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DEPTARTMENT: NURSING

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PHARAMACOLOGY ASSIGNMENT

QUESTION:

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

Answer

Classification of antimalarial drugs :

1. 4-Aminoquinolines

2. Cinchona alkaloid

3. 8-aminoquinoline

4. Quinolone methanol

5. Diaminopyrimidines

6. Sulphonamides & sulfone

7. Sesquiterpine lactones

8. Biguanides

9. Antibiotics

10. Amino alcohols

11. Naphtyridine

12. Naphthoquinone

13. Tissue schizonticides

14. Erythrocytic schizonticides

Mechanism of action

1. 4-Aminoquinolines – e.g Chloroquine

Chloroquine and other similar quinolones (e.g. hydroxychloroquine, quinine) become concentrated in parasite food vacuoles, preventing the polymerization of the hemeoglobin product, heme, into hemozoin and thus eliciting parasite toxicity due to the build up of heme.

It is not active against liver stage parasites (and primaquine must be added for the radical cure of these species).

Malarial parasites have a limited ability to synthesize amino acids, and rely upon amino acids obtained by the breakdown of host hemoglobin molecules in digestive vacuoles. Degradation of hemoglobin releases both amino acids as well as a toxic heme metabolite ferriprotoporphyrin IX, which is normally detoxified by a pH-dependent polymerization to an unreactive malarial pigment named hemozoin . When polymerization of ferriprotoporphyrin IX is inhibited, its increased concentration in the parasites food vacuole will cause oxidative damage to membranes and death of the parasite.

2. Cinchona alkaloid - E.g Quinine

This is the same as chloroquine

• It is a weak base: gets concentrated in the acidic food vacuoles of sensitive plasmodia

• inhibits polymerization of haeme to hemozoin

• free haem increases(toxic) or haem-quinine complex damages parasite membranes and kills it

• After oral administration, quinine is rapidly absorbed, reaches peak plasma levels in 1–3 hours, and is widely distributed in body tissues.

• The use of a loading dose in severe malaria allows the achievement of peak levels within a few hours.

3. 8-aminoquinoline - E.g Primaquine

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.

Primaquine’s cellular mechanism of action is still poorly understood:

Fourteen primaquine metabolites have been detected, and few have been fully assessed for their biological activity.

Evidence suggests that one or more highly reactive metabolites of primaquine inflict extensive oxidative damage that interferes with mitochondrial electron transport in parasites (NOTE: primaquine is also known to increase the oxidative stress on human red blood cells, an effect that contributes to its hemolytic side effects.

4. Quinolone methanol- e.g Mefloquine

This is the same as Chloroquine.

Chemically related to quinidine. Has strong blood schizonticidal activity against P. falciparum and P. vivax, but not against hepatic stages or gametocytes.

5. Diaminopyrimidines- e.g Pyrimethamine

Folic acid antagonists. The rationale for their combination is a synergistic effect to inhibit folic acid synthesis, and a differential requirement between host and parasite for nucleic acid precursors involved in growth.

This activity is highly selective against plasmodia and Toxoplasma gondii.

Pyrimethamine is chemically related to trimethoprim. It acts slowly against erythrocytic forms of susceptible strains of all four human malaria species. It is not adequately gametocidal or effective against liver stages.

6. Sulphonamides & sulfone – e.g Sulfadoxine

Sulfadoxine is a sulfa drug, often used in combination with pyrimethamine to treat malaria. This medicine may also be used to prevent malaria in people who are living in, or will be traveling to, an area where there is a chance of getting malaria. Sulfadoxine targets Plasmodium dihydropteroate synthase and dihydrofolate reductase. Sulfa drugs or Sulfonamides are antimetabolites. They compete with para-aminobenzoic 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. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid.

7. Sesquiterpine lactones – e.g Artesunate

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. Artesunate inhibits malaria proteins EXP1, a glutathione S-transferase, responsible for breaking down cytotoxic hematin . It is unknown to what extent this inhibition contributes to the action of artesunate.

8. Biguanides – e.g Proguanil

Proguanil 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.

9. Antibiotics - e.g Tetrecyclins

Tetracycline 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.

10. Amino alcohols – e.g Halofantrine

The mechanism of action of Halofantrine may be similar to that of chloroquine, quinine, and mefloquine; by forming toxic complexes with ferritoporphyrin IX that damage the membrane of the parasite.

11. Naphtyridine – e.g Pyronaridine

12. Naphthoquinone – e.g Atovaquone

In Plasmodium species, the site of action appears to be the cytochrome bc1 complex (Complex III). Several metabolic enzymes are linked to the mitochondrial electron transport chain via ubiquinone. Inhibition of electron transport by atovaquone will result in indirect inhibition of these enzymes. The ultimate metabolic effects of such blockade may include inhibition of nucleic acid and ATP synthesis. Atovaquone also has been shown to have good in vitro activity against Toxoplasma gondii.

13. Tissue schizonticides – e.g Proguanil

Proguanil 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.

14. Erythrocytic schizonticides - e.g

These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented.