Chemical and Biochemical History of Antimalarials: A Podium of Plasmodium Unicellular Unit

Viraj P. Jatakiya*, Nadim M. R. Chhipa and Dhrubo Jyoti Sen

Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India

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ABSTRACT
Malaria is a potentially life-threatening disease caused by infection with Plasmodium protozoa transmitted by an infective female Anopheles mosquito. Plasmodium falciparum infection carries a poor prognosis with a high mortality if untreated, but it has an excellent prognosis if diagnosed early and treated appropriately. Five species of Plasmodium can infect and be transmitted by humans. The vast majority of deaths are caused by P. falciparum and P. vivax, while P. ovale and P. malariae cause a generally milder form of malaria that is rarely fatal. Clinical symptoms include the following: Headache, Cough, Fatigue, Malaise, Shaking chills, Arthralgia, Myalgia, Paroxysm of fever, shaking chills, and sweats. Malaria is prevalent in tropical and subtropical regions because rainfall, warm temperatures, and stagnant waters provide habitats ideal for mosquito larvae. Disease transmission can be reduced by preventing mosquito bites by using mosquito nets and insect repellents, or with mosquito-control measures such as spraying insecticides and draining standing water. The mainstay of malaria diagnosis has been the microscopic examination of blood, utilizing blood films. Although blood is the sample most frequently used to make a diagnosis, both saliva and urine have been investigated as alternative, less invasive specimens. More recently, modern techniques utilizing antigen tests or polymerase chain reaction have been discovered, though these are not widely implemented in malaria endemic regions. Areas that cannot afford laboratory diagnostic tests often use only a history of subjective fever as the indication to treat for malaria. Medications that can be used for the treatment of malaria include the following: Chloroquine, Quinine, Atovaquone-proguanil, Clindamycin, Mefloquine, Sulfadoxine-pyrimethamine, Artemether-lumefantrine, Artesunate and other antimalarials.

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Introduction

Facts of Malaria

Malaria remains an important public health concern in countries where transmission occurs regularly, as well as in areas where transmission has been largely controlled or eliminated. Malaria is a complex disease that varies widely in epidemiology and clinical manifestation in different parts of the world. Particular, young children, pregnant women and non-immune visitors to malarious areas are at greatest risk of severe or fatal illness. Many malaria control strategies exist, but none are appropriate and affordable in all contexts.

Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control today. Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated.

Drug resistance has also played a significant role in the occurrence and severity of epidemics in some parts of the world. Population movement has introduced resistant parasites to areas previously free of drug resistance.

The economics of developing new pharmaceuticals for tropical diseases, including malaria, are such that there is a great disparity between the public health importance of the disease and the amount of resources invested in developing new cures.

Disease incidence and trends

Geographical distribution and populations at risk

Malaria occurs in over 90 countries worldwide. According to figures provided by the World Health Organization, 36% of the global population live in areas where there is risk of malaria transmission, 7% reside in areas where malaria has never been under meaningful control, and 29% live in areas where malaria was once transmitted at low levels or not at all, but where significant transmission has been re-established. The development and spread of drug-resistant strains of malaria parasites has been identified as a key factor in this resurgence and is one of the greatest challenges to malaria control today.

Although there is currently an increase in attention and resources aimed at malaria, including such initiatives as Roll Back Malaria, the Multilateral Initiative on Malaria and the Medicines for Malaria Venture a history of unpredictable support for malaria related research and control activities in endemic countries have left many of these countries with little technical capacity for malaria control activities. Each year an estimated 300 to 500 million clinical cases of malaria occur, making it one of the most common infectious diseases worldwide. Malaria can be, in certain epidemiological circumstances, a devastating disease with high morbidity and mortality, demanding a rapid, comprehensive response.

In other settings, it can be a more pernicious public health threat. In many malicious are as of the world, especially sub-Saharan Africa, malaria is ranked among the most frequent causes of morbidity and mortality among children and is often the leading identifiable cause. WHO estimates that more than 90% of the 1.5 to 2.0 million deaths attributed to malaria each year occur in African children. Other estimates based on a more rigorous attempt to calculate the burden of disease in Africa support this level of mortality. In addition to its burden in terms of morbidity and mortality, the economic effects of malaria infection can be tremendous. These include direct costs for treatment and prevention, as well as indirect costs such as lost productivity from morbidity and mortality;
time spent seeking treatment and diversion of household resources. The annual economic burden of malaria infection in 1995 was estimated at US$ 8 billion, for Africa alone. This heavy toll can hinder economic and community development activities throughout the region.\(^4\)

Malaria transmission occurs primarily in tropical and subtropical regions in sub-Saharan Africa, Central and South America, the Caribbean island of Hispaniola, the Middle East, the Indian subcontinent, South-East Asia, and Oceania (Figure-1). In areas where malaria occurs, however, there is considerable variation in the intensity of transmission and risk of malaria infection. Highland (>1500 m) and arid areas (<1000 mm rainfall/year) typically have less malaria, although they are also prone to epidemic malaria when parasitaemic individuals provide a source of infection and climate conditions are favorable to mosquito development. Although urban areas have typically been at lower risk, explosive, unplanned population growth has counted.\(^5\)

Causative agents

In humans, malaria infection is caused by one or more of four species of intracellular protozoan parasite. \(P.\) \textit{falciparum}, \(P.\) \textit{vivax}, \(P.\) \textit{ovale} and \(P.\) \textit{malariae} differ in geographical distribution, microscopic appearance, clinical features (periodicity of infection, potential for severe disease, and ability to cause relapses) and potential for development of resistance to antimalarial drugs. To date, drug resistance has only been documented in two of the four species, \(P.\) \textit{falciparum} and \(P.\) \textit{vivax}.

Biology of malaria infection\(^6\)

Nearly all human malaria is caused by four species of obligate intracellular protozoa of the genus \textit{Plasmodium}. Although malaria can be transmitted by transfusion of infected blood, congenitally, and by sharing needles, infection usually is transmitted by the bite of infected female \textit{Anopheles} mosquitoes. Sporozoites from the mosquito salivary glands rapidly enter the circulation after a bite and localize via specific recognition events in hepatocytes, where they transform, multiply, and develop into tissue schizonts. This primary asymptomatic tissue (pre-erythrocytic or exo-erythrocytic) stage of infection lasts for 5 to 15 days, depending on the \textit{Plasmodium} species. Tissue schizonts then rupture each releasing thousands of merozoites that enter the circulation, invade erythrocytes, and initiate the erythrocytic cycle. Once the tissue schizonts burst in \(P.\) \textit{falciparum} and \(P.\) \textit{malariae} infections, no forms of the parasite remain in the liver. However, in \(P.\) \textit{vivax} and \(P.\) \textit{ovale} infections, tissue parasites (hypnozoites) persist that can produce relapses of erythrocytic infection months to years after the primary attack. Once plasmodia enter the erythrocytic cycle, they cannot rein invade the liver; thus, there is no tissue stage of infection for malaria contracted by transfusion. In erythrocytes, most parasites undergo asexual development from young ring forms to trophozoites and finally to mature schizonts. Schizont-containing erythrocytes rupture, each releasing 6 to 32 merozoites depending on the \textit{Plasmodium} species. It is this process that produces febrile clinical attacks. The merozoites invade more erythrocytes to continue the cycle, which proceeds until death of the host or modulation by drugs or acquired partial immunity. The periodicity of parasitemia and febrile clinical manifestations depends on the timing of schizogony of a generation of erythrocytic parasites. For \(P.\) \textit{falciparum}, \(P.\) \textit{vivax}, and \(P.\) \textit{ovale}, it takes about 48 hours to complete this process; for \(P.\) \textit{malariae}, about 72 hours is required.
For erythrocyte invasion, merozoites bind to specific ligands on the red cell surface. *P. falciparum* has a family of binding proteins that can recognize a number of host cell molecules, including glycophorins A, B and C, as well as band 3. It is able to invade all stages of erythrocytes and therefore can achieve high parasitemias. *P. vivax* is more selective in its binding; it needs to recognize the Duffy chemokine receptor protein as well as reticulocyte-specific proteins; thus, it will not establish infection in Duffy-negative individuals and will only invade reticulocytes. Because of this restricted subpopulation of suitable erythrocytes, *P. vivax* rarely exceeds 1% parasitemia in the bloodstream. *P. ovale* is similar to *P. vivax* in its predilection for young red blood cells, but the mechanism of its erythrocyte recognition is unknown. *P. malariae* recognizes only senescent red cells, maintains a very low parasitemia, and typically causes an indolent infection.

*P. falciparum* assembles cytoadherence proteins (the PfEMPs encoded by a highly variable family of var genes) into structures called knobs on the erythrocyte surface. This allows the parasitized erythrocyte to bind to the vascular endothelium, to avoid the spleen, and to grow in a lower oxygen environment. For the patient, the consequences are microvascular blockage in the brain and organ beds and local release of cytokines and direct vascular mediators such as nitric oxide, leading to cerebral malaria.

Some erythrocytic parasites differentiate into sexual forms known as gametocytes. After infected blood is ingested by a female mosquito, exflagellation of the male gametocyte is followed by fertilization of the female gametocyte in the insect gut. The resulting zygote, which develops as an oocyst in the gut wall, eventually gives rise to sporozoites, which invade the salivary gland of the mosquito. The insect then can infect a human host by taking a blood meal.

Symptomatic malaria is typified by high spiking fevers that may have a periodic pattern, chills, headache, myalgia, malaise and gastrointestinal symptoms. In addition, each *Plasmodium* species causes a distinct illness: (1) *P. falciparum* is the most dangerous. By invading erythrocytes of any age, sequestering in the vasculature, and producing endotoxin-like products, this species can cause an overwhelming parasitemia, hypoglycemia and shock with multi-organ failure. Delay in treatment may lead to death. If treated early, the infection usually responds within 48 hours. If treatment is inadequate, recrudescence of infection may result. (2) *P. vivax* infection has a low mortality rate in untreated adults and is characterized by relapses caused by the reactivation of latent tissue forms. (3) *P. ovale* causes a malarial infection with a periodicity and relapses similar to those of *P. vivax*, but it is milder. (4) *P. malariae* causes a generally indolent infection that is common in localized areas of the tropics. Clinical attacks may occur years or decades after infection.

Drugs available for the treatment of malaria

There are only a limited number of drugs which can be used to treat or prevent malaria. The most widely used are quinine and its derivatives and antifolate combination drugs.

Quinolines and related compounds

Quinolines have been the mainstay of antimalarial chemotherapy starting with quinine nearly 400 years ago. In the last century, legions of related compounds were synthesized and tested for antimalarial activity. From these programs have come a number of drugs that are useful for the prophylaxis and treatment of malaria.
Chloroquine and Hydroxychloroquine

Chemistry

The structure of chloroquine is shown in figure below. The D, L, and DL forms of chloroquine have equal potency in duck malaria, but the D-isomer is somewhat less toxic than the L-isomer in mammals. A chlorine atom attached to position 7 of the quinoline ring confers the greatest antimalarial activity in both avian and human malarias. Research on the structure-activity relationships of chloroquine and related alkaloid compounds continues in an effort to find new, effective antimalarials with improved safety profiles that can be used successfully against chloroquine- and multidrug-resistant strains of *P. falciparum* (examples include the bisquinolines and short-chain chloroquines).

Hydroxychloroquine, in which one of the *N*-ethyl substituents of chloroquine is β-hydroxylated, is essentially equivalent to chloroquine against *P. falciparum* malaria. This analog is preferred over chloroquine for treatment of mild rheumatoid arthritis and lupus erythematosus because, given in the high doses required, it may cause less ocular toxicity than chloroquine.

Mechanisms of Antimalarial Action

Asexual malaria parasites flourish in host erythrocytes by digesting hemoglobin in their acidic food vacuoles, a process that generates free radicals and heme (ferriprotoporphyrin-IX) as highly reactive by products. Perhaps aided by histidine-rich proteins and lipids, heme is sequestered as an insoluble un-reactive malarial pigment termed hemozoin. Many theories for the mechanism of action of chloroquine have been advanced. The weight of the current evidence suggests that quinolines interfere with heme handling. Chloroquine concentrates in the food vacuoles of susceptible plasmodia, where it binds to heme as it is released during hemoglobin degradation and disrupts heme sequestration. Failure to inactivate heme or even enhanced toxicity of drug-heme complexes is thought to kill the parasites via oxidative damage to membranes, digestive proteases, and possibly other critical biomolecules. Other quinolines such as quinine, amodiaquine and mefloquine, as well as other aminoalcohol analogs (lumefantrine, halofantrine) and Mannich base analogs (pyronaridine), may act by a similar mechanism, although differences in their actions have been proposed.

Therapeutic Use

It is useful against is very effective in prophylaxis or treatment of acute attacks of malaria caused by *P. vivax*, *P. ovale* and *P. malariae*. Chloroquine has no activity against primary or latent liver stages of the parasite.

Quinoline and Quinidine

Chemistry

Cinchona contains a mixture of more than 20 structurally related alkaloids, the most important of which are quinine and quinidine. Both compounds contain a
quinoline group attached through a secondary alcohol linkage to a quinuclidine ring. A methoxy side chain is attached to the quinoline ring and a vinyl to the quinuclidine. They differ only in the steric configuration at two of the three asymmetrical centers: the carbon bearing the secondary alcohol group and at the quinuclidine junction. Although quinine and quinidine have been synthesized, the procedures are complex; hence they still are obtained from natural sources. Quinidine is both somewhat more potent as an antimalarial and more toxic than quinine. Structure-activity relationships of the cinchona alkaloids provide the basis for the discovery of more recent antimalarials such as mefloquine.

Quinine

\[
\text{CF}_3 \quad \text{CF}_3
\]

(Mefloquine)

Mechanism of Antimalarial Action
As per stated in chloroquine above.

Therapeutic Use
It is a telling commentary of the current state of antimalarial therapy that quinine is the treatment of choice for drug-resistant \textit{P. falciparum} malaria despite its antiquity and considerable toxicity.

Mefloquine\textsuperscript{11}
Chemistry
Mefloquine is a product of the Malaria Research Program established in 1963 by the Walter Reed Institute for Medical Research to develop promising new compounds to combat emerging strains of drug-resistant \textit{P. falciparum}. Of many 4-quinoline methanols tested based on their structural similarity to quinine, mefloquine displayed high antimalarial activity in animal models and emerged from clinical trials as safe and highly effective against drug-resistant strains of \textit{P. falciparum}.

\[
\begin{align*}
\text{N} & \quad \text{CF}_3 \\
\text{N} & \quad \text{F}_3\text{C} \\
\text{HO} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{OH} & \quad \text{H}
\end{align*}
\]

(Mefloquine)

Mechanism of Antimalarial Action
The exact mechanism of action of mefloquine is unknown but may be similar to that of chloroquine.

Therapeutic Use
Mefloquine should be reserved for the prevention and treatment of malaria caused by drug-resistant \textit{P. falciparum} and \textit{P. vivax}. The drug is especially useful as a prophylactic agent for non-immune travelers who stay for only brief periods in areas where these infections are endemic. In areas where malaria is due to drug-resistant strains of \textit{P. falciparum}, recent evidence indicates that mefloquine is more effective when used in combination with an artemisinin compound.
Primaquine

Chemistry

From a large series of quinoline derivatives synthesized with methoxy and substituted 8-amino groups, pamaquine was the first introduced into medicine. During World War II the search for more potent and less toxic 8-aminoquinoline antimalarials led to the selection of primaquine. This compound, in contrast with other antimalarials, acts on tissue stages (exoerythrocytic) of plasmodia in the liver to prevent and cure relapsing malaria. The striking hemolysis that may follow primaquine therapy led directly to the landmark discovery of G6PD deficiency, the first genetic disorder associated with an enzyme. Hemolysis remains notoriously identified with primaquine therapy, and there is a pressing need for alternatives to this important drug. 8-Aminoquinoline shows promise but needs more evaluation.12

![Primaquine](image)

Mechanism of Antimalarial Action

Primaquine destroys primary and latent hepatic stages of *P. vivax* and *P. ovale* and thus has great clinical value for preventing relapses of *P. vivax* or *P. ovale* malaria. The drug will not treat ongoing attacks of malaria, even though it displays some activity against the erythrocytic stages. The 8-aminoquinolines exert a marked gametocidal effect against all four species of plasmodia that infect humans, especially *P. falciparum*. Some strains of *P. vivax* exhibit partial resistance to the action of primaquine, which makes it imperative that strict adherence to drug regimen be maintained and that other liver-stage antimalarials be developed.13

