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ASSIGNMENT TITLE: CHEMOTHERAPY OF MALARIAL PARASITES

ASSIGNMENT QUESTION: Classify the antimalarial agents and state the mechanism of action of each class of drugs listed.

**CLASSIFICATION OF ANTIMALARIAL AGENTS**

 Antimalarial drugs can be classified according to anti malarial activity and according to structure.

1. **According to the structure:**
* **Aryl amino alcohols:** Quinine, mefloquine, halofantrine .
* **4-aninoquinolines:** Chloroquine, amodiaquine
* **8-aminoquinolines:** Primaquine
* **Antimicrobials:** Tetracycline, doxycycline
* **Peroxides:** Artemisinin [ artemether, arteether, artesunate]
* **Naphthoquinones:** Atovaquone
1. **According to anti malarial activity:**
* **Tissue schizonticides for causual prophylaxis:** Pyrimethamine and primaquine.
* **Tissue schizonticides for preventing relapse:** Primaquine is the prototype drug; pyrimethamine also has such activity.
* **Blood schizonticides:** Chloroquine, quinine, tetracyclines, mefloquine
* **Sporontocides:** Primaquine and Chloroguanide

**ARYL AMINO ALCOHOLS [ Quinine, mefloquine, halofantrine]:** They have been found to produce swelling of the *p. falciparum* food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components. It is effective against the blood forms of falciparum malaria, including the chloroquine resistant types.

**4-AMINOQUINOLINES [Chloroquine and Amadioquine]:** The mechanism of action of chloroquine is unclear. Being alkaline, the drug reaches high concentration within the food vacuoles of the parasite and raises its *pH* . It is found to induce rapid clumping of the pigment. Chloroquine inhibits the parasitic enzyme heme polymerase that converts the toxic heme into non-toxic hemazoin, thereby resulting in the accumulation of toxic heme within the parasite. It may also interfere with the biosynthesis of nucleic acids. Other mechanisms suggested include formation of drug-heme complex, intercalation of the drug with the parasitic DNA etc.

**8-AMINOQUINOLINES [Primaquine] :** It eliminates tissue erythrocyte infection. It may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite. Also, although its mechanism of action is unclear, primaquine may bind to and alter the properties of protozoal DNA.

**ANTIMICROBIAL [Tetracycline, doxycycline]:** Tetracyclines are bacteriostatic agents, supposedly acting by inhibiting protein synthesis by binding to the 30s ribosome subunit. They are effective against a wide range of organisms, including aerobic and anaerobic gram positive and gram negative bacteria, some atypical mycobacteria and plasmodia.

**PERIOXIDES [ Artemether, arteether, artesunate]:** Artemether is a drug which works against the erythrocytic stages of P.falciparum by inhibiting nucleic acid and protein synthesis. Artemether is administered in combination with lumefantrine for improved efficacy. Artemether has a rapid onset of action and is rapidly cleared from the body.

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.

**NAPHTHOQUINE [Atovaquone]:** It has been found to be useful against the plasmodia. It has a highly lipophilic molecule that supposedly interferes with mitochondrial electron transport and thereby ATP and pyrimidine biosynthesis and in plasmodia, it is found to target cytochrome bc1 complex and disrupt the membrane potential.

**TISSUE SCHIZONTICIDES FOR CAUSUAL PROPHYLAXIS [Pyrimethamine]** : Pyrimethamine inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are so essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.

**SPORONTOCIDES [ Chloroguanide]:** It exerts its antimalarial action by inhibiting parasitic dihydrofolate reductase enzyme. It has causal prophylactic and suppressive activity against p.falciparum and cures the acute infection. It is also effective in suppressing the clinical attacks of vivax malaria. However it is slower compared to 4-aminoquinolines.