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**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 CAUSAL PROPHYLAXIS:**

These drugs act on the primary tissue forms of the 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. However since it is impossible to predict the infections before clinical symptoms begin, this mode of therapy is more theoretical than practical.

1. **TISSUE SCHIZONTICIDES FOR PREVENTING RELAPSE:**

These drugs act on the hypnozoites of P.vivax and P.ovale in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

1. **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 anti-malarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracycline etc.

1. **GAMETOCYTOCIDES:**

These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against P.vivax and P. malariae, but not against P. falciparum. Primaquine has gametocytocidal activity against all plasmodia, including P.falciparum.

1. **SPORONTOCIDES:**

These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroquine have this action.

* **ACCORDING TO THE STRUCTURE:**

1. **4-AMINOQUINOLINES;** chloroquine, Amodiaquine
2. **QUINOLINE METHANOL;** Mefloquine
3. **CINCHONA ALKALOID;** Quinine, Quinidine
4. **BIGUANIDES;** Proguanil (Chloroguanide)
5. **DIAMINOPYRIMIDINE;** Pyrimethamine
6. **8-AMINOQUINOLINE;** Primaquine, Tafenoquine
7. **SULFONAMIDE & SULFONE;** Sulfadoxine, Sulfamethopyrazine, Dapsone
8. **ANTIBIOTICS;** Tetracycline, Doxycycline
9. **SESQUITERPINE LACTONES;** Artesunate, Artemether, Arteether
10. **AMINO ALCOHOLS;** Halofantrine, Lumefantrine
11. **NAPHTHYRIDINE;** Pyronaridine
12. **NAPHTHOQUINONE;** Atovaquone

**MECHANISMS OF ACTIONS**

* **4-AMINOQUINOLINES (CHLOROQUINE)**

The erythrocyte stages of plasmodium are sensitive to chloroquine. At this stage of its cycle, the parasite digests hemoglobin in a food vacuole to energy for the parasite. The food vacuole is acidic and the weak base chloroquine is concentrated within it by diffusion ion-trapping. Chloroquine and 4-aminoquinolines are believed to inhibit the malarial haem polymerase within the food vacuoles of the plasmodial parasite, thereby inhibiting the conversion of toxic haemin (ferriprotoporphyrin IX) to haemozoin (a pigment which accumulates in infected cells and is not toxic to the parasite). Ferriprotoporphyrin IX accumulates in the presence of chloroquine and is toxic to parasite, which is killed by the waste product of its own appetite.

* **CINOCHONA ALKALOID (QUININE)**

Quinine is theorized to be toxic to the malarial pathogen*, plasmodium falciparum,* by interfering with the parasite’s ability to dissolve and metabolize hemoglobin. As with other quinoline antimalarial drugs, the mechanism of action of quinine has not been fully resolved. The most widely accepted hypothesis of its action is based on the well-studied and closely related quinoline drug, chloroquine.

In *plasmodium falciparum* quinine has been found to inhibit nucleic acid synthesis, protein synthesis, and glycolysis; it also binds with hemazoin in parasitized erythrocytes. Quinine is effective as a malarial suppressant and in control of clinical attacks. Its primary action is schizontocidal, no lethal effect is exerted on sporozoites or pre-erythrocitic tissue forms.

* **BIGUANIDES (PROGUANIL)**

When used alone, proguanil functions as a prodrug. Its active metabolite, cycloguanil, is an inhibitor of dihydrofolate reductase (DHFR). Although both mammals and parasites produce DHFR, cycloguanil’s inhibitory activity is specific for parasitic DHFR. This enzyme is a critical component of the folic acid cycle. Inhibition of DHFR prevents the parasite from recycling dihydrofolate back to tetrahydrofolate (THF). THF is required for DNA synthesis, amino acid synthesis, and methylation; thus, DHFR inhibition shuts down these processes. Proguanil displays synergism when used in combination with the antimalarial atovaquone.

* **DIAMINOPYRIMIDINES (PYRIMETHAMINE)**

Pyrimethamine interferes with the regeneration of tetrahydrofolic acid from dihydrofolate by competitively inhibiting the enzyme dihydrofolate reductase. Tetrahydrofolic acid is essential for DNA and RNA synthesis in many species, including protozoa. It has also been found to reduce the expression of SOD1, a key protein involved in amyotrophic lateral sclerosis.

* **8-AMINOPYRIMIDINES (PRIMAQUINE)**

Active against the hepatic stages of all human malarial parasites. Some gametocytes are destroyed while others cannot undergo maturation division in the gut of the mosquito. 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 damage to the cell.

* **SULFONAMIDES & SULFONE (SULFADOXINE)**

Sulfadoxine is a sulfa drug, often used in combination with pyrimethamine to treat malaria. This medicine may also be used to prevent malaria in people who are living in, or will be traveling to, an area where there is a chance of getting malaria. Sulfadoxine targets plasmodium dihydropteroate synthase and dihydrofolate reductase. Sulfa drugs or sulfonamides are antimetabolites. They compete with para-aminobenzoic acid (PABA) for incorporation folic acid. The action of sulfonamides exploits the difference between mammal cells and other kind of cells in their folic acid for growth.

* **ANTIBIOTICS (TETRACYCLINE)**

Tetracycline antibiotics are protein synthesis inhibitors. They inhibit the initiation of translation in variety of ways binding to the 30S ribosomal subunit, which is made up of 16S rRNA and 21 proteins. They inhibit the binding of aminoacyl-tRNA to the mRNA translation complex. Tetracycline also has been found to inhibit matrix metalloproteinase. This mechanism does not add to their antibiotic effects, but has led extensive research on chemically modified tetracycline or CMTs for the treatment of rosacea, acne, diabetes and types of neoplasms.

* **SESQUITERPINE LACTONES (ARTESUNATE)**

Artesunate is a drug that is rapidly converted to its active form dihydroartemisinin (DHA). This process involves hydrolysis of 4-carbon ester group via plasma esterase enzyme. It is hypothesized that the cleavage of Endoperoxide Bridge in the pharmacophore of DHA generates reactive oxygen species (ROS), which increases oxidative stress and causes malarial protein damage via alkylation. In addition, Artesunate potently inhibits the essential *plasmodium falciparum* exported protein 1, a membrane glutathione S-transferase. As a result, the amount of glutathione in the parasite is reduced.

* **AMINO ALCOHOLS (LUMEFANTRINE)**

The exact mechanism by which lumefantrine exerts its antimalarial effect 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.

* **NAPHTHYRIDINE (PYRONARIDINE)**

In erythrocytic *p.falciparum* and *p.berghei* cultured in vitro in human erythrocytes, pyronaridine induced modifications to the food vacuoles followed by the rapid formation of multilameliate whorls in the pellicular complexes of trophozoites. Similarly, ultra structural analysis of *P.falciparum* after pyronaridine treatment of infected primates showed the earliest and most distinct effect of therapy was on the parasite food vacuole of late trophozoites and schizonts; specifically, undigested endocytic vesicles surround by a single membrane in the vascular space were observed.

* **NAPHTHOQUINONE (ATOVAQUONE)**

Atovaquone selectively inhibits the malarial cytochrome bc1 complex in the parasitic electron transport chain, collapsing the mitochondrial membrane potential. The malarial electron transport chain does not contribute significantly to ATP synthesis; thus, it is believed that parasite death is due to the indirect inhibition of dihydroorotate dehydrogenase, which requires transport chain function and is essential to pyrimidine biosynthesis.