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Review Article

Malaria therapeutics: A Review

Ogundele SO[1], Mutiu WB[2], Salisu MA[3]
[1]Department of Pharmacology, Lagos State University College of Medicine Ikeja, Lagos.
[2]Department of Medical Microbiology, Lagos State University College of Medicine Ikeja, Lagos.
Department of Paediatrics, Lagos State University College of Medicine Ikeja, Lagos

[*]***Author for Correspondence:***
Ogundele S. O.
Email: soogundele@hotmail.com

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ABSTRACT
Malaria is a preventable and treatable disease, yet it is associated with high rates of morbidity and mortality particularly in children and pregnant women in sub-Saharan Africa. The disease occurs in 104 countries and territories worldwide with half of the world population under its threat. It is estimated that 207 million cases are recorded annually, about 81% of these occur in sub-Saharan Africa. Deaths from malaria and its complications is estimated to be about 627 000 annually, with 91%of these occurring in Africa, 86% of malaria burden affect children under 5 years of age.
It is advised that before treating for malaria there must be a parasitological confirmation of the infection. Currently recommended treatment for malaria are the artemisinin-based combination therapies (ACTs). ACT is a combination of at least two drugs, one of which must be an artemisinin derivative.
Perenteral formulations of artesunate, either by intramuscular or intravenous route for at least 24 hours is the preferred option for the treatment of severe malaria. This is to be followed by the full oral dose of ACTs as soon as the patient can tolerate orally. Evidence now abounds to support safety and effectiveness of ACTs in the treatment of malaria in pregnancy.

INTRODUCTION

Malaria is a preventable and treatable disease, yet it is associated with high rates of morbidity and mortality particularly in children and pregnant women in sub-Saharan Africa.[1] The disease is caused by different species of *Plasmodium*, a protozoan transmitted through the bites of infected female Anopheles mosquitoes.[2] Over 200 species of *plasmodium* have been identified but only 5are pathogenic in man. Plasmodium species causing malaria include; *P. ovale*, *P. vivax*, *P. malariae*, *P. falciparum* and *P. Knowlesi*.[11] Most deaths due to malaria are caused by infection due to *P. falciparum*.[3,4]

Malaria occurs in 104 countries and territories worldwide with half of the world population under the threat of the disease. It is estimated that annually 207 million cases of malaria are recorded, about 81% of these occur in sub-Saharan Africa. Deaths from malaria and its complications is estimated to be about 627 000 annually, with 91% of these occurring in Africa, 86% of malaria burden affect children under 5 years old. It is reported that 17 countries account for 80% of cases of malaria and 14 countries account for 80% of deaths. In 2015 no indigenous case of malaria was recorded in any of the European countries. Eight countries outside of Europe also reported zero cases of the disease in 2014.[5]

In Nigeria it is estimated that 50% of the population suffer at least one episode of malaria attack each year. Children under five years of age have 2-4 attacks of malaria in a year.[1] Mortality from malaria in Nigeria ranges between 1 to 3 million deaths each year and 90% of these deaths occur in children and pregnant women. Nigeria loses over N132 billion each year from cost of treatment and absenteeism from work, schools and farms due to malaria.[1]

The spread of malaria requires that the following conditions are met; presence of competent Anopheles mosquitoes, ideal temperature and humidity. Human factors like socio-economic factors and control measures are also important in the spread of malaria. The World Health Assembly has recently called for the elimination of local transmission of malaria in at least 10 countries by 2020. WHO estimates that 21 countries are in a position to achieve this goal, including 6 countries in the African region, where the burden of the disease is heaviest.

The currently recommended treatment for acute uncomplicated malaria are the artemisinin-based combination therapies (ACTs).[2] It is advised that before treating for malaria there must be a parasitological confirmation of the infection. Presumptive treatment based on clinical suspicion alone is only acceptable when a parasitological diagnosis is not available. Where parasitological diagnosis cannot be done, patients with suspected severe malaria, and other high risk groups, can be treated promptly on clinical grounds.[5]

History of malaria

The term malaria originated from the Italian words 'malaria', which translates to 'bad air'.[6] This was because the

disease was originally thought to be caused by bad air, the word was first used by an Italian physician Francisco Torti in 1740. Malaria is one of the oldest diseases known to mankind. The disease was said to have its origins in the jungles of Africa and it is still highly prevalent in sub-Saharan Africa till date.[6] Description of a disease now known as malaria can be found in ancient Chinese, Indian and Egyptian manuscripts.[3,7] Detailed description of the clinical features of malaria and the use of cinchona bark in its treatment was first presented in 1696.3,6In 1998 malariologists celebrated the centenary of the demonstration of the female anopheles mosquito as the transmitter of the parasite that causes malaria.[8] Ronald Ross reported in 1897 that the parasite causing malaria is transmitted by the female anopheles mosquito.[6,7,9] He was awarded a Nobel prize in 1902 for this discovery. Despite the huge stride in biology and medicine more than 100 years after this discovery, malaria still remains a serious public health problem till date in many countries of the world, especially in sub-Saharan Africa.