Therapeutic Use

Primaquine is used primarily for the terminal prophylaxis and radical cure of *P. vivax* and *P. ovale* (relapsing) malarias because of its high activity against the latent tissue forms of these plasmodial species. The compound is given together with a blood schizontocide, usually chloroquine, to eradicate erythrocytic stages of these plasmodia and reduce the possibility of emerging drug resistance. For terminal prophylaxis, a primaquine regimen is initiated shortly before or immediately after the patient leaves an endemic area. Radical cure of *P. vivax* or *P. ovale* malaria can be achieved if the drug is given either during the long-term latent period of infection or during an acute attack. Limited studies also have shown efficacy in prevention of *P. falciparum* and *P. vivax* malaria when primaquine is taken prophylactically. The drug generally is well tolerated when taken for up to 1 year.14

![Amodiaquine](image)

Other Quinolines and Related Antimalarials

A number of quinolines and structurally related antimalarials are available. Amodiaquine is a congener of chloroquine that is no longer recommended for chemoprophylaxis of *P. falciparum* malaria because its use is associated with hepatic toxicity and agranulocytosis. It is inexpensive and has substantial activity in
chloroquine-resistant strains; its use in endemic areas with few alternatives is being debated and re-evaluated.\textsuperscript{15}

Isoquine

Isoquine is an isomer of amodiaquine that may yield fewer toxic metabolites and is being assessed.\textsuperscript{15}

Pyronaridine

Pyronaridine is a Mannich base antimalarial that is structurally related to amodiaquine. This compound, developed by the Chinese in the 1970s, was shown to be well tolerated and effective against \textit{P. falciparum} and \textit{P. vivax} malarias. However, it cannot be recommended for routine use at this time because of a lack of standardized dosage regimens and because it’s possible long-term toxicity has yet to be evaluated adequately. This drug currently is being developed in combination with artemesunate.\textsuperscript{16}

Piperaquine

Piperaquine is a bisquinoline that has been used extensively in Asia. It has activity against chloroquine-resistant parasites and currently is being assessed as a combination with dihydroartemisinin.\textsuperscript{17}

Halofantrine

Halofantrine is a phenanthrene methanol antimalarial drug with blood schizontocidal properties similar to those of the quinoline antimalarials. This compound was developed originally to treat acute malarial attacks caused by drug-resistant strains of \textit{P. falciparum}. Because halofantrine displays erratic bioavailability, potentially lethal cardio toxicity, and extensive cross-resistance with mefloquine, its use generally is not recommended.\textsuperscript{17}

Lumefantrine

Lumefantrine is a drug with structural similarities to mefloquine and halofantrine. It is marketed in combination with artemether for treatment of malaria. It appears to be effective and well tolerated, but experience is limited.\textsuperscript{17}
Chemistry

Proguanil is the common name for chloroguanide, a biguanide derivative that emerged in 1945 as a product of British antimalarial drug research. The antimalarial activity of proguanil eventually was ascribed to cycloguanil, a cyclic triazine metabolite and selective inhibitor of the bifunctional plasmodial dihydrofolate reductase-thymidylate synthetase. Indeed, investigation of compounds bearing a structural resemblance to cycloguanil resulted in the development of antimalarial dihydrofolate reductase inhibitors such as pyrimethamine. Accrued evidence also indicates that proguanil itself has intrinsic antimalarial activity independent of its effect on parasite dihydrofolate reductase-thymidylate synthetase.

Mechanisms of Antimalarial Action and Resistance

The active triazine metabolite of proguanil selectively inhibits the bifunctional dihydrofolate reductase-thymidylate synthetase of sensitive plasmodia, causing inhibition of DNA synthesis and depletion of folate cofactors. By cloning and sequencing dihydrofolate reductase-thymidylate synthetase genes from sensitive and resistant *P. falciparum*, investigators found that certain amino acid changes near the dihydrofolate reductase-binding site are linked to resistance to either cycloguanil or pyrimethamine, or both.

