**CLASSIFICATION OF ANTIMALARIAL AGENTS AND MECHANISM OF ACTIONS**

**CLASSIFICATION**

Antimalarial drugs can be classified according to antimalarial activity and according to structure.

**ACCORDING TO ANTIMALARIAL ACTIVITY:**

**1.TISSUE SCHIZONTICIDES FOR CASUAL PROPHYLAXIS:** these drugs act on primary issue forms of plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented. Pyrimethamine and primaquine have this activity. How ever since it is impossible to predict the infections before clinical symptoms begin, this mode of therapy is more theoretical than practical.

2.TISSUE SCHIZONTICIDES FOR PREVENTING RELAPSE: these drugs act on the hypnozoites of p.vivax and p.ovule in the liver that causes relapse of symptoms on reactivation. Primaquine is the prototype pyrimethamine also has such activity.

3.BLOOD SCHIZONTICIDES: these drugs act on the blood forms of parasite and there by terminate clinical attacks of malaria. These are the most important drugs in anti-malaria chemotherapy. These includes chloroquine, quinine, mefloquine.

MECHANISM OF ACTION:

1.TISSUE SCHIZONTICIDES FOR CASUAL PROPHYLAXIS: these drugs act on the primary tissue forms of plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented

2.TISSUE SCHIZONTICIDES FOR PREVENTING RELAPSES: these drugs act on the hypnozoites of p.ovaleo the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug: pyrimethamine, sulfadoxine, sulfones etc.

3.BLOOD SCHIZONTICIDES: these drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in antimalarial chemotherapy. These includes chloroquine, quinine, mefloquine, sulfadoxine, sulfones

4.GAMETOCYTOCIDES: these drugs destroy the sexual forms of the parasite in the blood thereby prevent transmission of the infections to the mosquito. Chloroquine and quinine have gametocytocidal activity against p.vivax and p . malariae .but not against p.falciparu

5.SPORONTOCIDES: these drugs prevents the development of oocystin the mosquito and thus aabalte the transmission primaquine and chloroquine have these action

**ACCORDING TO STRUCTURE:**

1. 4-AMINOQUINOLINES: chloroquine, Amodiaquine

2. QUINOLINE METHANOL: mefloquine

3. CINCHONA ALKALOID: quinine, quinidine

4. BIGUANIES: proguanil (chloroguanide)

5. DIAMINOPYRIMIDINE: pyrimethamine

6.8-AMINOQUINOLINE: primaquine, tafenoquine

7. SULFONAMIDE AND SULFONE: sulfadoxine, Sulfamethopyrazine, Diapsone

8. ANTIBIOTICS: tetracycline, doxicyline

9. SESQUITERPINE LACTONES: Artesunates artemeter, arteether

10. AMINO ALCOHOLS: halofantrine, lumefantrine

11. NAPHTHOQUINONE: pyronaridine

12. NAPHTHOQUINONE: ATOVAQUONE

MECHANISMS OF ACTION:

1. BINGUANIDES (proguanil) when used alone, proguanil functions as a prodrug. Its active metabolite, cycloguanil, is an inhibitor of dihydrofolate reductase(DHFR). Although both mammals and parasite produce (DHFR) although both mammals and DHFR parasite DHFR, cylogunali inhibitory activity is specific for parasite DHFR prevent. This enzyme is a critical content component of the folic acid cycle. Inhibition of DHFR prevent the parasite from recycling dilhydrofolate back to terahydrofolate thus, DHFR inhibition shuts down these process. Proguanail display synergism when used in combination with the atovaqone.
2. DIAMIONOPYRIMINES (PYRIMETHAMINE) pyrimethamine interferes with regeneration of tetrahydrofolic acid from dihydrofolate by competitively inhibiting the enzyme dihdrofolate reductase terahydrrofolics acid is essentials for DNA AND RNA synthesis in many species, including protozoa .it has also been found to reduces the expression of SOD1, a key protein involved in amyotrophic lateral sclerosis
3. Amnionopryimides(PRIMAQUINE) active against the hepatic stages of all human malarial parasite. some gametocytes are destroyed while others are cannot undergo maturation division the gut of the mosquitoes. Primaquine is lethal to p.vivax and p.ovale in the liver stage and to p.vivax in the blood stage through its ability to do oxidative damages to the cell
4. SULFONAMIDES AND SULFONE (SULFADOXINE) sulfonamides is a sulfa drug, often used in combination with pyrimethamine to treat malarial. This medicine can also be used to preuctavent malaria to those living in, or will be travelling to an area, where there is a chance of getting malarial. Sulfonamides target plasmodium dihydropteroate synthase and dihydrofolate reductase. Sulfa drugs or sulfonamides are antimettrasalation abolics. They occur of sulfonamides exploits the differences between mammal cells and other kind of cells in their folic acids growth.
5. ANTIBIOTICS (TETRACYCLINE) tetracycline antibiotics are protein synthesis inhibitors. They inhibit the initiation of translations in variety of ways binding to the 30s ribosomal subunit, which is made up of 16s, Rrna a 21 proteins. They inhibit the binding of aminoacyl-Trana to the mRna translation complex. Tetracycline also has been found to inhibit matrix metalloproteinase. This mechanism does not add to their antibiotics effects, hut has led extensive research on chemically modified tetracycline or CCMTs for the treatment of rosacea, acne diabetes and types of neoplasms.
6. SEQUITERPRINE LACTONES (ARTESUNATE)the artesunate is a drug that rapidly converted to its active from dihydroarteminsinin (DHA). This process involved hydrolysis of 4-carbon ester group via plasmas esterase enzyme. It is hypothesized that the cleavage of End peroxide bridge in the pharmacophore of DHA generate reactive oxygen species (ROS), which increases oxidative stress and cause malarial protein damages via alkylation. In addition,
7. AMINO ALCOHOLS (LUMEFANTRINE) the exact mechanism by which lumefantrine exert its antimalarial effects is unknown. However, available data suggest that lumefantrine inhibits the formation of B-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis
8. NAPHTHYRIDINE (pryonaridine) in erythrocyte falciparum and p.berghei cultured in vitro in human erythrocytes, pyronaridine induced modification to the food vacuoles followed by the rapid formation of multiametiate whorls in the pellicular or complex of trophozoites. Similarly ,ultra structural analysis of p.falciparum after pyronardine treatment of infected primates showed the earliest and the most distinct effect of therapy was on the endocytic vesicles surround by a single membrane in the vascular space were observed
9. NAPHTHOQUINONE (ATOVAQUONE) atovaquone selectively inhibits the malarial cytochrome bc1 complex in the parasite electron transport chain, collapsing the mitochondrial membrane potentials. The malarial electron transport chain does not contributes significantly to ATP synthesis thus, it is believed that parasite death is due to the indirect inhibition of dihydroorotate dehydrogenase, which requires transport chain functions and its essentials to pyrimidine biosynthesis