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REVIEW ON ANTIMALARIAL DRUGS

Resist to Malaria

¹Mr.Akash S. Aher, ²Mr.Hemant V. Kamble, ³Mr.Santosh A. Waghmare, ⁴Mr.Vivek M. Satpute

¹Student, ²Principal, ³Assistant Professor, ⁴Assistant Professor,

¹Department of M. Pharmacology,

¹Loknete Shri. Dadapatil Pharate College of M.pharm., Mandhavgan Pharata, India

Abstract: This study has been undertaken to study the Malaria and treatment for prevention of Malaria.

Keywords - Antimalarials, Chloroquine, Treatments, etc.

- Introduction

Malaria is the Disease that spreads through Anopheles mosquito.

For this study secondary data has been collected. From the website of Antimalarial drug and with the help of internet.

CLASSIFICATION OF ANTIMALARIAL DRUGS :

It can be classified as follows:

- A) **4-Aminoquinolines:** Chloroquine, Primaquine
- B) **Quinoline methanol:** Mefloquine .
- C) **Chinchona alkaloids:** Quinine, Quinidine.
- D) **8-Aminoquinoline:** Primaquine
- E) **Biguanides:** Proguanil
- F) **Napthoquinone:** Atovaquone
- G) **Sesquiterpine lactone:** Artemether, Artesunate.
- H) **Antibiotics:** Tetracycline, Doxycycline
- I) **Amino alcohol :** Halofantrine

ANTIMALARIAL THERAPY:

a) Causal prophylaxis:

-It destroys paracytes in liver cells and prevent the invasion of erythrocytes.

- Drug: Proguanil

Primaquine

b) Suppressive prophylaxis:

- It suppress the erythrocytic phase and thus attack of malarial fever can be used as prophylactics.

- Drug: Chloroquine, Primaquine, Proguanil, Mefloquine

c) Clinical cure: Erythrocytic schizonticides:

- To terminate the malarial fever episodes.

•Fast acting high efficacy:-

Chloroquine, mefloquine, Quinine, etc.

•Slow acting low efficacy:-

Proguanil, Tetracycline

d) Radical Curatives:

It eradicates the all forms of *P. vivax* and *P. ovale* from the body.

Suppressive drugs + hypnozoitocidals

eg: For *P. vivax*, Primaquine 15 mg daily.

e) Gametocidal:

It destroys the gametocyte and prevent transmission.

Drugs: Primaquine, artemisinin against all plasmodium.

Chloroquine, Quinine for *P. vivax*.

A) 4-Aminoquinoline:**Chloroquine:**

Is the Antimalarial drug which sold under brand 'Chloram'.

It has activity against the blood stages of *P. ovale*, *P. malariae* and susceptible strains of *P. vivax* and *P. falciparum*.

Widespread resistance to the most malaria countries and has remained its action against the *P. malariae*, *P. ovale* and some *P. vivax*.

Pharmacokinetics:

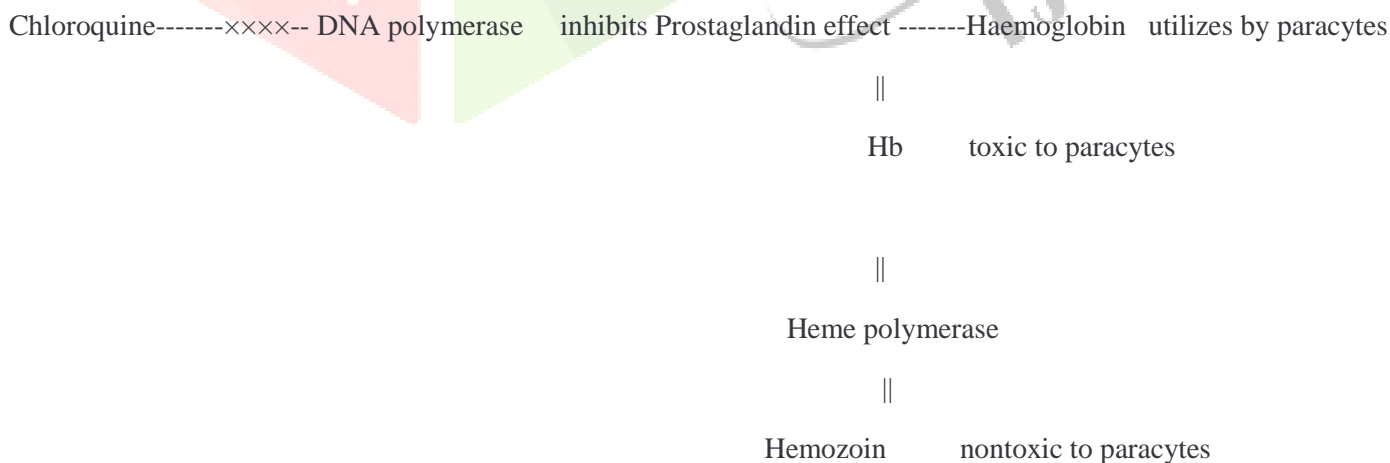
Route of administration	Oral
Bioavailability	52-107 %
Metabolism	Cyt. P450
Excretion	Kidney

Mechanism of action:

It binds and inhibits the DNA polymerase and ma of interfere with the metabolism and haemoglobin utilizes by paracytes and inhibits prostaglandin effect.

Paracytes digest human haemoglobin in order to get amino acid but from it Hb comes which is harmful to paracytes .

It converts to Hemozoin which is not harmful to malaria with the help of heme polymerase.

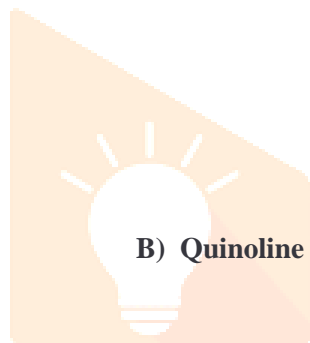


Uses:

- 1) Malaria
- 2) Lepra reaction
- 3) Rheumatoid arthritis
- 4) Extra intestinal amoebiasis.

Contraindications:

- 1) Porphyria crisis
- 2) Changes in retinal vision
- 3) Hypersensitivity to Chloroquine



Mefloquine was developed during Vietnam war and is chemically related to quinine . It was developed to protect e. American troops against multi-drug resistant *P. falciparum*. It is a very potent blood schizonticide with a long half-life.

Pharmacokinetics

Route of administration	Oral
Bioavailability	50-67 %
Metabolism	Liver
Excretion	Kidney

Mechanism of action:

Mefloquine-----××××-- DNA polymerase inhibits Prostaglandin effect -----Haemoglobin utilizes by paracytes

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Hb toxic to paracytes

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Heme polymerase

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Hemozoin nontoxic to paracytes

Uses :

- 1) To treat Malaria
- 2) To treat Fungal infections

Primaquine :

Taking High dose of it, causes haemolysis and haemolytic anemia in patients with G6PD deficiency. It is highly active 8-aminoquinolone that is effective against *P. falciparum* gametocytes but also acts on merozoites in the bloodstream and on hypnozoites, the dormant hepatic forms of *P. vivax* and *P. ovale*. [11] 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.

Uses :

- 1) Radical cure for acute *P. ovale* and *P. vivax* infection.
- 2) Termination of *P. vivax* and *P. ovale* infection.
- 3) Chemoprophylaxis of Malaria.
- 4) Gametocidal action
- 5) *Pneumocystis jirovecii* infection.

C) Chinchona alkaloids:

Quinine :

It is the Antimalarial drug which comes under Chinchona alkaloid category. It has activity against malarial paracytes in the inhibition of their lives. It was discovered in 1820 for malaria treatment.

