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CHEMOTHERAPHY OF MALARIA PARASITE

CLASSIFY THE ANTIMALARIAL AGENTS AND STATE THE MECHANISM OF ACTION OF EACH CLASS OF DRUG LISTED.

ANSWER

There are 13 classification of antimalarial agent

CLASSIFICATION OF ANTIMALARIAL AGENT

1. . 4-Aminoquinolines: example of drugs are

**Chloroquine**:

**Mechanism of action**

 Chloroquine enters the red blood cell by simple diffusion, inhibiting the parasite cell and digestive vacuole. Chloroquine then becomes protonated (to CQ2+), 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 bio crystallization 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 auto digestion. Parasites that do not form hemozoin are therefore resistant to chloroquine

 **Amodiaquine**

**Mechanism of action**

It is thought to inhibit heme polymerase activity. This results in accumulation of free heme, which is toxic to the parasites. The drug binds the free heme preventing the parasite from converting it to a form less toxic. This drug-heme complex is toxic and disrupts membrane function.

 And Piperaquine

1. **Quinoline-methanol**: e.g. Mefloquine

**Mechanism of action**

Mefloquine has been found to produce swelling of the Plasmodium falciparum food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodia components.

1. **Cinchona alkaloid**: e.g. quinine ,Quinidine

**Mechanism of action**

The drugs interfere with the parasite's ability to break down and digest hemoglobin. Consequently, the parasite starves and/or builds up toxic levels of partially degraded hemoglobin in itself.

1. **Biguanides**: e.g**. Proguanil** and cholrproguanil

**Mechanism of action**

Proguanil selectively inhibit the bifunctional dihydrofolare reductase-thymidylte synthesis and depletion of folate cofactors

1. **Diaminopyrimidine**: e.g. pyrimethamine

**Mechanism of action**

Pyrimethamine inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidine, 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. **8-aminoquinolie**: **primaquine**, tafenoquine

**Mechanism of action**

May converted into electrophilic intermediate that acts as oxidation-reduction mediator. This could contribute to antimalarial effect by generative reactive oxygen species or by inferring with mitochondrial electron transports in the parasite

1. **Sulfonamide and sulfone**: **suldadoxine**,diapason,sulfamthopyrazine

**Mechanism of action**

Sulfadoxine targets Plasmodium dihydropteroate synthase and dihydrofolate reductase. Sulfa drugs or Sulfonamides are antimetabolites. They compete with para-amino benzoic 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

1. **Antibiotics/tetracycline**: tetracycline, doxycycline

**Mechanism of action**

Tetracycline passively diffuses through porin channels in the bacterial membrane and reversibly binds to the 30S ribosomal subunit, preventing binding of tRNA to the mRNA-ribosome complex, and thus interfering with protein synthesis.

1. **Sesquiterpine lactose: e.g. artesunate**, artemether

**Mechanism of action**

The mechanism of artesunate is thought to involve cleavage of the endoperoxide bond through reaction with haeme 3. This produces free radicals which alkylate parasitic proteins. It has been shown to inhibit an essential parasite calcium adenosine triphosphates enzyme. Artesunate inhibits malaria proteins EXP1, a glutathione S-transferase, responsible for breaking down cytotoxic haematin

1. **Amino alcohols**: e.g. halofantrine, **lumefantrine**

**Mechanism of action**

Available data suggest that lumefantrine inhibits the formation of β-hematic by forming a complex with hemin and inhibits nucleic acid and protein synthesis.

1. **Naphthyrindine**: pyronarindine

**Mechanism of action**

They react with additional aldehyde and carbon acid to produce larger adducts with multiple acidic hydrogen atoms on the carbon acid higher adducts are also possible. Ammonia can be split off in an elimination reaction to form enals and enones.

1. **Napthoquione**: atovaquone

**Mechanism of action**

Collapse mitochondrial membrane, interferes with ATP production and pyrimidine biosynthesis. It prevents development in resistance and contraindicated pregnancy

Combined therapies

1. **Artemisinins and other derivatives**

**Mechanism of action**

The heme iron within the parasite catalyze cleavage of the endo peroxide bridge. This releases highly active carbon centered free radical species that bind to membrane protein, causes lipid peroxidation, damage endoplasmic reticulum