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 **CLASSIFICATION OF ANTIMALARIAL AGENTS**

The antimalarial drugs can be classified into four major classes which are; the quinoline related class, the antifolates, the artemisinin derivatives and the antibiotic or antimicrobial class. Other classes of antimalarial agents include; phenanthrene methanol and hydroxynaphthoquinones

1. **The Quinoline** related class has a subdivision of the following;

**.** 4-Aminoquinolines: the drugs under this class include chloroquine, amodiaquine and hydroxychloroquine.

**.** 8-Aminoquinolines: the drugs under this class include primaquine, pentaquine, tafenoquine and isopentaquine

**.** Quinolinemethanols: the drug under this class is mefloquine.

**.** Cinchona alkaloid: the drugs under this class include quinine and quinidine.

1. **The Antifolates:** the drugs under this class includes pyrimethamine, proguanil, sulfamethopyrazine, dapsone and sulfadoxine.

**.** sulfonamides and sulfones: the drugs under this class include sulfadoxine, sulfamethopyrazine and dapsone.

**.** Diaminopyrimidines: the drug under this class is pyrimethamine.

**.** Biguanides: the drug under this class is proguanil.

1. **The Artemisinin Derivatives**: the drugs under this class includes artemisinin, artesunate, artemether and arteether.
2. **Antibiotics**: the drugs under this class includes tetracycline, doxycycline, minocycline.
3. **Naphthyridine**: the drug under this class is pyronaridine.
4. **Naphthoquinones**: the drug under this class is atovaquone
5. **Amino Alcohols:** the drugs under this class include halofantrine and lumefantrine.

 **MECHANISM OF ACTION FOR QUINOLINES**

Quinoline containing antimalarial drugs are mainstays of chemotherapy against malaria, these drugs interfere with the digestion and degradation of haemoglobin in the blood stages of the malaria parasite’s life cycle. The parasite degrades haemoglobin in an acidic food vacuole, producing free heme and reactive oxygen species as toxic by-products. The haeme moieties are neutralized by polymerisation, while the free radical species are detoxified by a vulnerable series of antioxidant mechanisms.

Chloroquine which is a dibasic drug, is actively concentrated by sensitive intra-erythrocytic plasmodia accumulating in the acidic vesicles of the parasite. The high intravacuolar chloroquine concentration is proposed to interfere with the degradation and polymerisation of haeme and or the detoxification of the reactive oxygen species, which effectively results in the killing of the parasite with its own metabolic waste.

Whereas, the quinolinemethanol and cinchona alkaloid drugs which include mefloquine, quinine and quinidine do not appear to be concentrated as extensively in the food vacuole like chloroquine. Chloroquine causes clumping of the malaria pigment, while quinine antagonizes this process. Quinine is a weaker base than chloroquine and has less affinity for haeme but it also inhibits the spontaneous formation of beta-haematin (malaria pigment) which is a toxic product of the digestion of haemoglobin by parasites. Quinidine does this as well.

Mefloquine has the same mechanism of action as chloroquine and is a fast acting erythrocytic schizonticidal drug. It is an effective therapy for many chloroquine resistant strains of P falciparum. Other related anti-malarials apart from mefloquine and quinine that act in an analogous manner with chloroquine include amodiaquine and lumefantrine.

Primaquine which falls under the class of 8-aminoquinoline is a poor erythrocytic schizonticide, it acts at gametocytes and hence it is used as a prophylactic drug. It is used in combination with chloroquine for the complete eradication of malaria but has no well-established mechanism of action.

 **MECHANISM OF ACTION FOR ANTIFOLATES**

The antifolates can be majorly classified into two;

1. The Type-1 antifolates: which consists of sulfonamides and sulfones (sulfadoxine, sulfamethopyrazine and dapsone). They prevent the formation of dihydropteroate from hydoxymethyldyhidropterin catalysed by dihydropteroate synthase (DHPS) by competing for the active site of DHPS which is a bifunctional enzyme in the plasmodia coupled with 2-amino-4-hydroxy-6-hydroxymethyl-dihydropteridine pyrophosphokinase (PPPK).
2. The Type-2 antifolates: which consists of the biguanides (proguanil) and the diaminopyrimidines (pyrimethamine). They inhibit dihydrofolate reductase (DHFR) which is also a bifunctional enzyme in plasmodia coupled with thymidylate synthase (TS).

