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**Classification of antimalarial agents**

1. 4-Aminoquinolines: - Chloroquine, Amodiaquine, Piperaquine
2. Quinoline-methanol: - Mefloquine
3. Cinchona alkaloid: - Quinine, Quinidine
4. Biguanides: -Proguanil, Chlorproguanil
5. Diaminopyrimidine: - Pyrimethamine
6. 8-aminoquinoline: -Primaquine, Tafenoquine
7. Sulfonamide and sulfone: - Dapsone, Sulfamethopyrazine
8. Antibiotics: -Tetracycline, Doxycycline Clindamycin
9. Sesquiterpene lactones: - Artesunate, Artemether Arteerther, Arterolane
10. Amino alcohols: -Halofantrine, Lumefantrine
11. Naphthyridine: -Pyronaridine
12. Naphthoquinone: - Atovaquone

**Mechanism of action of 4-Aminoquinolines (Chloroquine)**

The slightly basic chloroquine (pKa1 = 8.1, pKa2 = 10.1) accumulates down the pH gradient into the acidic digestive vacuole of the *P. falciparum* parasite, where the haemoglobin digestion occurs. While the environment outside of the digestive vacuole is at physiological pH (pH = 7.4), the inside of the digestive vacuole has pH = 5.5. In this acidic environment the chloroquine structure become chloroquine2+, and cannot readily diffuse back out of the digestive vacuole and instead begins to accumulate. In the digestive vacuole, chloroquine2+ inhibits heme crystallization to hemazoin by intercalating between the polymeric crystal packing and forms a dimeric hematin complex through π-π stacking interactions with the heme protoporphyrin ring. This form of heme- drug complexation therapy results in the steady increase in heme concentration within the acidic digestive vacuole, which is toxic to the parasite and will eventually lead to death of the *P. falciparum*.

**Mechanism of action of Quinoline-methanol (Mefloquine)**

The exact mechanism of action in unknown but may be similar to chloroquine as Membrane-bound mefloquine may inhibit merozoite invasion and interact with proteins involved with parasite membrane lipid trafficking and nutrient uptake. Mefloquine binds to haem, forming a complex that may also be toxic to the parasite.

**Mechanism of action Cinchona alkaloid (Quinine)**

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. This model involves the inhibition of hemozoin biocrystallization in Heme Detoxification pathway, which facilitates the aggregation of cytotoxic heme. It means it interfere with the parasite’s ability to digest haemoglobin and free cytotoxic heme accumulates in the parasites, causing their deaths.

**Mechanism of action of Biguanides: Proguanil**

Proguanil inhibits plasmodial dihydrofolate reductase through cycloguanil, its active metabolite, which inhibits folate production in both pre-erythrocytic and erythrocytic parasites.

**Mechanism of action of Diaminopyrimidine: Pyrimethamine**

Pyrimethamine 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.

**Mechanism of action of 8-aminoquinoline: Primaquine**

Primaquine is \ active against the liver stages including the hypnozoite (dormant stage) of P. vivax. In addition to its effect on the parasite, tafenoquine causes red blood cell shrinkage in vitro. Tafenoquine is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of P. vivax. The activity of tafenoquine against the pre-erythrocytic liver stages of the parasite prevents the development of the erythrocytic forms of the parasite, which are responsible for relapses in P. vivax malaria.

**Mechanism of action Sulfonamide and sulfone (Sulfametopyrazine)**

Sulfametopyrazine is a competitive inhibitor of the bacterial enzyme dihydropteroate synthetase. Para-aminobenzoic acid (PABA), a substrate of the enzyme is prevented from binding. The inhibited reaction is necessary in these organisms for the synthesis of folic acid.

**Mechanism of action of Antibiotics (Tetracycline)**

Tetracyclines work by inhibiting bacterial protein synthesis. This is accomplished primarily by reversibly binding to the 30S ribosomal subunit of the bacteria. This inhibits the enzyme binding of aminoacyl tRNA to the adjacent ribosomal acceptor site, which in turn prevents peptide chain elongation and inhibits protein synthesis. Because the binding of tetracyclines to the 30S ribosomal subunit is reversible, it is postulated that this is the explanation as to why they exhibit bacterio- static properties. In order for tetracyclines to get to the 30S ribosomal subunit, they need to be able to penetrate cell walls, which is accomplished by passive diffusion. With gram-negative organisms, tetracy- clines become positively charged cation complexes, presumably with magnesium. They then use OmpF and OmpC porin channels to cross the outer membrane. After entering the periplasmic space, tetracycline dissociates, resulting in an accumulation of uncharged tetracycline.

**Mechanism of action of Sesquiterpene lactones (Artemether)**

Artemether is a semisynthetic chiral acetal derivative of artemisinin. It interferes with parasite transport proteins, produces disruption of mitochondrial function, inhibits angiogenesis, and modulates host immune function. Artemether and its active metabolite have been estimated to reduce parasite biomass by approximately 10,000-fold per reproductive cycle (every 2 days). It is used with Lumefantrine which is a racemic mixture of a synthetic fluorine derivative and is structurally related to quinine, mefloquine, and halofantrine. It interferes with the conversion of heme, the toxic intermediate step produced during hemoglobin break-down, to non-toxic hemozoin. Due to heme-mediated decomposition of the endoperoxide bridge to produce carbon-centred free radicals, accumulation of the heme and free radicals results in parasites death.

**Mechanism of action of Amino alcohols Halofantrine**

Like other quinoline derivatives, the mechanism of action of halofantrine appears to be in the inhibition of the formation β-haematin crystals but the precise mechanism is unclear. Halofantrine forms complexes with ferriprotoporphyrin IX and the inhibition of the haemozoin formation occurs principally at the liquid-aqueous interface, an environment more compatible with the crystal structure of the halofantrine ferriprotoporphyrin IX.

**Mechanism of action of Naphthyridine (Pyronarindine)**

Pyronaridine inhibits the formation of β-haematin thus, preventing the malarial parasite from neutralizing haem, which is toxic to the parasite. Additionally, by forming a drug-haematin complex pyronaridine inhibits glutathione-dependent degradation of haematin and enhances haematin-induced lysis of red blood cells. Both these actions lead to parasite death.

**Mechanism of action of Naphthoquinone (Atovaquone)**

Atovaquone is a competitive inhibitor of ubiquinol, specifically inhibiting the mitochondrial electron transport chain at the *bc*1 complex. Inhibition of *bc*1 activity results in a loss of mitochondrial function. Consistent with this, inhibition of the *bc*1 complex by atovaquone affects the concentrations of metabolites in the pyrimidine biosynthetic pathway. Further cellular consequence of mitochondrial inhibition by Atovaquone is the inhibition of purine biosynthesis. Blood stage parasite death as a result of atovaquone is relatively slow compared to other antimalarials such as artemisinin and chloroquine.