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TITLE: CHEMOTHERAPY OF MALARIA PARASITE

DEPT: NURSING

LEVEL: 300 LVL

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

CLASSIFICATION OF ANTIMALARIAL AGENTS

1. 4- Aminoquinolines; Chloroquine and Amodiaquine
2. Quinoline methanol; Mefloquine
3. Cinchona alkaloid; Quinine, Quinidine
4. Biguanides; Proguanil (Chloroguanide)
5. Diaminopyrimidines;Pyrimethamine
6. 8-Aminoquinoline;Primaquine, Tafenoquine
7. Sulfonamides & sulfone; Sulfadoxine, Sulfamethopyrazine, Dapsone
8. Antibiotics;Tetracyclins, Doxycycline
9. Sesquiterpine lactones; Artesunate, Artemether, Arteether
10. Amino alcohols; Halofantrine, Lumefantrine
11. Naphthyridine;Pyronaridine
12. Naphthoquinone; Atovaquone

MECHANISM OF ACTION OF ANTIMALARIAL AGENTS

1. 4 AMINOQUINOLINES (Chloroquine and Amodiaquine): It accumulates in very high concentrations in the parasite food vacuole. Once in the food vacuole, Chloroquine is thought to inhibit the detoxification of heme. Chloroquine becomes protonated (to CQ2+) because the digestive vacuole is acidic (pH 4.7) and subsequently cannot leave the vacuole by diffusion. Chloroquine caps hemozoin molecules and prevents the further biocrystallization of heme, thus leading to heme buildup. Chloroquine binds to heme (or FP) to form what is known as the FP-Chloroquine complex; this complex is highly toxic to the cell and disrupts membrane function. The actions of the toxic FP-Chloroquine complex and FP result in cell lysis and ultimately the auto-digestion of the parasite cell. In essence, the parasite cell drowns in its own metabolic products.
2. QUINOLINE METHANOL (Mefloquine): It is actively concentrated in the sensitive intra erythrocytic plasmodia by accumulating in the acidic vesicles of the parasite and the weakly basic nature. It raises the vesicular ph and thereby interfering with the degradation of hemoglobin by parasitic lysosomes. Polymerization of toxic heame to nontoxic parasite pigment hemozoin is inhibited by formation of the Mefloquine-heame complex. Heame itself or in complex with Mefloquine then damages the plasmodial membranes. Clumping of pigment and changes in parasite membranes follows death.
3. CINCHONA ALKALOID (Quinine, Quinidine): Quinine acts in a manner similar to that of Chloroquine but with some differences; Chloroquine causes clumping of the malaria pigment, whereas quinine antagonizes this process. In addition, quinine is a weaker base than Chloroquine and has less affinity for heme, implying that mechanisms other than ion transport into the food vacuole and heme-drug interactions are required for the action of these drugs. Quinine also interacts rather weakly with heme (Kd = 2.63 × 10-6 M) but has been shown to inhibit heme polymerization and heme catalase activity. In the absence of a specific transporter, quinine is likely to be accumulated less efficiently in the food vacuole than Chloroquine.
4. BIGUANIDES (Proguanil (Chloroguanide)): It inhibit dihydrofolate reductase (DHFR, also a bifunctional enzyme in plasmodia coupled with thymidylate synthase [TS]), thus preventing the NADPH-dependent reduction of H2folate (DHF) to H4folate (THF) by DHFR. Inhibition of this metabolic pathway leads to the inhibition of the biosynthesis of pyrimidines, purines, and some amino acids.
5. DIAMINOPYRIMIDINES (Pyrimethamine): It inhibits plasmodial hydrofolate reductase, reducing the production of folic acid required for nucleic acid synthesis in the malaria parasite. It is used to treat acute malaria but not for prophylaxis.
6. 8-AMINOQUINOLINES (Primaquine, Tafenoquine): It eliminates tissue erythrocyte infection. Thereby, it prevents the development of the erythrocytic forms of the parasite which is responsible for relapse in vivax and ovale malaria. Primaquine phosphate is also active against gametocyte of Plasmodium falciparum.
7. SULFONAMIDE AND SULFONE (Sulfadoxine, Sulfamethopyrazine, and Dapsone): They mimic p-aminobenzoic acid (PABA). They prevent the formation of dihydropteroate from hydroxymethyldihydropterin catalyzed by dihydropteroate synthase (DHPS) by competing for the active site of DHPS (a bifunctional enzyme in plasmodia coupled with 2-amino-4-hydroxy-6hydroxymethyl-dihydropteridine pyrophosphokinase [PPPK]). Inhibition of this metabolic pathway leads to the inhibition of the biosynthesis of pyrimidines, purines, and some amino acids.
8. ANTIBIOTICS (Tetracyclins, Doxycycline): 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.
9. SESQUITERPINE LACTONES (Artesunate, Artemether, and Arteether): The mechanism of action for Artesunate is thought to involve the cleavage of the endoperoxide bond. Though it reacts with heame. This produces free radicals with alkylate parasitic proteins. It has been shown to inhibit an essential parasite calcium adenosine triphosphate enzyme.
10. AMINO ALCOHOLS (Halofantrine, Lumefantrine): It is actively concentrated in the sensitive intra erythrocytic plasmodia by accumulating in the acidic vesicles of the parasite and the weakly basic nature. It raises the vesicular ph and thereby interfering with the degradation of hemoglobin by parasitic lysosomes. Polymerization of toxic heame to nontoxic parasite pigment hemozoin is inhibited by formation of the Lumefantrine-heame complex. Heame itself or in complex with Lumefantrine then damages the plasmodial membranes. Clumping of pigment and changes in parasite membranes follows death.
11. NAPHTHYRIDINE (Pyronaridine): It is actively concentrated in the sensitive intra erythrocytic plasmodia by accumulating in the acidic vesicles of the parasite and the weakly basic nature. It raises the vesicular ph and thereby interfering with the degradation of hemoglobin by parasitic lysosomes. Polymerization of toxic heame to nontoxic parasite pigment hemozoin is inhibited by formation of the Pyronaridine-heame complex. Heame itself or in complex with Pyronaridine then damages the plasmodial membranes. Clumping of pigment and changes in parasite membranes follows death.
12. NAPHTHOQUINONE (Atovaquone): It possesses a novel mode of action against Plasmodium falciparum through inhibition of the electron transport system at the level of cytochrome bc1 complex.Avotaquone also causes the collapse of the parasite mitochondrial membrane potential in Plasmodium falciparum.