



DIVERSIFICATION IN MALARIA CHEMOTHERAPY: A REVIEW ARTICLE

Chemistry

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ABSTRACT

Malaria is commonly associated with poverty; it is also cause of poverty and a major hindrance to economic development. *P. falciparum* is responsible for most of the deaths, and it has developed resistance to nearly all available drugs. In this article we will discuss diversified drugs which have been used to cure malaria disease and will discuss antimalarial drug resistance and its possible cause.

KEYWORDS

malaria, drugs, parasite, drug resistance.

INTRODUCTION

Malaria is a complex disease that varies widely in epidemiology and clinical manifestation in different parts of the world. This variability is because of factors such as the species of malaria parasites that occur in each area, their susceptibility to commonly used or available antimalarial drugs, the distribution and efficiency of mosquito vectors, climate and other environmental conditions and the behavior and level of acquired immunity of the exposed human populations. Young children, pregnant women, and non-immune visitors to malaria infected areas are at greatest risk of severe or fatal illness¹. Malaria is commonly associated with poverty; it is also cause of poverty and a major hindrance to economic development. The female anopheles' mosquito is the carrier of malaria protozoans. In humans, malaria infection is caused by four species of intracellular protozoan parasites *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae* which differ in geographical distribution². *P. falciparum* is the most deadly species. Life cycle of *P. falciparum* is completed in two hosts: i) female anopheles' mosquito and ii) Humans³.

Symptoms of Malaria

Malarial symptoms include fever and flu-like illness including shaking chills, headache, muscle aches and tiredness. Nausea, vomiting and diarrhoea may also occur. Malaria may cause anemia and jaundice (yellow coloring of the skin and eyes) because of the loss of red blood cells. Infection caused by parasite *P. falciparum*, if not promptly treated, may cause kidney failure, seizures, mental confusion, coma and death.

Chemotherapy of Malaria

Many drugs are available in market to cure malaria. Mainly two types of antimalarial drugs are identified, i) Prophylactic drugs and ii) Therapeutic drugs.

Prophylactic Drugs: These drugs are preventive and require continuous administration to reduce the disease. The commonly present prophylactic antimalarial drugs in market are Quinine, Chloroquine, Amodiaquine, Pyrimethamine, Sulphadoxime, Proguanil, Mefloquine, Atovaquone, Primaquine, Artesiminine and its derivatives.

Therapeutic Drugs: These drugs taken once the person is already infected e.g. Halofantane, Doxycycline and Clindamycine.

The most widely used are quinine and its derivatives and antifolate combination drugs.

Major Families of Antimalarial Drugs

Quinine and Related Drug

Quinine, along with its dextroisomer quinidine⁴ has been used for treatment of malaria, especially severe one. Chloroquine is a 4-aminoquinoline derivative of quinine, first synthesized in 1934 and has since been most widely used for the treatment of non-severe or uncomplicated malaria, although drug resistance has dramatically reduced its usefulness^{5,6}. Amodiaquine, Primaquine, Mepacrine and Mefloquine⁷ (a quinoline methanol derivative of quinine) are other chloroquine related compound used to cure malaria (given in figure 1). Primaquine is specifically used for eliminating the exoerythrocytic forms of *P. vivax* and *P. ovale* that cause re-lapses. Stages of plasmodium life cycle when antimalarial drugs act are given in figure-5.

