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**DEPTARTMENT:** NURSING

**LEVEL:** 300LEVEL

 **Pharmacology**

**1.Classify antimalarial agents and state the mechanism of action of each class of drug listed.**

* **CLASSIFICATION OF ANTI-MALARIAL DRUGS :**
1. 4-Aminoquinolines
2. Cinchona alkaloid
3. 8-aminoquinoline
4. Quinolone methanol
5. Diaminopyrimidines
6. Sulphonamides & sulfone
7. Sesquiterpine lactones
8. Biguanides
9. Antibiotics
10. Amino alcohols
11. Naphtyridine
12. Naphthoquinone
13. Tissue schizonticides
14. Erythrocytic schizonticides

**MECHANISM OF ACTION OF THE DRUGS**

1. **4-Aminoquinolines** **(Chloroquine, Amodiaquine)**
* It is actively concentrated by sensitive intra-erythrocytic plasmodia by accumulating in the acidic vesicles of the parasite and weakly basic nature it raises the vesicular pH and thereby interferes with degradation of haemoglobin by parasitic lysosomes

Polymerization of toxic heme to nontoxic parasite pigment hemozoin is inhibited by formation of chloroquine-heme complex.

* Heme itself or its complex with chloroquine then damages the plasmodial membranes. Clumping of pigment and changes in parasite membranes follow death.
1. **Quinoline methanol (Mefloquine): same as chloroquine**
* It is a weak base: gets concentrated in the acidic food vacuoles of sensitive plasmodia
* inhibits polymerization of heme to hemozoin
* free haem increases(toxic) or haem-quinine complex damages parasite membranes and kills it
* After oral administration, quinine is rapidly absorbed, reaches peak plasma levels in 1–3 hours, and is widely distributed in body tissues.
* The use of a loading dose in severe malaria allows the achievement of peak levels within a few hours.
1. **Cinchona alkaloid: Quinine, Quinidine**
* It is a weak base: gets concentrated in the acidic food vacuoles of sensitive plasmodia, inhibits polymerization of haeme to hemozoin then free haeme increases(toxic) or haeme-quinine complex damages parasite membranes and kills it.
1. **Biguanides: Proguanil, (Chloroguanide)**
* It is cyclized in the body to cycloguanil which inhibits plasmodial. Proguanil inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.
1. **Diaminopyrimidines: Pyrimethamine**
* This is the same as Chloroquine. Chemically related to quinidine. Has strong blood schizonticidal activity against P.falciparum and P. vivax, but not against hepatic stages or gametocytes.
1. **8-aminoquinoline -** E.g 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’s cellular mechanism of action is still poorly understood:
* Fourteen primaquine metabolites have been detected, and few have been fully assessed for their biological activity.
1. **Sulfonamides & sulfone: Sulfadoxine , Sulfamethopyrazine, Dapsone**
* 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 into folic acid. The action of sulfonamides exploits the difference between mammal cells and other kinds of cells in their folic acid metabolism. All cells require folic acid for growth. Folic acid (as a vitamin) diffuses or is transported into human cells. However, folic acid cannot cross bacterial (and certain protozoan) cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid.

1. **Antibiotics: Tetracyclines, Doxycycline**
* Tetracycline antibiotics are protein synthesis inhibitors. They inhibit the initiation of translation in variety of ways by 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.
1. **Sesquiterpine lactones :Artesunate, Artemether.**
* The mechanism of artesunate is thought to involve cleavage of the endoperoxide bond through reaction with haeme. This produces free radicals which alkylate parasitic proteins. It has been shown to inhibit an essential parasite calcium adenosine triphosphatase enzyme. Artesunate inhibits malaria proteins EXP1, a glutathione S-transferase, responsible for breaking down cytotoxic hematin. It is unknown to what extent this inhibition contributes to the action of artesunate.
1. **Amino alcohols: Halofantrine, Lumefantrine:**
* Same as chloroquine. The mechanism of action of Halofantrine may be similar to that of chloroquine, quinine, and mefloquine; by forming toxic complexes with ferritoporphyrin IX that damage the membrane of the parasite.
1. **Naphthyridine: Pyronaridine**
2. **Naphthoquinone: Atovaquone:**
* In Plasmodium species, the site of action appears to be the cytochrome bc1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain via ubiquinone. Inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis. Atovaquone also has been shown to have good in vitro activity against Toxoplasma gondii.
1. **Tissue schizonticides** – e.g Proguanil
* Proguanil inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.
1. **Erythrocytic schizonticides** - e.g
* 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.