NAME: BAKARE BOSOLA OPEMIPO

MATRIC NO: 17/MHS02/029

DEPARTMENT: NURSING

LEVEL: 300L

COURSE:PHARMACOLOGY ASSIGNMENT

1.Chloroquine

Chloroquine was, until recently, the most widely used anti-malarial. It was the original prototype from which most methods of treatment are derived. It is also the least expensive, best tested and safest of all available drugs. The emergence of drug-resistant parasitic strains is rapidly decreasing its effectiveness; however, it is still the first-line drug of choice in most sub-Saharan African countries. It is now suggested that it is used in combination with other antimalarial drugs to extend its effective usage. Popular drugs based on chloroquine phosphate (also called nivaquine) are Chloroquine FNA, Resochin and Dawaquin.

MECHANISM OF ACTION

Chloroquine is a 4-aminoquinolone compound with a complicated and still unclear mechanism of action. It is believed to reach high concentrations in the vacuoles of the parasite, which, due to its alkaline nature, raises the internal pH. It controls the conversion of toxic heme to hemozoin by inhibiting the biocrystallization of hemozoin, thus poisoning the parasite through excess levels of toxicity. Other potential mechanisms through which it may act include interfering with the biosynthesis of parasitic nucleic acids and the formation of a chloroquine-haem or chloroquine-DNA complex. The most significant level of activity found is against all forms of the schizonts (with the obvious exception of chloroquine-resistant *P. falciparum* and *P. vivax* strains) and the gametocytes of *P. vivax*, *P. malariae*, *P. ovale* as well as the immature gametocytes of *P. falciparum*. Chloroquine also has a significant anti-pyretic and anti-inflammatory effect when used to treat *P. vivax* infections, and thus it may still remain useful even when resistance is more widespread.

2.QUININE

Quinine has a long history stretching from Peru, and the discovery of the cinchona tree, and the potential uses of its bark, to the current day and a collection of derivatives that are still frequently used in the prevention and treatment of malaria. Quinine is an alkaloid that acts as a blood schizonticidal and weak gametocide against *Plasmodium vivax* and *Plasmodium malariae*. As an alkaloid, it is accumulated in the food vacuoles of *Plasmodium* species, especially *Plasmodium falciparum*. It acts by inhibiting the hemozoin biocrystallization, thus facilitating an aggregation of cytotoxic heme. Quinine is less effective and more toxic as a blood schizonticidal agent than chloroquine; however, it is still very effective and widely used in the treatment of acute cases of severe *P. falciparum*. It is especially useful in areas where there is known to be a high level of resistance to chloroquine, mefloquine, and sulfa drug combinations with pyrimethamine. Quinine is also used in post-exposure treatment of individuals returning from an area where malaria is endemic.

Mechanism of Action:

The mechanism of action is interference with the parasite's ability to digest haemoglobin. Quinine and quinidine also inhibit the spontaneous formation of beta-haematin (haemozoin or malaria pigment) which is a toxic product of the digestion of haemoglobin by parasites. Quinine, an alkaloid, acts by interfering with the growth and reproduction of the malarial parasites, which inhabit the red blood cells

(erythrocytes). ... This recurrence stems from the failure of quinine to kill the malarial parasites in cells of the body other than the red blood cells.

3.Amodiaquine

Amodiaquine is a 4-aminoquinolone anti-malarial drug similar in structure and mechanism of action to chloroquine. Amodiaquine has tended to be administered in areas of chloroquine resistance while some patients prefer its tendency to cause less itching than chloroquine. Amodiaquine is now available in a combined formulation with artesunate (ASAQ) and is among the artemisinin-combination therapies recommended by the World Health Organization. Combination with sulfadoxine=pyrimethamine is not recommended.

Mechanism of action

amodiaquine is not completely certain. Like other quinoline derivatives, it is thought to inhibit heme polymerase activity. This results in accumulation of free heme, which is toxic to the parasites.

4.Pyrimethamine

Pyrimethamine is used in the treatment of uncomplicated malaria. It is particularly useful in cases of chloroquine-resistant *P. falciparum* strains when combined with sulfadoxine. It acts by inhibiting dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, thereby halting the processes of DNA replication, cell division and reproduction. It acts primarily on the schizonts during the erythrocytic phase, and nowadays is only used in concert with a sulfonamide.

Mechanism of action

Pyrimethamine interferes with the regeneration of tetrahydrofolic acid from dihydrofolate by competitively inhibiting the enzyme dihydrofolate reductase. Tetrahydrofolic acid is essential for DNA and RNA synthesis in many species, including protozoa.