Therapeutic Use

Proguanil is effective and well tolerated when given orally once daily for 3 days in combination with atovaquone for the treatment of malarial attacks owing to chloroquine- and multidrug-resistant strains of *P. falciparum* and *P. vivax*.

Diaminopyrimidines

Chemistry

On their structural analogy with the antimalarial proguanil, in the late 1940s a large series of 2, 4-diaminopyrimidines was tested for inhibitory activity against malaria parasites. Pyrimethamine exhibited potent activity and was chosen by Hitchings for further development.

Mechanism of Antimalarial Action

The 2, 4-diaminopyrimidines inhibit dihydrofolate reductase of plasmodia at concentrations far lower than those required to produce comparable inhibition of the mammalian enzymes. Unlike its counterpart in human cells, the dihydrofolate reductase in malaria parasites resides on the same polypeptide chain as thymidylate synthase and, importantly, is not up regulated in the
face of inhibition. The latter property contributes to the selective toxicity of the antifolates.

Therapeutic Use

Pyrimethamine is virtually always given with either a sulfonamide or sulfone to enhance its antifolate activity, but it still acts slowly relative to the quinoline blood schizontocides, and its prolonged elimination encourages the selection of resistant parasites. The use of pyrimethamine should be restricted to the treatment of chloroquine-resistant *P. falciparum* malaria in areas where resistance to antifolates has not yet fully developed.¹⁹

Artemisinin and its derivatives

Chemistry

Artemisinin is a sesquiterpene lactone endoperoxide derived from the weed Qinghao (*Artemisia annua*), also called sweet wormwood or annual wormwood. The Chinese have ascribed medicinal value to this plant for more than 2000 years. As early as 340 A.D., Ge Hong prescribed tea made from qinghao as a remedy for fevers and in 1596, Li Shizhen recommended it to relieve the symptoms of malaria. By 1972, Chinese scientists had extracted and crystallized the major antimalarial ingredient, Qinghaosu, now known as artemisinin. Three semisynthetic derivatives with improved potency and bioavailability have since largely replaced the use of artemisinin. These include dihydroartemisinin, a reduced product; artemether, an oil soluble methyl ether; and artemesunate, the water-soluble hemi succinate ester of dihydroartemisinin.

Mechanism of Antimalarial Action

The current model of artemisinin action involves two steps. First, heme iron within the parasite catalyzes cleavage of the endoperoxide bridge. This is followed by rearrangement to produce a carbon-centered radical that alkylates and damages macromolecules in the parasite, likely including the ortholog of sarco/endoplasmic reticulum Ca²⁺-ATPase. Artemisinin and its derivatives exhibit antiparasitic activity in-vitro against other protozoa, including *Leishmania major* and *Toxoplasma gondii*, and have been used alone or in combination in patients with schistosomiasis.²⁰
The therapeutic use of artesunate for the treatment of severe *P. falciparum* infections is discussed. Artesunate, when compared favorably with a standard quinine regimen, was found to be effective and safe. However, the artemisinins are generally not used alone because of their incomplete efficacy and to prevent the selection of resistant parasites. In a series of trials in Africa, South America, and Asia, artesunate has proven useful when combined with other antimalarials for the first-line treatment of malaria. Artemisinin combination therapy (ACT) now is espoused because it reduces the likelihood of resistance and may decrease disease transmission by reducing gametocyte carriage.

Sulfonamides and sulfones

Shortly after their introduction into therapeutics, the sulfonamides were found to have antimalarial activity, a property investigated extensively during World War II. The sulfones also were shown to be effective; the first trial of dapsone was against *P. falciparum* in 1943. The sulfonamides are used together with pyrimethamine and often in addition to quinine to treat chloroquine-resistant *P. falciparum* malaria, especially in parts of Africa. The sulfonamides and sulfones are slow-acting blood schizontocides that are more active against *P. falciparum* than *P. vivax*. As p-aminobenzoate analogs that competitively inhibit the dihydropteroate synthase of *P. falciparum*, the sulfonamides are used together with an inhibitor of parasite dihydrofolate reductase to enhance their antiplasmodial action. The synergistic "antifolate" combination of sulfadoxine, a long-acting sulfonamide, with pyrimethamine is used to treat malarial attacks in parts of Africa. The sulfone dapsone given with the biguanide chlorproguanil also has been effective for therapy of chloroquine-resistant *P. falciparum* malaria.