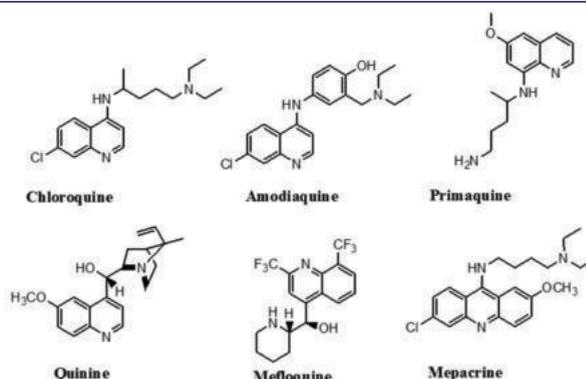


Figure 1: Quinine and Related Drugs

Antifolate Combination Drugs

Antifolate combination drugs are various combinations of dihydrofolate reductase (DHFR) inhibitors⁸ given in figure 2 like Proguanil, Chlorproguanil, Pyrimethamine, Trimethoprim; and dihydropteroate synthase (DHPS) inhibitors⁹ sulfa drugs as Dapsone, Sulfadoxine and others (given in figure 3). In *P. falciparum*, DHFR is one domain of a bifunctional protein that also contains thymidylate synthase (TS). DHFR is a key enzyme in the redox cycle for the production of tetrahydrofolate, a cofactor that is required for the transfer of C1 units used in the biosynthesis of DNA and protein¹⁰. When these drugs were used alone, they developed parasitological resistance faster. Further, if drug were used in combination, they produce a synergistic effect on the parasite and can be effective even in the presence of resistance to the individual components. Typical combinations include Sulfadoxine / Pyrimethamine (SP or Fansidar1), Sulfalene Pyrimethamine (Metakelfin) and sulfamethoxazole-trimethoprim (co-trimoxazole). A new antifolate combination drug is currently being tested in Africa. This drug, a combination of chlorproguanil and dapsone, also known as Lap-Dap, has a much more potent synergistic effect on malaria than existing drugs such as SP. Benefits of this combination include i) a greater cure rate even in areas currently experiencing some level of SP resistance, ii) a lower likelihood of resistance developing because of a more advantageous pharmacokinetic and pharmacodynamic profile, and iii) probable low cost¹¹.

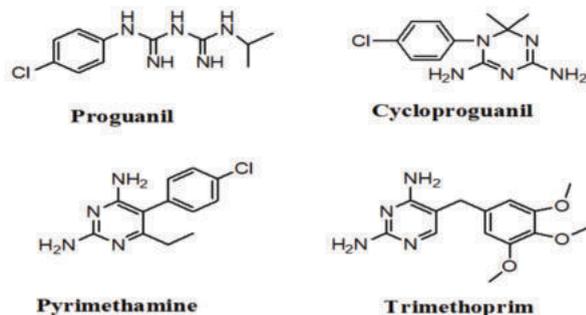


Figure 2: DHFR Inhibitors

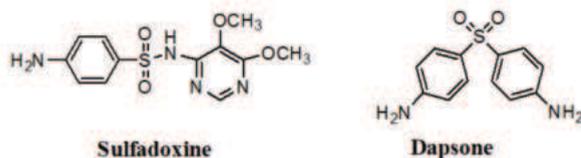


Figure 3: DHPS Inhibitors

Antibiotics

Various classes of antibiotics also exhibit antimalarial activity. Sulphonamide and sulphones have shown antimalarial activity. They are very effective usually in combination with Pyrimethine, Tetracycline, Rifampin, Clindamycin, Erythromycin and Chloramphenicol showing antimalarial activity in vivo either alone or in combination with other commonly used antimalarial drugs¹²⁻¹⁵. Tetracycline and derivatives such as Doxycycline are very potent antimalarials (figure 4) and are used for both treatment and prophylaxis¹⁶. In areas where response to quinine has deteriorated, tetracyclines are often used in combination with quinine to improve cure rates. Clindamycin has been used but offers only limited advantage as compared to other available antimalarial drugs. Parasitological response is slow to clindamycin and recrudescence rates are high^{17,18}. Its efficacy among non-immune individuals has not been fully established.

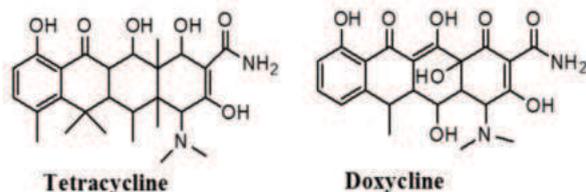


Figure 4: Antibiotics Which are Used as Antimalarial Drugs

Endoperoxides

Artemisinin, the first natural example which showed antimalarial activity is extracted from plant *artemisia annua*. In China, artemisinin has been used since ancient times to treat malaria. It is a heterocyclic natural product and belongs to sesquiterpenoids with an unusual 1,2,4-trioxane substructure.