Researches into the study of malaria has produced four Nobel laureates till date; Sir Ronald Ross (1902), Charles Louis Alphonse Laveran (1907), Julius Wagner-Jauregg (1927) and Paul Hermann Muller (1948).[3,7] Laveran, a French physician that worked in Algeria indentified the *Plasmodium* parasite as the causative agent for human malaria in 1880. He was awarded the Nobel Prize in 1907 for his works on malaria.[3,7,10]

Epidemiology of malaria

Malaria occurs throughout most of the tropical region of the world. *P.falciparum* is common in the sub-Saharan Africa region, *P.vivax* is more common in Central America and Indian sub-continent. The prevalence of these two species is approximately equal in South America, eastern Asia and Oceania. *P.malariae* is found in most endemic areas, especially throughout sub-Saharan Africa, but is much less than *P.falciparum*. *P.ovale* is unusual outside Africa.[3] *P. Knowlesi* was recently shown to be a significant cause of zoonotic malaria in Southeast Asia, particularly in Malaysia.[4] The parasite is a natural pathogen of long-tailed and pig-tailed macaques.

In areas where malaria is endemic, spread and exposure to the disease is categorized into stable, unstable and epidemic.11Stableexposure to malaria is when a population is continuously exposed to a fairly constant rates of malarial transmission throughout the year. When exposure of a population to malaria is subjected to a less permanent transmission with a large fluctuations in rates of transmission among individuals within a population the pattern is termed unstable.[11] In terms of developing immunity, these fluctuations become significant when it occurs at intervals of a year to several years between inoculations of the malaria parasite. This cause immunity to be lost and such individuals then become immuno-naive again.[11] The third type of spread is malaria epidemic. Malaria epidemic is an extreme form of unstable malaria. It occurs when a population or even a small group of individuals are subjected to increase rates in malaria transmission that is above rates previously or normally experienced.11Epidemics of *P. falciparum* infection is one of the most lethal forces of nature.[4]

A proxy for assessing exposure to malaria in children aged 2 to 9 years is the spleen rate.[12] Malaria exposure based on the spleen rate is classified into four categories by estimating the proportion of children aged 2 to 9 years with palpable splenomegaly. Using this classification exposure is categorized into; hypoendemic, with rates of 0 to 10%; mesoendemic, 11 to 50%; hyperendemic, rates constantly over 50% but less than 75%) and holoendemic, with rates constantly over 75%.[12] However, these markers cannot be taken as a reliable index since the spleen and parasites rates are arbitrary and do not capture the seasonal nature of transmission and other causes of splenomegaly.

Intensity of malaria transmission is the frequency of bites by female anopheles mosquitoes carrying malaria sporozoites.[2] Transmission is said to be intense if bites by the vector is up to one or more per day. People living in areas of intense transmission are infected repeatedly throughout their lifetime. They acquire immunity early in life, usually before the age of 5 years. In areas with low transmission and unstable malaria, symptomatic and severe diseases are common in both the young and the old.[13]

Mode of transmission and life cycle of malaria parasite

The commonest mode of transmission of malaria infection is through the bite of an infected female anopheles mosquito. Other modes of transmission include; trans-placental, transfusion of infected blood and accidental inoculation in the laboratory during parasite culture.

The female anopheles mosquitoes lay an average of 30-150 eggs every 2-3 days and these eggs require human blood for their nourishment.[3] The female mosquitoes also have two pairs of cutting stylets that slide against one another slicing through the skin at the end of their slender proboscis. Once through the skin the proboscis begins probing for a tiny blood vessel. If the proboscis does not strike one on the first try, the mosquito will pull back slightly and try again at another angle through the same hole in the skin. Inside the proboscis are two hollow tubes, one that injects saliva into the microscopic wound and the other that withdraws blood. Anopheles mosquitoes enter the house usually between 5 p.m. and 9.30 p.m. and again in the early hours of the morning.[3] They start biting from late evening and the peak of biting activity is at the midnight and the early hours of the morning.

The average life span of a mosquito is 2-3 weeks. It can be longer in ideal living conditions. The Duffy blood group antigen is required for *P. vivax* infection, this antigen is absent in black people of west African descent, hence people from this region are resistant to *P. vivax* infection.

The life cycle of the malaria parasite starts from the inoculation of the host with sporozoites when bitten by the female anopheles mosquito, female anopheles mosquito requires a blood meal for egg production.[14] During such meals, a mosquito infected with *P. falciparum* injects 5-20 sporozoites, which invade hepatocytes within minutes. Sporozoites migrate through several hepatocytes before settling in one. Development within the liver takes approximately 6-15 days depending on the specie of the parasite. *P falciparum* takes an average of 6 days; *P. ovale* and P. vivax take up to 10 days and for *P. malariae* it takes about 15 days. Replication within the liver is followed by schizont rupture, releasing 20,000–30,000 merozoites per original sporozoite into the hepatic venous circulation from where they disseminate systemically.[14] Each merozoite that is not engulfed by phagocytic cells invades a new red blood cell,

thereby initiating the erythrocyte stage of the cycle. The asexual erythrocytic stage produces more merozoites that are released with the accompanying destruction of red blood cells after 48 hours in *P. falciparum*. The asexual cycle continues until controlled by the immune response, chemotherapy or death in the non-immune if there is no intervention. Some merozoites differentiate into male or female gametocytes, which can be taken up by a female anopheles mosquito during a blood meal. Fertilization occurs within the mosquito midgut, this leads to completion of the life cycle. The sporozoites then migrate to the salivary glands and become infective.[14]

Clinical presentation

The clinical presentation of malaria is caused by direct red blood cell invasion and destruction by the asexual parasites and the host reaction. *P. falciparum* has a predilection for young red blood cells but it can also infect red cells of all ages, *P. vivax* and *P. ovale* preferentially invade reticulocytes, while *P.malariae* has predilection for old red blood cells.

The signs and symptoms of malaria are non-specific. Malaria is suspected clinically mostly when there is a history of fever .[2] Diagnosis based on clinical presentations alone has very low specificity and usually results in over-treatment.[2] Exclusion of other causes of fever and the need for alternative or additional treatment must always be carefully considered.

The incubation period for malaria varies between different species, for *P.falciparum* it is between 5-7 days, *P.ovale*/*P.vivax* 6-9 days and13-16 days in *P.malariae*.[2] The *P. knowlesi* specie has a 24-hour replication cycle and diseases caused by it can rapidly progress from an uncomplicated to a severe infection; fatal cases have also been reported.[2,4]

Diseases due to the different species of malaria parasite share the characteristic febrile episodes with their tendency to regular periodic paroxysm with chills, rigor, and sweating.

Repeated malaria infections are characterized by enlargement of the spleen and the liver. In *P. falciparum* malaria, severe and life-threatening conditions commonly arise. Malaria can cause life threatening conditions leading to dysfunction of vital organs.[3] The dysfunction of the vital organs is associated with most of the mortality of severe malaria. Chronic infection with *P. malariae* can result in nephrotic syndrome and this too can eventually be fatal.

Diagnosis of malaria

The two main methods routinely used for parasitological diagnosis of malaria are light microscopy and rapid diagnostic tests (RDTs).[2] RDTs detect parasite-specific antigens or enzymes and some have a certain ability to differentiate species. Deployment of microscopy and RDTs must be accompanied by quality assurance. The choice of which test to use depends on the following; available skills, patient case-load, epidemiology of malaria and the need to use microscopy for diagnosis of other diseases. Where the case-load of patients with febrile illness is high, microscopy is likely to be less expensive than RDTs, but may be less operationally feasible. Microscopy has further advantages in that it can be used for specie identification and parasite quantification and these help in assessing response to antimalarial treatment. Microscopy can also be used in the identification of other agents that can cause fever.[4] However, a major drawback of light microscopy is its requirement for well-trained and skilled Microscopists.

Malaria chemotherapy

General Classification of antimalarial drugs

Antimalarial drugs can be classified according to activities on different stages of the parasite life cycle or according to the structures of the drugs.

Classifications in relation to different stages of life cycle of malaria parasite[15,16]

Tissue schizonticides for causal prophylaxis: Drugs in this class act on the primary tissue forms of the plasmodia that initiate the erythrocytic stage after growth within the liver. Blocking this stage, prevents further development of the infection. Pyrimethamine and Primaquine have this property. However since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.

