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ANTIMALARIAL DRUGS: A REVIEW

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ABSTRACT

Malaria causes about 400-900 million cases of fever and approximately 1-3 million deaths annually; this represents at least one death every 30 seconds. The vast majority of cases occur in children under the age of 5 years, pregnant women are also especially vulnerable. Resistance to antimalarial drugs as well as resistance of vectors to insecticides is proving to be a challenging problem in malaria control in most parts of the world. Furthermore, the difficulty of creating efficient vaccines and also adverse side-effects of the existing anti-malarial drugs highlight the urgent need for novel, well-tolerated antimalarial drugs for both prophylaxis and treatment of malaria, therefore researchers had discovered other antimalarial agents, mainly from plant sources. In this article, we would like to address current status of recent advances in malaria chemotherapy.

Keywords: Malaria, *Plasmodium falciparum*, Resistance, Current antimalarial drugs

INTRODUCTION

Malaria is a vector borne infectious disease caused by protozoan parasites of the genus *Plasmodium*.[1] The disease is widespread in tropical and subtropical regions, including parts of the Americas, Asia and Africa.[2] Ma**l**aria has infected humans for over 50,000 years and *Plasmodium* may have been a human pathogen for the entire history of man. Also, a close relative of the human malaria parasites infects the chimpanzees. [3]

Malaria is not just a disease commonly associated with poverty, but is also a cause of poverty and a major hindrance to economic development. The economic impact of malaria has been estimated to cost Africa $12 billion every year. The economic impact includes costs of health care, working days lost due to sickness, days lost in education. [4]

Since drug resistance had become a major problem with the emergence of resistance of *P. falciparum* to nearly all used antimalarial drugs. [5] Increased prevalence of multi drug resistant strains of *P. falciparum* continue to reduce the effectiveness of currently available antimalarial drugs .While we wait for malaria vaccine, effective chemotherapy remains the mainstay of malaria control. [6] The cost of effectiveness of chemotherapy constitutes the greatest threat to the control of malaria, therefore, to overcome malaria, new knowledge is needed, especially new drugs are required. [7]

Plants from different botanical sources have been used by various traditional medical practitioners (TMPs) for the treatment and cure of malaria. [8] Both quinine and artemisinin have been derived from traditional medicine and plant extracts. Artemisinin derivatives are now recommended by the World Health Organization worldwide, in combination with other drugs, such as lumefantrine, amodiaquine, mefloquine, sulphadoxine-pyrimethamine (SP), as the first-line treatment of malaria. [9]This article gives overview of recent advances in malaria chemotherapy.

TREATMENT OF MALARIA

Treatment of malaria depends on many factors including disease severity, the species of malaria

parasite causing the infection and the part of the world in which the infection was acquired. The latter two characteristics help determine the probability that the organism is resistant to certain antimalarial drugs. Additional factors such as age, weight, and pregnancy status may limit the available options for malaria treatment. [9]

Antimalarial Drugs

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 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.

Use of quinine is characterized by a frequently experienced syndrome called cinchonism. Tinnitus (a hearing impairment), rashes, vertigo, nausea, vomiting and abdominal pain are the most common symptoms. Neurological effects are experienced in some cases due to the drug's neurotoxin properties. These actions are mediated through the interactions of quinine causing a decrease in the excitability of the motor neuron end plates. This often results in functional impairment. [10]

Other alkaloids: Quinimax and quinidine are the two most commonly used alkaloids related to quinine, in the treatment or prevention of malaria. Quinimax is a combination of four alkaloids (quinine, quinidine, cinchonine and cinchonidine). This combination has been shown in several studies to be more effective than quinine, supposedly due to a synergistic action between the four cinchona derivatives. Quinidine is a direct derivative of quinine; it is a distereoisomer, thus having similar antimalarial properties to the parent compound. Quinidine is recommended only for the treatment of severe cases of malaria. [11]

Chloroquine: Chloroquine was until recently the most widely used antimalarial. It was the original prototype from which most other methods of treatment are derived. No abortifacient or teratogenic effects have been reported during this time, therefore it is considered very safe during pregnancy. However, itching can occur at intolerable level. [12]

Amodiaquine: Amodiaquine is most frequently used in combination with chloroquine, but is also very effective when used alone. It is thought to be more effective in clearing parasites in uncomplicated malaria than chloroquine, thus leading to a faster rate of recovery. However, some fatal adverse effects of the drug were noted during the 1980s, thus reducing its usage in chemoprophylaxis. The WHO' s most recent advice on the subject still maintains that the drug should be used when the potential risk of not treating an infection outweighs the risk of developing side effects. It has been suggested that it is particularly effective, and less toxic than other combination treatments in HIV positive patients. [13]