Tetracyclines

The tetracyclines are slow-acting blood schizontocides that are used alone for short term prophylaxis in areas with chloroquine and mefloquine resistance. Tetracyclines are particularly useful for the treatment of the acute malarial attack owing to multidrug-resistant strains of *P. falciparum* that also show partial resistance to quinine. Their relative slowness of action makes them ineffective as single agents for malaria treatment. As an adjunct to quinine or quinidine, they are quite useful therapy. Several tetracyclines appear equivalent, but tetracycline or doxycycline usually is recommended. Clindamycin is an alternative. Tetracyclines have shown marked activity...
against primary tissue schizonts of chloroquine-resistant \textit{P. falciparum}. Doxycycline is used alone by travelers for short-term prophylaxis of multidrug-resistant strains.

\[ \text{(Tetracycline)} \]

Causes of resistance

Definition of antimalarial drug resistance\textsuperscript{23}

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”. This definition was later modified to specify that the drug in question must “gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action”. Most researchers interpret this as referring only to persistence of parasites after treatment doses of an antimalarial rather than prophylaxis failure, although the latter is a useful tool for early warning of the presence of drug resistance. This definition of resistance requires demonstration of malaria parasitaemia in a patient who has received an observed treatment dose of an antimalarial and simultaneous demonstration of adequate blood drug and metabolite concentrations using established laboratory methods (such as high performance liquid chromatography) or \textit{in-vitro} tests. In practice, this is rarely done with \textit{in-vivo} studies. \textit{In-vivo} studies of drugs for which true resistance is well known (such as chloroquine) infrequently include confirmation of drug absorption and metabolism; demonstration of persistence of parasites in a patient receiving directly observed therapy is usually considered sufficient. Some drugs, such as mefloquine, are known to produce widely varying blood levels after appropriate dosing and apparent resistance can often be explained by inadequate blood levels.

Malaria Treatment Failure

A distinction must be made between a failure to clear malarial parasitaemia or resolve clinical disease following a treatment with an antimalarial drug and true antimalarial drug resistance. While drug resistance can cause treatment failure, not all treatment failure is due to drug resistance. Many factors can contribute to treatment failure including incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality, drug interactions, poor or erratic absorption and misdiagnosis. Probably all of these factors, while causing treatment failure (or apparent treatment failure) in the individual, may also contribute to the development and intensification of true drug resistance through increasing the likelihood of exposure of parasites to suboptimal drug levels.

Mechanisms of Antimalarial Resistance

In general, resistance appears to occur through spontaneous mutations that confer reduced sensitivity to a given drug or class of drugs. For some drugs, only a single point mutation is required to confer resistance, while for other drugs, multiple mutations appear to be required. Provided the mutations are not deleterious to the survival or reproduction of the parasite, drug pressure will remove susceptible parasites while resistant parasites survive. Single malaria isolates have been found to be made up of heterogeneous populations of parasites that can have widely varying drug response characteristics, from highly resistant to
completely sensitive. Similarly, within a geographical area, malaria infections demonstrate a range of drug susceptibility. Over time, resistance becomes established in the population and can be very stable; persisting long after specific drug pressure is removed.24

The biochemical mechanism of resistance has been well described for chloroquine, the antifolate combination drugs and atovaquone.

Chloroquine Resistance

As the malaria parasite digests haemoglobin, large amounts of a toxic by-product are formed. The parasite polymerizes this by-product in its food vacuole, producing non-toxic haemozoin (malaria pigment). It is believed that resistance of P. falciparum to chloroquine is related to an increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of haem polymerization.25 This chloroquine efflux occurs at a rate of 40 to 50 times faster among resistant parasites than sensitive ones. Further evidence supporting this mechanism is provided by the fact that chloroquine resistance can be reversed by drugs which interfere with this efflux system. It is unclear whether parasite resistance to other quinoline antimalarials (amodiaquine, mefloquine, halofantrine, and quinine) occurs via similar mechanisms.26