1. **Tissue schizonticides for preventing relapse**: Target of drugs in this class is the dormant liver stage of the parasite, which is the hypnozoites of *P. vivax* and *P. ovale*. This stage is the cause of relapse of symptoms upon reactivation. Primaquine is the prototype drug and pyrimethamine also has such activity.
2. **Blood schizonticides**: Drugs in this class act on the blood forms of the parasite leading to termination of clinical attacks of malaria. Schizontocides antimalarial drugs are the most important in malarial chemotherapy. Example of these drugs include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones and tetracyclines.
3. **Gametocytocides**: Drugs in this class destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against *P. vivax* and *P. malariae*, but not against *P. falciparum*. Primaquine has gametocytocidal activity against all plasmodia, including *P. falciparum*.
4. **Sporontocides**: These drugs prevent the development of oocysts in the mosquito thus breaking the transmission cycle. Primaquine and chloroguanide are example of drugs in this category.

Classifications according to drug structure:16

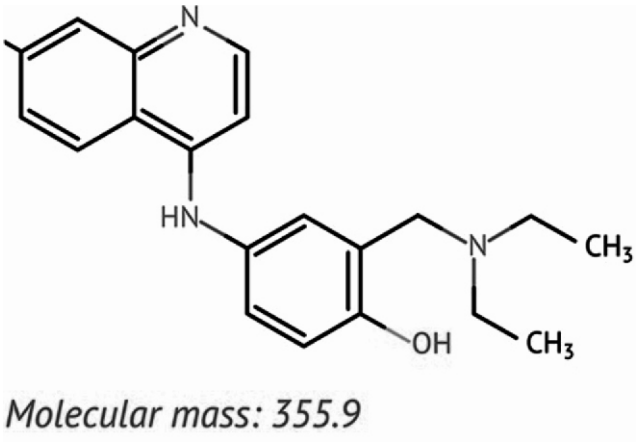
1. Aryl amino alcohols: Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine.
2. 4-aminoquinolines: Chloroquine, amodiaquine.
3. 8-aminoquinolines:Primaquine
4. Folate synthesis inhibitors: Type 1 - competitive inhibitors of dihydropteroate synthase - sulphones, sulphonamides. Type 2 - inhibit dihydrofolate reductase - biguanides like proguanil and chloroproguanil; diaminopyrimidine like pyrimethamine.
5. Antimicrobials: Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones.

6. Peroxides: Artemisinin (Qinghaosu) derivatives and analogues - artemether, arteether, artesunate, artelinic acidz
7. Naphthoquinones: Atovaquone
8. Iron chelating agents: Desferrioxamine

Pharmacology of common antimalarial drugs[2]

Amodiaquine

Structure and mechanism of action



Amodiaquine is a Mannich base 4-aminoquinoline, its mechanism of action and structure are similar to chloroquine. It is metabolised to desethylamodiaquine, an active metabolite. It acts by accumulating inside the parasite food vacuole and interfering with haem detoxification. Amodiaquine is effective against some parasite strains that are resistant to chloroquine, although some cross-resistance exists.

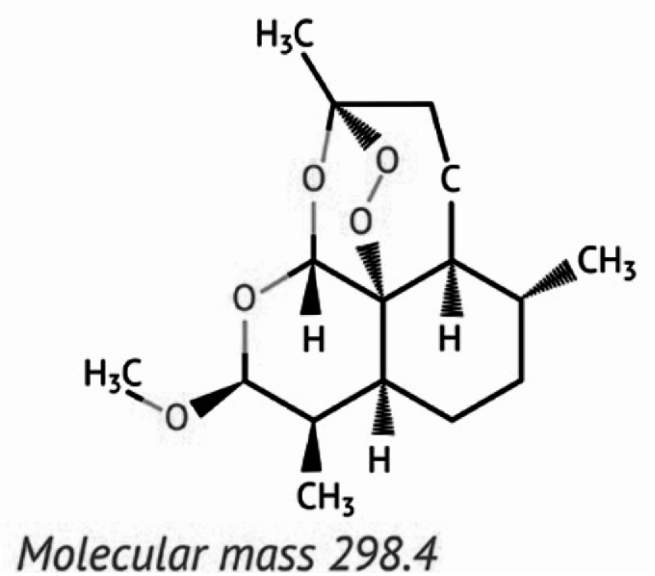
Therapeutic indications

Amodiaquine should be used in combination with artesunate. It is indicated in the treatment of uncomplicated malaria caused by all the strains of Plasmodium. It is also indicated for follow-up treatment in severe malaria when the patient is stable enough to take oral medication.

Amodiaquine plus sulfadoxine–pyrimethamine (SP) is given at full treatment doses at monthly intervals as seasonal malaria chemoprevention to young children (aged 3–59 months) in areas of seasonal, high-intensity malaria transmission. This combination is currently recommended in the Sahel region of sub-Saharan Africa in areas where malaria transmission is intense and where the majority (>60%) of clinical malaria cases occur during a short period (≤4 months).Artesunate–amodiaquine should not be used for prophylaxis, as its accumulation increases the risks for hepatotoxicity and agranulocytosis.

Artemether

Structure and mechanism of action



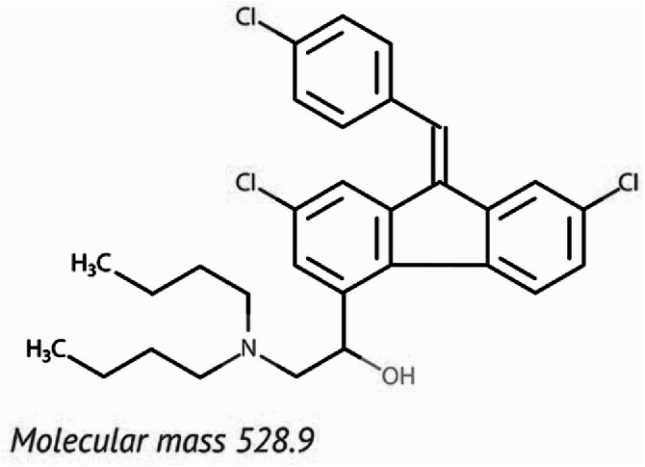
Artemether is the methyl ether derivative that is metabolized to dihydroartemisinin which is its active metabolite. It is two- to threefold less active than dihydroartemisinin. The ethers are metabolized to dihydroartemisinin to a lesser extent than artesunate. Like the other artemisinin derivatives, artemether has broad stage specificity against blood-stage parasites, from the ring stages through to early schizonts. It also reduces gametocyte carriage, limiting malaria transmission from the treated infection.

Therapeutic indications

Intramuscular artemether is an alternative for treatment of severe malaria when parenteral artesunate is not available. Artemether is superior to quinine in the treatment of severe malaria in adults but it is not so effective in children. Its absorption is unpredictable, which may affect treatment responses in the most severely ill patients. Artemether is an alternative to parenteral artesunate in adults and to parenteral or rectal artesunate in children in the treatment of severe malaria when the preferred choices are not available. Artemether is also used in a fixed-dose oral combination with lumefantrine for the treatment of uncomplicated malaria caused by all the strains of *Plasmodium*.

Artemether-Lumefantrine

Structure and mechanism of action of Lumefantrine



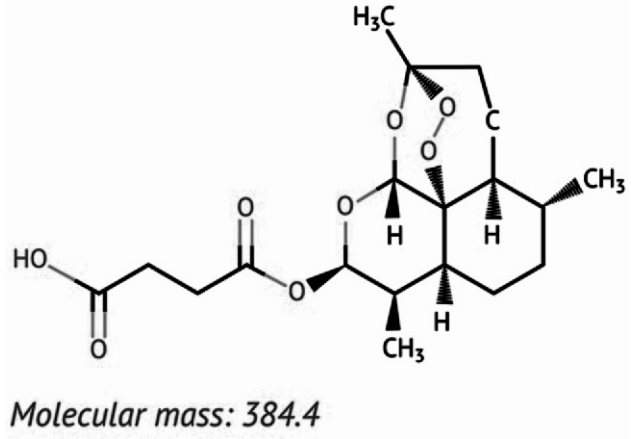
Lumefantrine (benflumetol) is a fluorene derivative. It belongs to the aryl amino-alcohol group of antimalarials, which also includes quinine, halofantrine and mefloquine. Its mechanism of action is by preventing haem detoxification within the parasite food vacuole, thus causing accumulation of the toxic haem complex. Lumefantrine is not indicated as a monotherapy, this slows the selection and spread of resistance to the drug.

Therapeutic indications

Artemether–lumefantrine is indicated for the treatment of uncomplicated malaria caused by all the strains of *Plasmodium*.

