**NAME**: Bamisaye Mary Odunayo

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**QUESTION**

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

 **Answers**

The classes of antimalarial agents include:

1. 4-Aminoquinolines eg; Chloroquine , Amodiaquine

2. Quinoline methanol eg; Mefloquine

3. Cinchona alkaloid eg; Quinine ,Quinidine

4. Biguanides eg; Proguanil (Chloroguanide)

5. Diaminopyrimidines eg; Pyrimethamine

6. 8-Aminoquinoline eg; Primaquine, Tafenoquine

7. Sulfonamides & sulfone eg; Sulfadoxine, Sulfamethopyrazine , Dapsone

8. Antibiotics eg; Tetracyclins, Doxycycline

9. Sesquiterpine lactones eg; Artesunate ,Artemether ,Arteether

10. Amino alcohols eg; Halofantrine ,Lumefantrine

11. Naphthyridine eg; Pyronaridine

12. Naphthoquinone eg; Atovaquone

Mechanism of Action of 4-Aminoquinolines(Chloroquine)

The drug concentrates in the acidic food vacuole of the parasite and interferes with essential processes. Inside red blood cells, the malarial parasite, which is then in its asexual lifecycle stage, must degrade hemoglobin to acquire essential amino acids, which the parasite requires to construct its own protein and for energy metabolism. Hemoglobin is composed of a protein unit (digested by the parasite) and a heme unit (not used by the parasite). During this process, the parasite releases the toxic and soluble molecule heme. The heme moiety consists of a porphyrin ring called Fe(II)-protoporphyrin IX (FP). To avoid destruction by this molecule, the parasite biocrystallizes heme to form hemozoin, a nontoxic molecule. Hemozoin collects in the digestive vacuole as insoluble crystals. Chloroquine enters the red blood cell by simple diffusion, inhibiting the parasite cell and digestive vacuole. Chloroquine then becomes protonated , as the digestive vacuole is known to be acidic (pH 4.7); chloroquine then cannot leave by diffusion. Chloroquine caps hemozoin molecules to prevent further biocrystallization of heme, thus leading to heme buildup. Chloroquine binds to heme to form the FP-chloroquine complex; this complex is highly toxic to the cell and disrupts membrane function. Action of the toxic FP-chloroquine and FP results in cell lysis and ultimately parasite cell autodigestion.

Mechanism of Action of Quinoline Methanol

Mefloquine, a weak base, preferentially accumulates in lysosomes and disrupts lysosomal function and integrity, thereby leading to host cell death. The chemosensitizing and radiosensitizing activities of this agent may be related to its inhibition of autophagocytosis, a cellular mechanism involving lysosomal degradation that minimizes the production of reactive oxygen species (ROS) related to tumor reoxygenation and tumor exposure to chemotherapeutic agents and radiation.

Mechanism of Action of Cinchona Alkaloid

 The mechanism of action is interference with the parasite's ability to digest haemoglobin. Quinine and quinidine also inhibit the spontaneous formation of beta-haematin (haemozoin or malaria pigment) which is a toxic product of the digestion of haemoglobin by parasites.

Mechansm of Action of Biguanides

This is a group that is converted to an active metabolite called cycloguanil. 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.

Mechanism of Action of Diaminopyrimidines

 This group electively inhibits the plasmodial form of dihydrofolate reductase, reducing the production of folic acid required for nucleic acid synthesis in the malarial parasite. This drugs in other words, 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.

Mechanism of Action of 8-Aminoquinolines

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. It inflict extensive oxidative damage that interferes with mitochondrial electron transport in parasites.

Mechanism of Action of Sulfonamides and Sulfones

This kind of drugs inhibit either dihydrofolate reductase HFR) (pyrimethamine, cycloguanil) or dihydropteroate synthase (DHPS) (sulfadoxine). Sulfonamides and Sulfones antimalarial drugs interfere with folate metabolism, a pathway essential to malaria parasite survival,

Mechanism of Action of Antibiotics

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.

Mechanism of Action of Sesquiterpine lactones

This drugs is first activated by intraparasitic heme-iron which catalyzes the cleavage of this endoperoxide. A resulting free radical intermediate may then kill the parasite by alkylating and poisoning one or more essential malarial protein(s).

Mechanism of Amino Alcohols

Halofantrine may share the same mechanism(s) of action as the 4-aminoquinolines since it forms a complex with ferriprotoporphyrin IX in vitro and interferes with the degradation of haemoglobin. This drugs caps hemozoin molecules to prevent further biocrystallization of heme, thus leading to heme buildup. It binds to heme and this complex is highly toxic to the cell and disrupts membrane function.

Mechanism of Action of Naphthyridine

It has a mechanism of action similar to that of the well-known 4-aminoquinoline chloroquine, namely, it inhibits β-hematin formation in vitro (a process which closely parallels hemozoin formation within the parasite food vacuole), forms a drug-hematin complex, inhibits glutathione-dependent degradation of hematin, and enhances hematin-induced lysis of red blood cells, but at 1/100 of the concentration seen with chloroquine.

Mechanism of Action of Naphthoquinone

This group of drugs selectively inhibits the malarial cytochrome bc1 complex in the parasitic electron transport chain, collapsing the mitochondrial membrane potential. Naphthoquinone derivatives reduce mitochondrial membrane potential (MMP) by the opening of the mitochondrial permeability transition pore resulting in cytochrome C release into the cytosol and activating caspase-3; key features of the intrinsic pathway of apoptosis