5.Proguanil

Proguanil (chloroguanide) is a biguanide; a synthetic derivative of pyrimidine. It was developed in 1945 by a British Antimalarial research group. It has many mechanisms of action but primarily is mediated through conversion to the active metabolite cycloguanil. This inhibits the malarial dihydrofolate reductase enzyme. Its most prominent effect is on the primary tissue stages of *P. falciparum, P. vivax* and *P. ovale*. It has no known effect against hypnozoites therefore is not used in the prevention of relapse. It has a weak blood schizonticidal activity and is not recommended for therapy of acute infection. However it is useful in prophylaxis when combined with atovaquone or chloroquine (in areas where there is no chloroquine resistance). The pharmacokinetic profile of the drugs indicates that a half dose, twice daily maintains the plasma levels with a greater level of consistency, thus giving a greater level of protection. The proguanil- chloroquine combination does not provide effective protection against resistant strains of *P. falciparum*. There are very few side effects to proguanil, with slight hair loss and mouth ulcers being occasionally reported following prophylactic use.

MECHANISM OF ACTION

Proguanil is a prophylactic antimalarial drug, which works by stopping the malaria parasite, Plasmodium falciparum and Plasmodium vivax, from reproducing once it is in the red blood cells. It does this by inhibiting the enzyme, dihydrofolate reductase, which is involved in the reproduction of the parasite

6.Sulfonamides

Sulfadoxine and sulfamethoxypyridazine are specific inhibitors of the enzyme dihydropteroate synthetase in the tetrahydrofolate synthesis pathway of malaria parasites. They are structural analogs of *p*-aminobenzoic acid (PABA) and compete with PABA to block its conversion to dihydrofolic acid. Sulfonamides act on the schizont stages of the erythrocytic (asexual) cycle. When administered alone sulfonamides are not efficacious in treating malaria but co-administration with the antifolate pyrimethamine, most commonly as fixed-dose sulfadoxine-pyrimethamine (Fansidar), produces synergistic effects sufficient to cure sensitive strains of malaria.

MECHANISM OF ACTION

Inhibition of other metabolic processes. Sulfonamides interfere with folic acid synthesis by preventing addition of para-aminobenzoic acid (PABA) into the folic acid molecule through competing for the enzyme dihydropteroate synthetase.

7.Mefloquine

Mefloquine was developed during the Vietnam War and is chemically related to quinine. It was developed to protect American troops against multi-drug resistant *P. falciparum*. It is a very potent blood schizonticide with a long half-life. It is thought to act by forming toxic heme complexes that damage parasitic food vacuoles. Mefloquine is effective in prophylaxis and for acute therapy. It is now used solely for the prevention of resistant strains of *P. falciparum* (usually combined with Artesunate) despite being effective against *P. vivax*, *P. ovale* and *P. marlariae*. Chloroquine/proguanil or sulfa drug-pyrimethamine combinations should be used in all other plasmodia infections.

Mechanism of Action:

Mefloquine is an antimalarial agent which acts as a blood schizonticide. Its exact mechanism of action is not known. Activity In Vitro and In Vivo: Mefloquine is active against the erythrocytic stages of Plasmodium species

8.Atovaquone

Atovaquone is available in combination with proguanil under the name Malarone, albeit at a price higher than Lariam. It is commonly used in prophylaxis by travelers and used to treat falciparum malaria in developed countries. A liquid oral suspension of Atovaquone is available under the name Mepron.

Mechanism of action

Atovaquone selectively inhibits the malarial cytochrome bc_1 complex in the parasitic electron transport chain, collapsing the mitochondrial membrane potential.

9.Primaquine

Primaquine is a highly active 8-aminoquinolone that is effective against *P. falcipaum* gametocytes but also acts on merozoites in the bloodstream and on hypnozoites, the dormant hepatic forms of *P. vivax* and *P. ovale*.[7] It is the only known drug to cure both relapsing malaria infections and acute cases. The mechanism of action is not fully understood but it is thought to block oxidative metabolism in Plasmodia. It can also be combined with methylene blue.

Mechanism of action

is not well understood. It may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite. Also, although its mechanism of action is unclear, primaquine may bind to and alter the properties of protozoal DNA.

10.Artemisinin and derivatives

The active compound was isolated first in 1971 and named artemisinin. It is a sesquiterpene lactone with a chemically rare peroxide bridge linkage. It is thought to be responsible for the majority of its anti-malarial action, although the target within the parasite remains controversial. At present it is strictly controlled under WHO guidelines as it has proven to be effective against all forms of multi-drug resistant *P. falciparum*, thus every care is taken to ensure compliance and adherence together with other behaviors associated with the development of resistance. It is also only given in combination with other anti-malarials.