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 sulphadoxine. [14]

Sulphadoxine: Sulphadoxine usage is restricted due to the long half life of the combination which exerts a potentially large selection pressure on the parasite thereby encouraging the possibility of resistance developing. This combination is not recommended for chemoprophylaxis because of the severe skin reactions commonly experienced. However it is used frequently for clinical episodes of the disease. [15]

Proguanil: Proguanil when combined with atovaquone, has been shown to be effective against resistant strains of *P. falciparum.* It is used as a prophylactic treatment in combination with another drug, most frequently chloroquine. 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. It should be noted that 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. [16]

Mefloquine: Mefloquine is now solely used for the prevention of resistant strains of *P. falciparum* despite being effective against *P. vivax*, *P. ovale*, and *P. malariae*. Mefloquine is effective in prophylaxis and for acute therapy. It is now strictly used for resistant strains (and is usually combined with artesunate). Chloroquine/Proguanil or sulfadrug pyrimthamine combinations should be used in all other *plasmodia* infection. In young children it

induces vomiting and oesophagitis. The effects during pregnancy are unknown, although it has been linked with an increased number of stillbirths. It is not recommended for use during the first trimester, although considered safe during the second and third trimesters. [17] Mefloquine frequently produces side effects, including nausea, vomiting, diarrhea, abdominal pain and dizziness. Several associations with neurological events have been made, namely affective and anxiety disorders, hallucination, sleep disturbances, psychosis, toxic encephalopathy, convulsions and delirium. Cardiovascular effects have been recorded with bradycardia and sinus arrhythmia being consistently recorded in 68% of patients treated with mefloquine . [18]

Halofantrine: 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 cardio toxicity. 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 malaria; the side effects include nausea, abdominal pain, diarrhea, and itching. Severe ventricular dysrhythmias, occasionally causing death are seen when high doses are administered. This is due to prolongation of the correction of Q wave and T wave interval (QTc interval). Halofantrine is not recommended for use in pregnancy and lactation, in small children, or in patients that have taken mefloquine previously. Lumefantrine is a relative of halofantrine that is used in some combination antimalarial regimens. [19]

Primaquine: Primaquine is the only known drug to cure both relapsing malaria infections and acute cases. There are few significant side effects although it has been shown that primaquine may cause anorexia, nausea, vomiting, cramps, chest weakness, anemia, some suppression of myeloid activity and abdominal pains. In cases of overdosage, granulocytopenia may occur. [20]

Artemesinin and derivatives: Artemesinin is a Chinese herb (Qinghaosu) that has been used in the treatment of fevers for over 1,000 years, thus predating the use of quinine in the western world. It is derived from the plant *Artemisia annua*, with the first documentation as a successful therapeutic agent in the treatment of malaria. 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 then thought to be responsible for the majority of its antimalarial action. It is also only given in combination with other antimalarials. [21]

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 antimalarial currently used and acts primarily on the trophozite phase, thereby preventing progression of the disease. Few side effects are associated with artemisinin use. However, headache, 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 clinical trials, notably non specific ST changes and a first degree atrioventricular block (these disappeared when the patients recovered from the malaria fever) . [22]

Artemether: Artemether is a methyl ether derivative of dihydroartemisinin. It is similar to artemisinin 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 artemisinin, to prevent the development of resistance. Therefore it is only used in combination therapy for severe acute cases of drug resistant *P. falciparum*. Side effects of the drug are few but include potential neurotoxicity developing if high doses are given. [23]

Artesunate: Artesunate is a hemisuccinate derivative of the active metabolite dihydroartemisinin. 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*. In large studies carried out on over 10,000 patients in Thailand no adverse effects have been shown. [24]

Dihydroartemisinin: Dihydroartemisinin is the active metabolite to which artemisinin is reduced. It inhibits the sarcoplasmic/ endoplasmic reticulum calcium ATPase encoded by *P. falciparum*. This is the most effective artemisinin 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. [23]

Arteether: Arteether is an ethyl ether derivative of dihydroartemisinin. It is used in combination therapy for cases of uncomplicated resistant *P.falciparum*. With the exception of a small number of cases demonstrating neurotoxicity following parenteral administration no side effects have been recorded. [25]

