**Name: Akinola marvellous oluwanifemi**

**Matric number: 17/mhs02/016**

**Department: nursing**

**Chemotherapy assignment**

**Antimalarial agent**

**Classification**

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

**1. According to anti malarial activity:**

A.**Tissue schizonticides for causal prophylaxis: T**hese 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.

**B. 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.

**C. 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.

D.**Gametocytocides: T**hese 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.

E. **Sporontocides:** These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide and a tissue schizonticide (in case of P. vivax and P. ovale). A combination of chloroquine and primaquine is thus needed in ALL cases of malaria.

2**. According to the structure:**

A .Aryl amino alcohols: Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine.

4-aminoquinolines: Chloroquine, amodiaquine.

B. Folate synthesis inhibitors: Type 1 – competitive inhibitors of dihydropteroate synthase – sulphones, sulphonamides; Type 2 – inhibit dihydrofolate reductase – biguanides like proguanil and chloroproguanil; diaminopyrimidine like pyrimethamine

C. 8-aminoquinolines: Primaquine, WR238, 605

D. Antimicrobials: Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones

E. Peroxides: Artemisinin (Qinghaosu) derivatives and analogues – artemether, arteether, artesunate, artelinic acid

F. Naphthoquinones: Atovaquone

G. Iron chelating agents: Desferrioxamine

The WHO accorded high priority to the development of fast acting artemisinin derivatives for the treatment of cerebral malaria as well as for the control of multi-drug resistant P. falciparum malaria. A water soluble ester called artesunate and two oil soluble preparations called artemether and arteether (artemotil) have now been developed.

Anti malarial activity: They act by inhibiting a P falciparum-encoded sarcoplasmic-endoplasmic reticulum calcium ATPase, and not by inhibiting the haem metabolic pathway as previously supposed. Most clinically important artemisinins are metabolised to dihydroartemisinin (elimination half-life of about 45 min), in which form they have comparable antimalarial activity. However, their use in monotherapy is associated with high incidences of recrudescent infection, suggesting that combination with other antimalarials might be necessary for maximum efficacy.

It is the fastest acting anti malarial available. It inhibits the development of the trophozoites and thus prevents progression of the disease. Young circulating parasites are killed before they sequester in the deep microvasculature. These drugs starts acting within 12 hours. These properties of the drug are very useful in managing complicated P. falciparum malaria. These drugs are also effective against the chloroquine resistant strains of P. falciparum.

**Artemisinin and derivatives**

Artesunate and artemether have been shown to clear parasitaemias more effectively than chloroquine and sulfadoxine/pyrimethamine. Meta analysis of mortality in trials indicated that a patient treated with artemether had at least an equal chance of survival as a patient treated with quinine. It has also been reported that artemisinin drugs cleared parasites faster than quinine in patients with severe malaria but fever clearance was similar. Also, parenteral artemether and artesunate are easier to use than quinine and do not induce hypoglycaemia.

Gametocytocidal action: Artemisinin compounds have been reported to reduce gametocytogenesis, thus reducing transmission of malaria, this fact being specially significant in preventing the spread of resistant strains.

Absorption, fate and excretion: Artemisinin derivatives are absorbed well after intra muscular or oral administration. The drug is fully metabolised and the major metabolite is dihydroartemisinin, which also has anti parasite effects. It is rapidly cleared, predominantly through the bile.

**Chloroquine**

Chloroquine is the prototype anti malarial drug, most widely used to treat all types of malarial infections. It is also the cheapest, time tested and safe anti malarial agent.

**Mechanism of action:** 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.

Absorption, fate and excretion: 90% of the drug is absorbed from G.I.T and rapidly absorbed from intra muscular and subcutaneous sites. It has a large distribution volume due to extensive sequestration in tissues of liver, spleen, kidney, lung etc. Hence the need for a larger loading dose. Therapeutic blood levels persist for 6-10 days and elimination half-life is 1-2 months. Half of the drug is excreted unchanged by the kidneys, remaining is converted to active metabolites in the liver.

Anti malarial activity: It is highly effective against erythrocytic forms of P. vivax, P. ovale and P. malariae, sensitive strains of P. falciparum and gametocytes of P. vivax. It rapidly controls acute attack of malaria with most patients becoming afebrile within 24-48 hours. It is more effective and safer than quinine for sensitive cases.

**Quinine**

quinine is obtained entirely from the natural sources due the difficulties in synthesising the complex molecule.