The antifolate drugs inhibit either dihydrofolate reductase or dihydropteroate synthase and these are the two key enzymes in the de novo folate biosynthesis. Inhibition of this metabolic pathway leads to the inhibition of the biosynthesis of pyrimidines, purines and some amino acids. Antifolate antimalarial drugs therefore interfere with folate metabolism which is a pathway essential to the malaria parasite for survival.

 **MECHANISM OF ACTION FOR ARTEMISININ**

 **DERIVATIVES**

Artemisinin and its derivatives are sesquiterpene lactones. Once administered, the artemisinin derivatives are hydrolyzed rapidly to the biologically active metabolite dihydroartemisinin. Their action involves the heme mediated decomposition of the endoperoxide bridge to produce carbon-centred free radicals.

 The involvement of haem explains why the drugs are selectively toxic to the malaria parasites or why there is alkylation of malaria specific proteins. The malaria parasite is rich in haem iron derived from a breakdown of the host cell haemoglobin and this haem is responsible for activating the artemisinin inside the parasite.

 **MECHANISM OF ACTION FOR ANTIBIOTICS**

The cyclines are family of antibiotics that act by inhibiting bacterial protein synthesis. Cyclines act by binding to several proteins in the 30S ribosomal small subunit and to different ribonucleic acids in the 16S ribosomal RNA.

They inhibit the binding of aminoacyl-tRNA to the mRNA translation complex.

There are three categories of ribosomes in plasmodium; mitochondrial, plastid, and nuclear. Tetracyclines directly inhibit mitochondrial protein synthesis and also decrease the activity of a mitochondria enzyme, dihydroorotate dehydrogenase involved in the de novo pyrimidine synthesis.

**MECHANISM OF ACTION FOR NAPHTHOQUINONES**

Atovaquone which is the effective compound in this class of naphthoquinone, is used for both the prevention and treatment of malaria in a fixed combination with proguanil. It acts primarily on mitochondrial functions, atovaquone acts on the mitochondrial electron transfer chain, although more recently its activity with proguanil has been ascribed to its interference with the mitochondrial membrane potential.

Atovaquone inhibits cytochrome c reductase activity in P falciparum, as it is a ubiquinone analogue that binds to the cytochrome bc1 complex of the parasite mitochondrial electron transport chain. The malaria mitochondria electron transport chain disposes of electrons generated by dihydroorotate dehydrogenase during the synthesis of pyrimidines and the inhibition of this process by atovaquone could kill the parasite.

**MECHANISM OF ACTION FOR NAPHTHYRIDINE**

Pyronaridine which is a drug under the class naphthyridine has evidences showing that it acts as an antimalarial with actions similar to chloroquine. It inhibits beta hematin formation in vitro (a process which closely parallels hemozoin formation within the parasite food vacuole). Pyronaridine forms a drug-hematin complex and inhibits glutathione-dependent degradation of hematin and is also capable of enhancing hematin induced lysis of the red blood cells.

**MECHANISM OF ACTION FOR AMINO ALCOHOLS**

The drugs under this class include halofantrine and lumefantrine. Halofantrine is a malaria drug with a rapid schizonticide activity against the erythrocytic forms of the plasmodium that are resistant to chloroquine.

Halofantrine may be similar in action to mefloquine by forming complexes with ferritoporphyrin IX which damages the membrane of the parasite and has been shown to bind to plasmpesin which is a haemoglobin degrading enzyme unique to the malarial parasite. It could be used as a second-line agent to mefloquine.

Lumefantrine is an antimalarial agent used to treat acute uncomplicated malaria. It is used in combination with artemether for an improved efficacy. This combination exerts its effects against the erythrocytic stages of plasmodium spp. And may be used to treat infections caused by P. falciparum, lumefantrine inhibits the formation of beta hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis, through the interaction with haem, lumefantrine is able to exert the antimalarial effect in the parasite’s acid food vacuole.