Doxycycline: Doxycycline is a tetracycline compound derived from oxytetracycline. The tetracycline's 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 resistance exists. It can be used in resistant cases of uncomplicated *P.falciparum* but has a very slow action in acute malaria; therefore it should never be used in monotherapy. When treating acute cases and given in combination with quinine; 100mg/ kg of doxycycline should be given per day for 7days. In prophylactic therapy, 100mg (adult dose) of doxycycline should be given every day during exposure to malaria. The most commonly experienced side effects are permanent enamel hyperplasia, transient depression of bone growth, gastrointestinal disturbances and some increased levels of photosensitivity. Due to its effect on bone and tooth growth it is not used in children under 8, pregnant or lactating women and those with a known hepatic dysfunction. [26]

Tetracycline: Tetracycline is 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, 250mg is the recommended adult dosage (it should not be used in children) for 5or 7 days depending on the level of adherence and compliance expected. Esophageal 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. [26]

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 expensive and toxic than the other antibiotic alternatives, it is used only in cases where the tetracyclines are contraindicated (for example in children). Clindamycin should be given in conjunction with quinine as a 300mg dose (in adults) four times a day for 5days. 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. Pseudo membranous colitis (caused by *Clostridium difficile*) has also developed in some patients; this condition may be fatal in a small number of cases. [27]

RECENT ADVANCES IN MALARIA CHEMOTHERAPY

WHO currently advocates two major therapeutic options:

1. Combination therapy (CT): CT is the simultaneous use of 2 or more blood scizonticidal antimalarial drugs with independent modes of action and different biochemical targets in the parasite. Multiple drug therapies that include a non-antimalarial drug to enhance the antimalarial effect of a blood schizonticidal drug are considered combination therapy. Similarly, certain antimalarial drugs that fit the criteria of synergistic fixed dose combinations are operationally considered as single products in that neither of the individual component would be given alone for antimalarial therapy e.g. sulfadoxine – pyrimethamine, chlorproguanil-dapsone, atovaquine-proguanil; use of blood schizonticidal with a tissue schizonticidal or gametocidal drug e. g. chloroquine + primaquine is not considered to be a combination therapy. [28]

2. ACT- Artemisinin – based combination therapy. ACT is antimalarial combination therapy with artemisinin derivative as one component of the combination. Combination therapy can be fixed combination medicinal products in which the components are co-administered in separate tablet or capsule e. g. Artequine^{R} (artesunate and mefloquine). The fixed combination is preferred because of it is easier to use and so encourages better compliance and minimizes the potential use of components of the combination as therapy. [29] Artemisinin derivatives have very short half-lives and so their use as monotherapy requires doses over a period of 7 days. Combination of one of these drugs with a longer half- life partner antimalarial drug allows a reduction in the duration of antimalarial treatment while at the same time enhancing efficacy and reducing the likelihood of resistance development. [29]

ANTIMALARIAL THERAPY COMBINATION DRUGS CURRENTLY IN USE

i. Chloroquine (CQ) plus sulfadoxine pyrimethamine (SP). Studies which compared the efficacy and safety of CQ + SP to that of SP alone show that the efficacy and safety of the combination is dependent on the levels of resistance to the individual component. Overall the available evidence has shown that the CQ + SP combination is unlikely to have a significant advantage over SP alone in areas of predominant *P. falciparum* transmission with high levels of resistance to CQ. Since this reflects the current situation in most sub-Saharan Africa, a change to the combination as a first –line treatment policy is unlikely to give significant useful long-term advantage. [9]

ii. Amodiaguine (AQ) plus sulfadoxine-pyrimethamine (SP). In some countries in west and central Africa where levels of resistance to AQ are generally less that those to CQ, a change to AQ + SP would probably be a more cost effective option with a longer useful therapeutic life than a change to monotherapy with SP. However there are still some concerns over the safety of AQ for widespread unsupervised repeated treatment of malaria. More data on safety including its use in pregnancy in required. [30]

iii. Atovaquone-proguanil (malarone Glaxowellcome)

The use of malarone in children with severe anaemia in whom oral medication is possible is currently being investigated. Malarone co-administered with artesunate has also been evaluated. The safety and efficacy of malarone in the management of malaria during pregnancy is being researched by WHO. Current contraindication includes hypersensitivity to atovaguone or proguanil or presence of renal insufficiency. Its use is not recommended in young children with a body weight of less than 11 kg, in pregnant women and in breast-feeding women. [30]

iv. Mefloguine- sulfadoxne pyrimethamine (MSP) (fansimef, Roche).

