖ Classification:-

- Polyeneantifungals
- azoleantifungals
  - Imidazoles

- Triazoles
- Thiazoles

- Allylamines
- Echinocandins
- Others

❖ Mode ofaction:-

- Antifungal work by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effects onthe host.
- Fungal and human cells are similar at the molecularlevel.
- This makes it more difficult to find or design drugs that targetfungi without affecting humancells.
- As a consequence, many antifungal drugs causeside-effects.
- Some of these side-effects can be life-threatening if the drugs are notused properly.
- Polyenes, triazoles, and imidazoles target ergosterol destroying the cell membrane'sintegrity.
- Allylamines inhibit ergosterolsynthesis.
- β-3-glucan syntheses inhibitor block the production of the β-(1,3)-glucan protein damaging the cellwall.
- Every component of the cell wall and membrane can betargeted.
- Drugs not available in the market such as Nikkomycin andPolyoxin target chitin synthase. Mannoproteins are another potentialtarget.

- Other antifungals such as flucytosine inhibit DNA/RNA synthesis and griseofulvin inhibits fungal cell mitosis preventing cell proliferationand function.

❖ **side-effects**:

- liver-damage
- affecting estrogenlevels
- Allergic reactions (the azole group of drugs is known to have caused anaphylaxis.

❖ **Classes:-**

❖ **Polyeneantifungals**:

- It is a molecule with multiple conjugated doublebonds.
- It is a macrocyclic polyene with a heavily hydroxylated region on the ring opposite the conjugatedsystem.(amphiphilic).
- The polyeneantimycoticsbind with sterolsin the fungal cell membrane, principally ergosterol. This changes the transition temperature (Tg) of the cell membrane, thereby he membrane in a less fluid, more crystallinestate.

Azoleantifungals:

Azole antifungal drugs inhibit the enzymelanosterol 14 α-demethylase; the enzyme necessary to convertlanosteroltoergosterol.

- Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth.
- Active pharmacophore of an azoleantifungal.

- The structure common to the majority of the earliest azoles, with an imidazole ring N-linked through a CH_2 group to an asymmetric carbon atom. The 2, 4 di-halogen-substituted benzene ring is common to all azoles (X= Cl orF).
- The most recent advances in azole chemistry involve substituting a triazole ring in place of an imidazole and, in some molecules, a methyl group (centre right) adjacent to the asymmetric carbonatom.

1. Imidazoles

Miconazole	Fenticonazole
Ketoconazole	Isoconazole
Clotrimazole	Oxiconazole
Econazole	Sertaconazole
Omoconazole	Sulconazole
Bifonazole	Tioconazole
Butoconazole	

2. Triazoles

*Firstgeneration	*second generation
Fluconazole	voriconazole
Itraconazole	ravuconazole

Isavuconazole posaconazole

- Voriconazole (VCZ) was first marketed in 2002. It has been approvedfor first-linetreatment.

- **Posaconazole** (PCZ) is a hydroxylated analogue ofItraconazole.
- It first became available in Europe in 2005 and it was approved by the FDA in 2006 for prophylaxis against invasive *Aspergillus and Candidainfections.*
- **Ravuconazole** (RCZ) is an investigational triazolecurrently
- undergoing phase II clinicaltrials

3. Thiazoles

Abafungin

❖ **Allylamines:**

Allylamines inhibitsqualene epoxidase, another enzyme required for ergosterolsynthesis:

Terbinafinehas been a very valuable antifungal for dermatophyte infections; it has become the widest used treatment for nail infections caused byfungi.

Naftifinewas developed as an allylamine agent for topicaluse.

Butenafine

❖ Echinocandins:-

Echinocandins inhibit the synthesis of glucan in the cell wall, probably via the enzyme 1,3-β glucan synthase:
Anidulafungin
Caspofungin
Micafungin

- Used for the treatment of patients with invasive *aspergillosis* who cannot tolerate or who are refractory to other antifungaltreatments.

- It was subsequently approved for treatment of esophageal candidacies, intra-abdominal abscesses, peritonitis and pleural space infectionscaused by *Candida*spp.,
- approved by the FDA in2001

❖ Micafungin:

first became available in 2005 when it was approved for the treatment of oesophageal candidiasis as well as prophylaxis in patients undergoing stem celltransplantation.

Anidulafungin: approved in 2006 for use in the treatment of oesophageal candidiasis, candidaemia, peritonitis and intra-abdominal abscesses due to *Candidaspp.*

❖ Others

- Polygodial- strong and fast-acting *in-vitro* antifungal activityagainst *Candida albicans*.
- Benzoic acid– has antifugal properties but must be combined witha keratolyticagent such as inWhitfield's Ointment
- Ciclopirox– (ciclopirox olamine), most useful against*Tineaversicolour*
- Undecylenic acid– anunsaturatedfatty acidderived from naturalcastor oil; fungistatic as well as anti-bacterial and anti-viral
- Flucytosine or 5-fluorocytosine – an antimetabolite. The compoundwas

first made as a potential anti-cancerdrug.

- Griseofulvin – binds to polymerized microtubules and inhibitsfungal mitosis. First tested as an antifungal agent in humans inthe1950s

- Haloprogin – discontinued due to the emergence of moremodern antifungals with fewer sideeffects
- Sodium bicarbonate ($NaHCO_3$) – shown effective against greenmold.