Artesunate

Structure and mechanism of action



Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide. In vivo, artesunate is rapidly converted to its active metabolite dihydroartemisinin. The mechanism of action of the artemisinin derivatives is not well-defined but involves cation-mediated generation of reactive intermediates and reduction of the peroxide bridge.

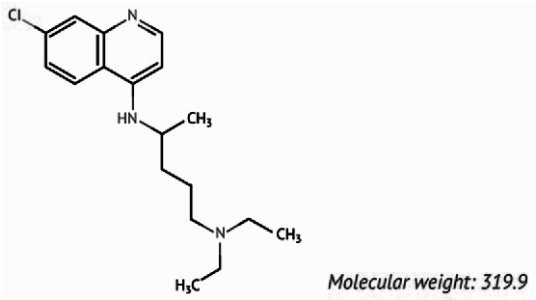
Artesunate, like other artemisinin derivatives, kills all erythrocytic stages of malaria parasites, including the ring stages and early schizonts, as well as the gametocytes responsible for continuing transmission, although it has only partial activity against the mature stage V gametocytes. It is essentially inactive against extra-erythrocytic forms, sporozoites, liver schizonts and merozoites. Artesunate is more water-soluble than other artemisinins and therefore can be administered intravenously. It can also be given orally, rectally or by the intramuscular route.

Therapeutic indications

Parenteral (intravenous or intramuscular) artesunate is indicated for the initial treatment of severe malaria. Rectal artesunate is indicated as pre-referral treatment for severe malaria. Artesunate–amodiaquine, artesunate–mefloquine or artesunate–SP are indicated for the treatment of acute uncomplicated *P. falciparum*, *P. vivax*, *P. ovale*, *P. knowlesi* or *P. malariae* malaria.

Chloroquine

Structure and mechanism of action



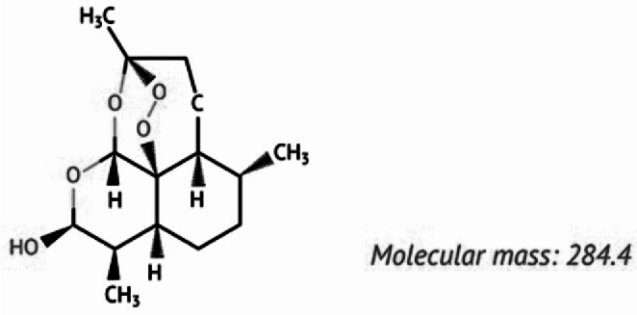
Chloroquine is a 4-aminoquinoline that inhibits intraparasitic haem detoxification; it may also interfere with the biosynthesis of nucleic acids. Chloroquine reaches high concentrations in the parasite's food vacuole. Chloroquine resistance is associated with genetic mutations in genes encoding trans-membrane proteins of the parasite's food vacuole (PfCRT and PfMDR).

Therapeutic indications

Chloroquine is indicated for the treatment of uncomplicated malaria due to *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. Chloroquine is no longer recommended for prophylaxis against *P. falciparum* (except in some parts of Central America) but may be used to prevent P. vivax infections.

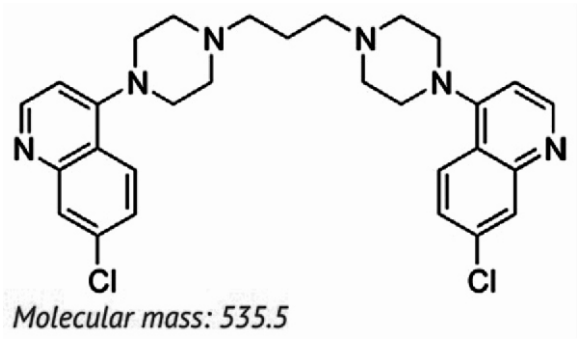
Dihydroartemisinin-Piperaquine

Structure and mechanism of action dihdroartemisinin



Dihydroartemisinin is a sesquiterpene peroxide and an active metabolite of artesunate and artemether. The mechanism of action of the artemisinin derivatives is not known but involves cation-mediated generation of reactive intermediates and reduction of the peroxide bridge.