MSP has not been recommended for general use by malaria control programmes for either prophylaxis or treatment since 1990 because of concern about the risk of severe reactions to the combination. [31]

v. Quinine plus tetracycline or doxycycline. Co – administration of quinine plus tetracycline has been employed in the treatment of uncomplicated *falciparum* malaria since 1970. However there is practical constraint with the combined treatment of quinine and tetracycline, which has to do with patient adherence and safety. Patient adherence is strongly influenced by adverse reactions to quinine and the cumbersome nature of the drug regime that requires eight – hourly doses of quinine for three to seven days and the six hourly doses of tetracycline for 7 days (in total 37 – 49 drug doses). The regimen can be simplified by the once daily use of doxycycline instead of tetracycline. The tetracycline and doxycycline are contra-indicated in pregnant women, breast-feeding women and children less than eight years old. It is therefore difficult to recommend quinine plus tetracycline as a first line treatment for uncomplicated malaria. However quinine +doxycycline (preferably) could be considered as an option for treating patients who have failed to respond to first line and/second-line treatment and are still able to take oral medication. [31]

vi. Research conducted by Ohrt *et al* [32] suggested that Chloroquine-Azithromycin combination should be evaluated for malaria prophylaxis and that a quinine-azithromycin combination should be evaluated for malaria treatment in areas of drug resistance.

vii. Verapamil, a Ca^{2+} channel blocker, has been found to restore both the chloroquine concentration ability as well as sensitivity to this drug. It has been shown that verapamil, when used in combination with chloroquine, enhances the accumulation of chloroquine within a parasitic cell's digestive vacuole, rendering it incapable of detoxifying itself and making it more susceptible to death. [33]

Viii. Propranolol along with a number of other membrane-acting drugs has been investigated for possible effects on *Plasmodium falciparum* and so the treatment of malaria. *In vitro* positive effects until recently had not been matched by useful *in vivo* anti-parasite activity against *P. vinckei*, or *P. yoelii nigeriensis*. However, a single study from 2006 has suggested that propranolol may reduce the dosages required for existing drugs to be effective against *P. falciparum* by 5- to 10-fold, suggesting a role for combination therapies. [34]

ix. Zinc –Quinine complex and Gold complex had been reported to possess *in vitro* antiplasmodial activity against malaria parasite *Plasmodium falciparum*. [35]

x. Artesunate + chloroquine. Efficiency and safety of the combination of artesunate + chloroquine had been evaluated. The combination was well tolerated with untoward adverse reactions. However, results showed very high chloroquine

failure vaules (>60%). Artesunate + CQ do not appear to be a viable option in areas with existing moderate to high levels of *P. falciparum* resistance to CQ. [36]

xi. Artesunate + sulfadoxine – pyrimethamine (SP). The increasing level of resistance to SP will limit the use of artesunate + SP, particularly in the eastern parts of Africa. However, it may still be a viable option for some countries of West Africa. Combination with less than 85% parasitological cure rate on the day fourteenth day. Based on this and other areas where SP efficacy is not yet compromised by resistance. [31]

xii. Artesunate + mefloquine. The combination of artesunate plus mefloquine is not considered a viable option for use as first-line therapy in Africa. There is concern that the long half-life of mefloquine may lead to the selection of resistant parasites in areas of intense transmission. Furthermore, there are also concerns of possible increase of mefloquine related adverse reactions when used unsupervised on a large scale for treatment of malaria. [32]

xiii. Artemeter – Lumefantrine (coartem, Raimet, norvartis).
This is a co-formulation of artemeter and lumefantrine (an aryl alcohol to quinine, mefloquine and halofantrine). This combination has proved as effective and better tolerated as artesunate + mefloquine in the treatment of multi-drug resistant *P. falciparum* when given as a single dose over three days. There are yet no serious adverse reactions documented and studies show no indication of cardiotoxicity. Artemeter – lumefantrine is the cost viable artemisinin combination treatment available at the moment (although it is not recommended for pregnant women and breast feeding mothers), because in addition to its efficacy, safety, and tolerance profile, it is available as a fixed dose formulation increasing the likelihood of patient compliance with the drug regime. [32]

CONCLUSION

One of the cornerstones of the current approach to malaria control is the provision of prompt, effective malaria treatment. Access to antimalarial drugs must be improved for those who need to be treated while at the same time reducing the inappropriate use of those same drugs. Interventions to improve the way drugs are used through improving prescribing, follow-up practices, and patient compliance; or using drugs or drug combinations will go a long way to prevent resistance or have properties that do not facilitate development or spread of resistant parasites.

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