In some areas of South-East Asia, combinations of artemisinin and mefloquine offer the only reliable treatment for even uncomplicated malaria, due to the development and prevalence of multidrug resistant falciparum malaria¹⁹. Combination therapy (an artemisinin compound given in combination with another antimalarial, typically a long half-life drug like mefloquine) has shown inhibition of drug resistance and for decreased malaria transmission levels in South-East Asia^{20,21}. Artemisinin has a limited availability with high cost and poor bioavailability. Its semi-synthetic derivatives such as artesunate and artemether show poor pharmacokinetic properties.

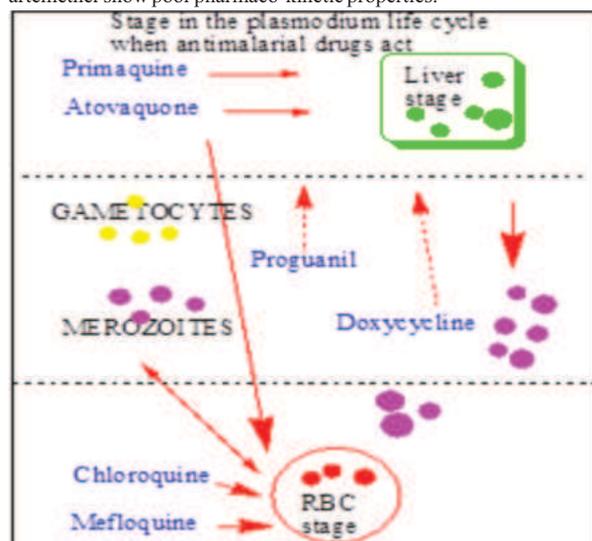


Figure 5: Stages In The Plasmodium Life Cycle When Antimalarial Drugs Act

Miscellaneous Compounds

Halofantrine, Atovaquone and Lumefantrine given in figure 6 are other drugs used for cure of malaria. Halofantrine is a phenanthrene-methanol showing activity against the erythrocytic stage of malarial parasite. Atovaquone is a hydroxyl naphthoquinone currently being used in combination with proguanil^{22,23}. Lumefantrine a Benflumetol compound, is being used as a fixed combination tablet with artemether^{24,25}.

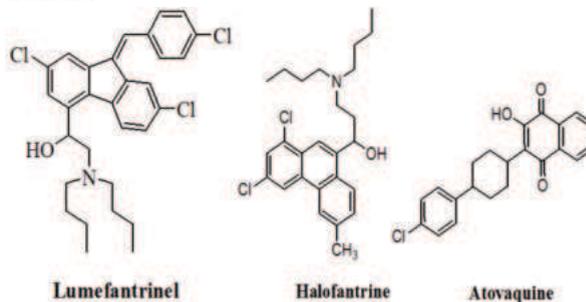


Figure 6: Miscellaneous Compounds

Antimalarial Drug Resistance

Antimalarial drug resistance has been defined as the 'ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject'²⁶. In general, resistance appears to occur through spontaneous mutations that confer reduced sensitivity to a given drug. For some drugs, only a single point mutation is required to confer resistance, while for other drugs, multiple mutations appear to be required. Antimalarial drug resistance is a major public health problem which hinders the control of malaria. Two of the four species of malarial parasite that naturally infect humans are *P. falciparum* and *P. vivax*. *P. falciparum* has developed resistance to nearly all antimalarials currently in use.

Chloroquine Resistance

As we know malaria parasite digest hemoglobin and large amount of toxic by-products are formed. The parasite polymerizes this by product in food vacuole, producing non-toxic hemozoin. It is proposed that resistant of *P. falciparum* is developed due to an increased capacity of the parasite to expel chloroquine, so the chloroquine does not reach at the level required to inhibit hemozoin formation. It is thought that parasite resistance for all quinolone antimalarial occurs via same mechanism, but it is not clear²⁷⁻²⁹. The drug resistance against the antifolates have also been reported due to specific gene mutations encoding for resistance to both dihydropteroate synthase (DHPS) and dihydrofolate (DHFR).

CONCLUSION

At present, many prophylactic and therapeutic drugs are used to cure malaria. Major families of antimalarial drugs are Quinine & related drugs, Antifolate combination drugs, antibiotics and endoperoxides like artemisinin. But *P. falciparum* has developed resistance to nearly all antimalarials currently in use. So, this study will open new window for researchers to develop new libraries of compounds to find more potent drugs to cure malaria that should be cost effective.

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