Structure and mechanism of action of piperaquine



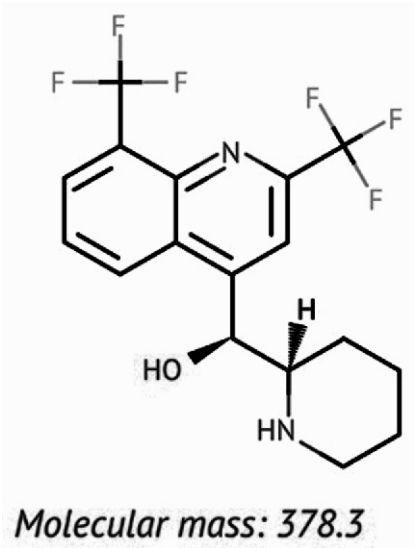
Piperaquine is a bisquinoline compound of the 4-aminoquinoline group of antimalarial drugs that include chloroquine. Piperaquine is thought to act similarly to chloroquine, which accumulates inside the parasite food vacuole and inhibits parasite-mediated haem detoxification, causing accumulation of the toxic haem complex. Piperaquine is also effective against chloroquine-resistant malaria parasites. In chloroquine resistance, mutation in the genes encoding trans-membrane parasite food vacuole proteins are thought to result in efflux of chloroquine, so that it cannot accumulate at its site of action. These mutated parasite membrane proteins are considered to be unable to efflux the bulky bisquinoline structure.

Therapeutic indications

Dihydroartemisinin–piperaquine is indicated for the treatment of uncomplicated *P. falciparum* or *P. vivax* malaria and is likely to be very effective in *P. ovale*, *P. knowlesi* and *P. malariae* malaria. It may also be used as follow-on treatment in severe malaria once the patient is well enough to take oral medication.

Mefloquine

Structure and mechanism of action



Mefloquine, a 4-methanolquinoline, is structurally related to quinine and belongs to the aryl amino-alcohol group of drugs. Mefloquine has two racemic forms, erythro- and threo-, each composed of a pair of enantiomers, of which the racemic mixture of the erythro- enantiomers is the most active against malaria parasites. Its mechanism of action is not fully understood but is thought to involve inhibition of parasite-mediated haem detoxification, a common mechanism of action of quinoline antimalarials. A more recent proposal is that it inhibits endocytosis of the cytosol by the parasite. Mefloquine has approximately the same stage specificity of action as quinine, killing primarily the large ring and trophozoite asexual parasites. It has no significant pre-erythrocytic activity.

Therapeutic indications

Mefloquine is indicated for the chemoprophylaxis of malaria caused by all species. In combination with artesunate, it is also recommended for treatment of uncomplicated malaria.

Malaria chemotherapeutics

The primary objective of treatment of malaria is to ensure rapid and complete elimination of the Plasmodium parasite from the patient's blood. This is to prevent progression of uncomplicated malaria to severe disease or death, and to prevent chronic infection that leads to malaria-related anaemia.[2]

The choice of antimalarial drug depends on the severity of infection, patient's age, degree of background immunity, pattern of drug susceptibility of the parasite, cost and availability.[17] It is important to note that in treating malaria in non-endemic areas, like in the temperate regions, the choice of the antimalarial drug should be determined by the sensitivity pattern of the parasite in the area where the infection was acquired.[17] This is important because of the importance of geographical variations in parasite sensitivity.
Drug discovery and development processes are long, risky and expensive. Only four new antimalarial drugs were developed within the last quarter of the 20th century out of the nearly over 1,400 drugs registered worldwide.[18]

Antimalarial drug resistance

Antimalarial drug resistance is defined as the ability of the malaria parasite strains to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually required but within tolerance of the subject.[19,20] The drug must gain access to the parasite or the infected red blood cells for the duration of the time necessary for its normal action. Persistence of the parasite after treatment with therapeutic doses of the antimalarial rather than prophylatic dosage implies failure by this definition.[19]

Chloroquine (CQ) resistant *P. falciparum* was first discovered in east-Africa and has since spread across the African continent, resistance to sulfadoxine-pyrimethamine (SP) had also been reported across many African countries as well.35 Several reports from studies done locally here in Nigeria and across Africa countries showed a progressive increase in the degree and distribution of resistance to CQ and SP by *P. falciparum*.[1,21,22] These reports are in support of removing both chloroquine and sulfadoxine-pyrimethamine

monotherapy from national formularies for the treatment of malaria and the adoption of the artemisinin-based combination therapy in the new Nigeria national antimalarial treatment policy.