Mechanism of action:

Quinine-----××××-- DNA polymerase inhibits Prostaglandin effect -----Haemoglobin utilizes by paracyte

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Hb toxic to paracytes

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Heme polymerase

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Hemozoin nontoxic to paracytes

Uses :

- 1) Malaria
- 2) Nocturnal leg cramps
- 3) Uncomplicated resistant falciparum Malaria.

Adverse effects:

- 1) Chinchonism
- 2) Nausea
- 3) Vomiting

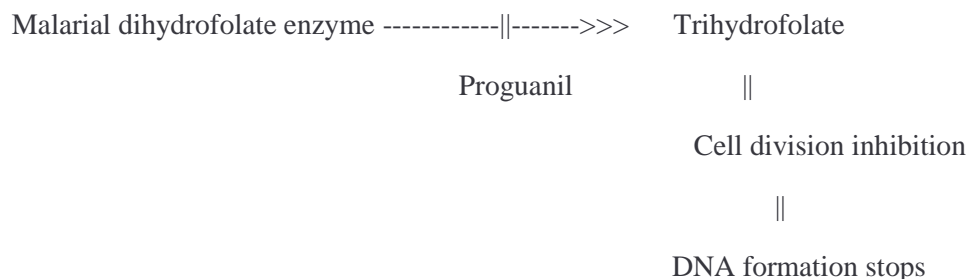
D] Biguanides:

Proguanil

It is the drug which is used as 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). 3 mg/kg is the advised dosage per day, (hence approximate adult dosage is 200 mg). The pharmacokinetic profile of the drugs indicates that a half dose, twice daily.

Mechanism of action:

Inhibition of malarial dihydrofolate reductase enzyme and disturbance of conversion to trihydrofolate and prevent cell division and DNA formation.

**Adverse effects:**

Slight hair loss and mouth ulcers being occasionally reported following prophylactic use.

E) Napthoquinone:**Atovaquone:**

It 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.

Primaquine : It is highly active 8-aminoquinolone that is effective against *P. falciparum* gametocytes but also acts on merozoites in the bloodstream and on hypnozoites, the dormant hepatic forms of *P. vivax* and *P. ovale*. 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.

For the prevention of relapse in *P. vivax* and *P. ovale* 0.15 mg/kg should be given for 14 days. As a gametocytocidal drug in *P. falciparum* infections a single dose of 0.75 mg/kg repeated seven days later is sufficient. This treatment method is only used in conjunction with another effective blood schizonticidal drug. There are few significant side effects although it has been shown that primaquine may cause anorexia, nausea, vomiting, cramps, chest weakness, anaemia, some suppression of myeloid activity and abdominal pains. In cases of over-dosage granulocytopenia may occur.

F) Sesquiterpine lactone:

Artemisinin:

It is a Chinese herb (qinghaosu) that has been used in the treatment of fevers for over 1,000 years. It is derived from the plant *Artemisia annua*, with the first documentation as a successful therapeutic agent in the treatment of malaria is in 340 AD by Ge Hong in his book *Zhou Hou Bei Ji Fang* (A Handbook of Prescriptions for Emergencies). Ge Hong extracted the artemisinin using a simple macerate, and this method is still in use today. The active compound was first isolated in 1971 and named artemisinin.

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 trophozoite 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. On the first day of treatment 20 mg/kg is often given, and the dose then reduced to 10 mg/kg per day for the six following days. Few side effects are associated with artemisinin use. However, headaches, nausea, vomiting, abnormal bleeding, dark urine, itching and some drug fever have been reported by a small number of patients. Some cardiac changes were reported during a clinical trial, notably non specific ST changes and a first degree atrioventricular block (these disappeared when the patients recovered from the malarial fever).