**Mechanism of action:** 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.

Absorption, fate and excretion: Quinine is readily absorbed when given orally or intramuscularly. Peak plasma concentrations are achieved within 1 – 3 hours after oral dose and plasma half-life is about 11 hours. In acute malaria, the volume of distribution of quinine contracts and clearance is reduced, and the elimination half-life increases in proportion to the severity of the illness. Therefore, maintenance dose of the drug may have to be reduced if the treatment is continued for more than 48 hours. The drug is extensively metabolised in the liver and only 10% is excreted unchanged in the urine. There is no cumulative toxicity on continued administration.

**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 and sulphadoxine are very useful adjuncts in the treatment of uncomplicated, chloroquine resistant, P. falciparum malaria. It is now used in combination with artesunate for the treatment of P. falciparum malaria. It is also used in intermittent treatment in pregnancy (IPTp)

Anti malarial activity: 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.

Absorption, fate and excretion: Pyrimethamine is slowly but completely absorbed after oral administration and is eliminated slowly with a plasma half-life of about 80-95 hours. Suppressive drug levels may be found in the plasma for up to 2 weeks. The drug is excreted in breast milk.

**Halofantrine**

Halofantrine was developed in the 1960s by the Walter Reed Army Institute of Research. It is a phenanthrene methanol structurally related to quinine. Its mechanism of action may be similar to that of chloroquine, quinine, and mefloquine; by forming toxic complexes with ferritoporphyrin IX that damage the membrane of the parasite. This synthetic anti malarial is effective against multi drug resistant (including mefloquine resistant) P. falciparum malaria.

Its bioavailability is low and variable (may be doubled if taken with a fatty meal). The peak plasma concentration is achieved in 4-8 hours after the oral dose. The elimination half-life is 1-3 days for the parent drug and 3-7 days for the active metabolite.

Halofantrine is no more used in the treatment of chloroquine resistant and multi-drug resistant, uncomplicated P. falciparum malaria.

**Mefloquine**

Mefloquine was born during the Vietnam war, as a result of research into newer anti malarials, to protect the American soldiers from the multi drug resistant falciparum malaria. Nothing much has happened after that and hence this ‘new’ drug should be restricted for use against multi drug resistant falciparum only.

Anti malarial activity: 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.

Absorption, fate and excretion: Mefloquine is available for oral administration only because parenteral preparations cause severe local reactions. It is absorbed rapidly and is extensively bound to plasma proteins. Elimination half-life is about 2-3 weeks. It is mainly excreted in the faeces.

**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.

**Atovaquone plus Proguanil**: A fixed dose combination of atovaquone and proguanil hydrochloride (Malarone™) is now approved for both treatment and prophylaxis of malaria. It is available as 250 mg atovaquone + 100 mg proguanil per tablet for adults and 62.5 mg atovaquone + 25 mg proguanil per tablet for children.

**Pyronaridine:** Structurally, it resembles amodiaquine and has been found to be highly effective against chloroquine resistant strains in China.

**Piperaquine**: Its activity is similar to that of chloroquine. A combination with artimisinin is undergoing studies.

**Lumefantrine is an** aryl alcohol related to quinine, mefloquine and halofantrine that is devoid of cardiac toxicity of halofantrine. It is being tried in combination with artemether.

**Other Drugs with Antimalarial Activity:**

Many drugs have been tested for their potential anti malarial effects. Research into newer anti malarials being scanty, such attempts might throw up one or two candidates for use in malaria, however, these drugs are yet to find a place in standard anti malarial regimen. Clindamycin, fluoroquinolones like ciprofloxacin and Norfloxacin, azithromycin etc. have been found to be effective against malarial parasites. Atovaquone; Desferrioxamine; Pyronaridine; Piperaquine; WR-288, 605; and 566C80 are drugs undergoing trials.

**Tetracyclines**

One among the first antibiotics to come into use in human beings, these drugs have stood the test of time and are continuing to be useful in treating a broad range of infections, including malaria.

**Mechanism of action**: 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.

**Doxyxyclin**e is also used for short term prophylaxis against P. falciparum malaria at 100mg once daily.

**Clindamycin: It acts by inhibiting the protein synthesis by binding to the 50s subunit of ribosomes. It can be used for drug r**esistant malaria along with quinine at a dose of 10 mg/kg 8 hourly for 5 days. Adverse effects include pseudomembrane colitis and skin rashes. In one study, a cure rate of only 50% was observed. (Hall et al, P. falciparum malaria semiresistant to clindamycin.

**Fluoroquinolones: B**oth ciprofloxacin and norfloxacin have been found to have anti malarial activity both in vitro and in vivo. However, results are not consistent.

**Azithromyci**n: Azithromycin is found to have anti malarial activity and has been found to be useful as a causal prophylactic agent. It was found to be effective at the dose of 300 mg stat, followed by 250 mg daily for 7 days as a prophylactic agent against chloroquine resistant P. falciparum infection.