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PHA 324

Assignment

Antimalarials are a type of antiparasitic chemical agent, often naturally derived and can be used to treat or to prevent malaria.

Anti-malarial drugs can be classified according to anti-malarial activity and according to structure.

1. **According to anti-malarial activity:**
   1. **Tissue schizonticides for causal prophylaxis:** 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. Pyrimethamine and Primaquine have this activity. However, since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.
   2. **Tissue schizonticides for preventing relapse:** These drugs act on the hypnozoites of P. vivax and P. ovale in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.
   3. **Blood schizonticides:** These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in anti-malarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines etc.
   4. **Gametocytocides:** These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against P. vivax and P. malariae, but not against P. falciparum. Primaquine has gametocytocidal activity against all plasmodia, including P. falciparum.
   5. **Sporontocides:** These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

A combination of chloroquine and primaquine is thus needed in ALL cases of malaria.

1. **According to the structure:**
   1. **Aryl amino alcohols:** Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine, lumefantrine.
   2. **4-aminoquinolines:** Chloroquine, amodiaquine.
   3. **8-aminoquinolines:** Primaquine.
   4. **Folate synthesis inhibitors or antifolate compounds:** Type 1 – competitive inhibitors of dihydropteroate synthase – sulphones, sulphonamides; Type 2 – inhibit dihydrofolate reductase – biguanides like proguanil and chloroproguanil; diaminopyrimidine like pyrimethamine.
   5. **Antimicrobials:** Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones.
   6. **Peroxides:** Artemisinin derivatives and analogues – artemether, arteether, artesunate, artelinic acid
   7. **Naphthoquinones:** Atovaquone
   8. **Iron chelating agents:** Desferrioxamine

MECHANISM OF ACTION

### **Antifolate Drugs**

Pyrimethamine, and biguanides such as cycloguanil interfere with folic acid synthesis, inhibiting the parasite enzyme known as dihydrofolate reductase-thymidilate synthase (DHFR). Sulfonamides act at the previous step in the folic acid pathway, inhibiting the parasite enzyme dihydropteroate synthase (DHPS). There is marked synergy between these two classes of drugs when they are taken together. However, resistance to pyrimethamine in *P. falciparum* developed within a few years of its introduction due to point mutations in the DHFR gene, which cause 100- to 1,000-fold reduced affinity of the enzyme complex to the drug. Progressive mutations in the DHFR gene of *P. falciparum* further decreased efficacy. Triple mutant infections are relatively resistant to antifolate treatment; with a fourth mutation within the malaria parasite, antifolate drugs become completely ineffective.

Quadruple mutant *P. falciparum* strains are now prevalent in parts of Southeast Asia, and South America. Resistance to partner antifols sulfonamide and sulfone results from progressive acquisition of mutations in the *P. falciparum* gene encoding the target enzyme DHPS.

**Artemisinin's**

Artemisinin's chemical structure is unlike any other known antimalarial. It includes an endoperoxide bridge necessary for its antimalarial action. Artemisinin treatment of membranes, especially in the presence of heme, causes lipid peroxidation; this event may occur as a result of the drug's interaction with intracellular heme or iron. With respect to artemisinin's direct effect on the malaria parasite, recent work suggests that artemisinin specifically inhibits PfATP6, the SERCA orthologue of Plasmodium *falciparum*, a calcium ATPase.

In vivo, artemisinin's kill malaria parasites within host erythrocytes, after which dead parasites are culled by the spleen, leaving formerly infected red blood cells intact and circulating. It is not yet clear which asexual parasite life-cycle stages are most sensitive to artemisinin derivatives: late rings and early trophozoites versus trophozoites. There is clear consensus, however, that artemisinin derivatives kill early-stage gametocytes and are more active over a broader range of the parasite life cycle than any other antimalarial drug currently in use.

## **Chloroquine**

The mechanism of action of chloroquine is unclear. Being alkaline, the drug reaches high concentration within the food vacuoles of the parasite and raises its ph. It is found to induce rapid clumping of the pigment. Chloroquine inhibits the parasitic enzyme heme polymerase that converts the toxic heme into non-toxic hemazoin, thereby resulting in the accumulation of toxic heme within the parasite. It may also interfere with the biosynthesis of nucleic acids. Other mechanisms suggested include formation of drug-heme complex, intercalation of the drug with the parasitic DNA etc.

## **Quinine**

Quinine acts as a blood schizonticide although it also has gametocytocidal activity against *P. vivax* and *P. malariae*. Because it is a weak base, it is concentrated in the food vacuoles of *P. falciparum*. It is said to act by inhibiting heme polymerase, thereby allowing accumulation of its cytotoxic substrate, heme.

As a schizonticidal drug, it is less effective and more toxic than chloroquine. However, it has a special place in the management of severe falciparum malaria in areas with known resistance to chloroquine.

## **Chloroguanide (Proguanil)**

More popularly known as proguanil, this drug was developed by British antimalarial research in 1945. It is a biguanide derivative that is converted to an active metabolite called cycloguanil pamoate. 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. It is also effective in suppressing the clinical attacks of vivax malaria. However, it is slower compared to 4-aminoquinolines.

Chloroguanide is slowly but adequately absorbed from the gastrointestinal tract. Peak plasma levels are attained within 5 hours and elimination half-time is about 16-20 hours.

Chloroguanide is available as tablets, each containing 100 mg of the drug. The dose for prophylaxis is 100-200 mg daily.

Chloroguanide along with chloroquine is used as prophylaxis effective against *P. falciparum* malaria.

At the prophylactic doses, it produces occasional nausea and diarrhoea. It is otherwise a safe drug and can be used in pregnancy.

## **Sulfadoxine+Pyrimethamine**

Pyrimethamine inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are so essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.

Sulfadoxine inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydropteroic acid. The combination of pyrimethamine and sulfa thus offers two step synergistic blockade of plasmodial division.

## **Mefloquine**

Mefloquine has been found to produce swelling of the *P. falciparum* food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components. It is effective against the blood forms of falciparum malaria, including the chloroquine resistant types.

## **Atovaquone**

A synthetic hydroxynaphthoquinone developed in the early 1980s, atovaquone has been found to be useful against the Plasmodia (as well as Toxoplasma and Pneumocystis carinii). It has a highly lipophilic molecule that supposedly interferes with the mitochondrial electron transport and thereby ATP and pyrimidine biosynthesis and in Plasmodia, it is found to target cytochrome bc1 complex and disrupt the membrane potential. Its bio-availability after oral administration is poor and may be increased by a fatty meal. It has a long half-life of 2-3 days and it undergoes entero-hepatic circulation. It is available as 750 mg tablets. It may cause rash, fever, vomiting, diarrhoea and head ache. Safety in pregnancy, lactation, children, and elderly is yet to be established.

**Tetracyclines**

Tetracyclines are bacteriostatic agents, supposedly acting by inhibiting protein synthesis by binding to the 30s ribosome subunit. They are effective against a wide range of organisms, including aerobic and anaerobic gram positive and gram-negative bacteria, Rickettsia, *Coxiella burnetii*, *Mycoplasma, Ureaplasma, Chlamydia, Legionella*, Spirochaetes, *Brucella, Helicobacter pylori, Yersinia*, some atypical mycobacteria and Plasmodia.