Artemether is a methyl ether derivative of dihydroartemesinin. It is similar to artemisinin in mode of action but demonstrates a reduced ability as a hypnozoitocidal compound, instead acting more significantly to decrease gametocyte carriage. Similar restrictions are in place, as with artemisinin, to prevent the development of resistance, therefore it is only used in combination therapy for severe acute cases of drug-resistant *P. falciparum*. It should be administered in a 7-day course with 4 mg/kg given per day for three days, followed by 1.6 mg/kg for three days. Side effects of the drug are few but include potential neurotoxicity developing if high doses are given.

Artesunate: is a hemisuccinate derivative of the active metabolite dihydroartemesinin. Currently it is the most frequently used of all the artemisinin-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*. The dosage recommended by the WHO is a five or seven day course (depending on the predicted adherence level) of 4 mg/kg for three days (usually given in combination with mefloquine) followed by 2 mg/kg for the remaining two or four days. In large studies carried out on over 10,000 patients in Thailand no adverse effects have been shown.

G) Amino alcohol:

Halofantrine:

It 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 that have severe and resistant forms of acute malaria.[citation needed] 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.

A dose of 8 mg/kg of halofantrine is advised to be given in three doses at six-hour intervals for the duration of the clinical episode. It is not recommended for children under 10 kg despite data supporting the use and demonstrating that it is well tolerated. The most frequently experienced side-effects include nausea, abdominal pain, diarrhea, and itch. Severe ventricular dysrhythmias, occasionally causing death are seen when high doses are administered. This is due to prolongation of the QTc interval. Halofantrine is not recommended for use in pregnancy and lactation, in small children, or in patients that have taken mefloquine previously.

H) Antibiotics:

Doxycycline :

It 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.

When treating acute cases and given in combination with quinine; 100 mg of doxycycline should be given per day for seven days. In prophylactic therapy, 100 mg (adult dose) of doxycycline should be given every day during exposure to malaria.

The most commonly experienced side effects are permanent enamel hypoplasia (although this is only relevant during the period of tooth development during the first decade of life), transient depression of bone growth, gastrointestinal disturbances and some increased levels of photosensitivity. Due to its effect of bone and tooth growth it is not used in children under 8, pregnant or lactating women and those with a known hepatic dysfunction.

Tetracycline :

Only used in combination for the treatment of acute cases of *P. falciparum* infections. This is due to its slow onset. Unlike doxycycline it is not used in chemoprophylaxis. For tetracycline, 250 mg is the recommended adult dosage (it should not be used in children) for five or seven days depending on the level of adherence and compliance expected. Oesophageal ulceration, gastrointestinal upset and interferences with the process of ossification and depression of bone growth are known to occur. The majority of side effects associated with doxycycline are also experienced.

Clindamycin

It should be given in conjunction with quinine as a 300 mg dose (in adults) four times a day for five days. The only side effects recorded in patients taking clindamycin are nausea, vomiting and abdominal pains and cramps. However these can be alleviated by consuming large quantities of water and food when taking the drug. Pseudomembranous colitis (caused by *Clostridium difficile*) has also developed in some patients; this condition may be fatal in a small number of cases.

Combination therapy:

Problem of the development of malaria resistance must be weighed against the essential goal of anti-malarial care; that is to reduce morbidity and mortality. Thus a balance must be reached that attempts to achieve both goals while not compromising either too much by doing so. The most successful attempts so far have been in the administration of combination therapy. This can be defined as, 'the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite'. There is much evidence to support the use of combination therapies, some of which has been discussed previously, however several problems prevent the wide use in the areas where its use is most advisable. These include: problems identifying the most suitable drug for different epidemiological situations, the expense of combined therapy (it is over 10 times more expensive than traditional mono-therapy), how soon the programmes should be introduced and problems linked with policy implementation and issues of compliance.

The combinations of drugs currently prescribed can be divided into two categories: non-artemesinin-based combinations and artemesinin based combinations. It is also important to distinguish fixed-dose combination therapies (in which two or more drugs are co-formulated into a single tablet) from combinations achieved by taking two separate antimalarials.

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