- **Artemisinin** has a very rapid action and the vast majority of acute patients treated show significant improvement within 1–3 days of receiving treatment. It has demonstrated the fastest clearance of all anti-malarials currently used and acts primarily on the trophozite phase, thus preventing progression of the disease. Semi-synthetic artemisinin derivatives (e.g. artesunate, artemether) are easier to use than the parent compound and are converted rapidly once in the body to the active compound dihydroartemesinin.
- **Artemether** is a methyl ether derivative of dihydroartemesinin. It is similar to artemesinin in mode of action but demonstrates a reduced ability as a hypnozoiticidal compound, instead acting more significantly to decrease gametocyte carriage. Similar restrictions are in place, as with artemesinin, to prevent the development of resistance, therefore it is only used in combination therapy for severe acute cases of drug-resistant *P. falciparum*.
- **Artesunate** is a hemisuccinate derivative of the active metabolite dihydroartemisin. Currently[it is the most frequently used of all the artemesinin-type drugs. Its only effect is mediated through a reduction in the gametocyte transmission. It is used in combination therapy and is effective in cases of uncomplicated *P. falciparum*.
- **Dihydroartemisinin** is the active metabolite to which artemesinin is reduced. It is the most effective artemesinin compound and the least stable. It has a strong blood schizonticidal action and reduces gametocyte transmission. It is used for therapeutic treatment of cases of resistant and uncomplicated *P. falciparum*.As with artesunate, no side effects to treatment have thus far been recorded.
- **Arteether** is an ethyl ether derivative of dihydroartemisinin. It is used in combination therapy for cases of uncomplicated resistant *P. falciparum*. The recommended dosage is 150 mg/kg per day for three days given by IM injections.

MECHANISM OF ACTION

Artemisinin is believed to act via a two-step mechanism. Artemisinin is first activated by intraparasitic heme-iron which catalyzes the cleavage of this endoperoxide. A resulting free radical intermediate may then kill the parasite by alkylating and poisoning one or more essential malarial protein(s). No clinically relevant artemisinin-resistant human malaria has yet been reported. However, an artemisinin-resistant strain of murine malaria has been developed and may offer clues to the kinds of resistance that may someday develop in human malarias.

11.Halofantrine

Halofantrine is a relatively new drug developed by the Walter Reed Army Institute of Research in the 1960s. It is a phenanthrene methanol, chemically related to Quinine and acts acting as a blood schizonticide effective against all *Plasmodium* parasites. Its mechanism of action is similar to other anti-malarials. Cytotoxic complexes are formed with ferritoporphyrin XI that cause plasmodial membrane damage. Despite being effective against drug resistant parasites, halofantrine is not commonly used in the treatment (prophylactic or therapeutic) of malaria due to its high cost. It has very variable bioavailability and has been shown to have potentially high levels of cardiotoxicity. It is still a useful drug and can be used in patients that are known to be free of heart disease and are suffering from severe and resistant forms of acute malaria. A popular drug based on halofantrine is Halfan. The level of governmental control and the prescription-only basis on which it can be used contributes to the cost, thus halofantrine is not frequently used.

Mechanism of action

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.

12.Lumefantrine

Lumefantrine is a relative of halofantrine that is used in some combination antimalarial regimens.

MECHANISM OF ACTION

The exact mechanism by which lumefantrine exerts its antimalarial effect is unknown. However, available data suggest that lumefantrine inhibits the formation of β-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis. Food increases absorption.

13.Doxycycline

Probably one of the more prevalent antimalarial drugs prescribed, due to its relative effectiveness and cheapness, doxycycline is a tetracycline compound derived from oxytetracycline. The tetracyclines were one of the earliest groups of antibiotics to be developed and are still used widely in many types of infection. It is a bacteriostatic agent that acts to inhibit the process of protein synthesis by binding to the 30S ribosomal subunit thus preventing the 50s and 30s units from bonding. Doxycycline is used primarily for chemoprophylaxis in areas where chloroquine resistance exists. It can also be used in combination with quinine to treat resistant cases of *P. falciparum* but has a very slow action in acute malaria, and should not be used as monotherapy.

Mechanism Of Action
Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria.

14.Clindamycin

Clindamycin is a derivative of lincomycin, with a slow action against blood schizonticides. It is only used in combination with quinine in the treatment of acute cases of resistant *P. falciparum* infections and not as a prophylactic. Being more toxic than the other antibiotic alternatives, it is used only in cases where the Tetracyclines are contraindicated (for example in children).

Mechanism of action

Clindamycin has a primarily bacteriostatic effect. At higher concentrations, it may be bactericidal. It is a bacterial protein synthesis inhibitor by inhibiting ribosomal translocation, in a similar way to macrolides.