Antifolate Combination Drugs Resistance

Antifolate combination drugs, such as sulfadoxine+pyrimethamine, act through sequential and synergistic blockade of 2 key enzymes involved with folate synthesis. Pyrimethamine and related compounds inhibit the step mediated by dihydrofolate reductase (DHFR) while sulfones and sulfonamides inhibit the step mediated by dihydropteroate synthase (DHPS). Specific gene mutations encoding for resistance to both DHPS and DHFR have been identified. Specific combinations of these mutations have been associated with varying degrees of resistance to antifolate combination drugs.27

Atovaquone Resistance

Atovaquone acts through inhibition of electron transport at the cytochrome bcl complex. Although resistance to atovaquone develops very rapidly when used alone, when combined with a second drug, such as proguanil or tetracycline, resistance develops more slowly. Resistance is conferred by single-point mutations in the cytochrome-β gene.27

Factors contributing to the spread of resistance

Numerous factors contributing to the advent, spread and intensification of drug resistance exist, although their relative contribution to resistance is unknown. Factors that have been associated with antimalarial drug resistance include such disparate issues as human behaviour, vector and parasite biology, pharmacokinetics, and economics. As mentioned previously, conditions leading to malaria treatment failure may also contribute to the development of resistance.28

Generally two main factors have deal with resistance.

Biological influences on resistance

It includes geographical condition, severity of disease, immune system, disease condition and age of the patient.29
Programmatic influences on resistance

It includes overall drug pressure, inadequate drug intake (poor compliance or inappropriate dosing regimens), pharmacokinetic and pharmacodynamic properties of the drug or drug combination, and drug interactions.

The Future: Priorities

A. Investigate combination therapy
   - Fast-track a chlorproguanil/dapsone/artesunate fixed dose formulation. From a theoretical basis, this would offer the best combination of overall efficacy, synergy between the antifolate-sulfa components, short half-life, reasonably well-matched pharmacokinetics, and probable cost. Because of growing use of and resistance to SP, an urgency exists to field this promising agent.
   - Investigate effectiveness of combination therapy in terms of robustness of strategy in face of high levels of self-treatment and unofficial use of component drugs (or related compounds) as monotherapy and in various epidemiological contexts (especially high-transmission areas).
   - Investigate how a combination therapy strategy could be financed. This strategy, if proven cost-effective, will nonetheless be more expensive than current strategies. What mechanisms might be developed to assist countries in adopting this strategy?

B. Invest significantly in identifying strategies to improve acceptance of and compliance with drug regimens, especially a combination therapy strategy, at all levels of official and unofficial health care systems, private sector, and community. Similarly, investigate to teach concepts of judicious use of antimicrobials (including antimalarial drugs) to health care providers.

C. Investigate ways to improve effectiveness of drug regulatory systems and ability to control introduction of new antimalarials within endemic countries. This is required to avoid uncontrolled use of new antimalarials resulting in development of resistance before they are needed which could significantly compromise their efficacy when they are needed.

D. Support new drug development. Investigate new approaches to drug delivery, such as time-released formulations or novel delivery systems that would allow use of short half-life drugs while optimizing compliance. Investigate drugs (or vaccines?) that have transmission-blocking effect that could be used in combination with drugs active against blood-stage parasites.

E. Improve access to and use of definitive diagnosis-based treatment.

F. Support more widespread use of insecticide-treated materials or other appropriate vector control strategies to reduce frequency of clinical illness (and therefore, treatment) as well as overall malaria transmission.

Conclusion

PLASMODIUM is a word when it is modified as PLASMODIUM then it becomes PODIUM which is a small platform on which a person may stand to be seen by an audience, as when making a speech or conducting an orchestra. Here the person is represented as Plasmodium which stands in the cell of living being and the speech given by him/her is hemozoin the endotoxin released from the causative organism and the conducting orchestra is various antimalarial drugs or vaccines which combats with the organism to cure the living being from malaria disease.

References


27. Ittarat I, Asawamahasakda W and Meshnick SR, “The effects of antimalarials on the...


Figure 3. Malaria cycle

Figure 4. Malaria’s vicious cycle