Current drugs options for treating malaria

Artemisinin based combination therapies (ACTs)

World Health Organisation currently recommends artemisinin-based combination therapy for the treatment of uncomplicated malaria caused by the *P. falciparum* parasite.[2,23] This is a combination of at least two antimalaria drugs, one of which must be an artemisinin derivative. The combination of two active ingredients with different mechanisms of action are the most effective option for the treatment of infectious diseases today.[2] Antimalarial drug combination therapy is defined as the simultaneous administration of two or more blood schizontocidal antimalarial drugs.[20] A consensus has emerged that the development of resistance to antimalarial drugs should be delayed through a strategy of routinely employing combination of antimalarial drugs. The basic tenet of combination therapy (CT) is that the probability of developing resistance to chemotherapeutic agents that are in combination and with independent modes of actions is extremely low, it is of the order of about one in 1012 treatments.[19,24] This frequency is the probability of the acquisition of a resistant mutation to each drug multiplied by the number of parasites in a typical infection.[25]

This concept of combination therapy is already a standard in multi-drug therapy for Leprosy, Tuberculosis, Cancer and more recently HIV infection.19 The concept of antimalarial drugs combination was first tried in Thailand with combination of mefloquine and sulfadoxine-pyrimethamine and later changed to mefloquine plus artesunate combination due to high failure rate of the individual drugs in the combination.[26]

The drugs in the combination can either be co-formulated or co-administered. They must have independent modes of action and different biochemical targets in the parasite. Multiple drug therapy in which neither of the components has significant schizontocidal effect when used alone is not considered a combination therapy, like sulfadoxine-pyrimethamine.[19] The use of a combination of blood schizontocide and tissue schizontocide or the combination of a drug with non-antimalarial property to enhance the antimalarial activities of another drug are not considered as combination therapy for the treatment of malaria.

The partner drug in an ideal antimalarial drugs combination must have efficacy of at least 75%. Amodiaquine efficacy has consistently been above this cut-off in Nigeria and was chosen as a partner drug to artesunate in the country's national treatment policy on that basis.[1,27,28] Combinations that include chloroquine and mefloquine are not recommended as a policy option for most African countries. This is because of the unacceptably high level of resistance to chloroquine and the resistance selection pressure effect of mefloquine in areas of intense transmission.[29]

The underlying science behind the therapeutic effect of the artemisinin-based combination is that the artemisinin derivatives kill rapidly most of the parasites. The companion drug then kills the remaining parasites. The short half-life (<1 hour) of the artemisinin protects them against resistance.[30,31] Artemisinin derivatives probably work by generation of free radicals in parasitized red blood cells, followed by alkylation of parasite proteins.[32,33] The main derivatives, artemether and artesunate are rapidly hydrolysed to an equally potent metabolite dihydroartemisinin (DHA), which is also used as an antimalarial. These three compounds have extremely short elimination half-lives.The artemisinin derivatives are well tolerated. Reported side effect profile of the drugs includes mild gastrointestinal and central nervous systems.[34]

Treatment guidelines

Acute uncomplicated malaria are usually treated with oral antimalarial medications, perenteral medications are not indicated if the patient can tolerate orally. The following ACTs are the recommended options for the treatment of acute uncomplicated malaria by WHO treatment guideline: artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine, artesunate-sulfadoxine-pyrimethamine anddihydroartemisinin-piperaquine.[2] The Nigeria national treatment policy recommended the use of either artemether-lumefantrine or artesunate-amodiaquine combinations.[1]

For the treatment of severe malaria, it is recommended thatperenteral formulations of artesunate be given either by intramuscular or intravenous route for at least 24 hours. This should be followed by a complete 3-day course of an ACT as soon as the patient can tolerate oral medicines. Children under 6 years of age with severe malaria should be given a pre-referral treatment with rectal artesunate before being referred to a health care facility where the full level of care can be provided.[2]

Management of malaria in pregnancy requires that the risks of use of antimalarial drugs be balanced with benefits of treatment because of the potential risk of harm to the unborn child.[35,36] Evidence now abounds to support safety and effectiveness of ACTs in the treatment of malaria in pregnancy.[35,36] For pregnant women living in areas of high malaria transmission it is recommended that they are given intermittent presumptive treatment with at least 2 full doses of sulfadoxine-pyrimethamine from the second trimester of pregnancy in addition to the use of the insecticide treated nets. WHO recommends use of quinine and clindamycin for the treatment of acute uncomplicated malaria in the first trimester of pregnancy.[2] Quinine is associated with risk of hypoglycaemia and there is increasing emergence of resistance parasites to the drug.[36]

CONCLUSION

Malaria remains a disease of public health importance particularly in Africa. The disease has no symptom that is specific to it and it is therefore often confused with other forms of febrile illnesses. It is important to adhere to the WHO guideline that requires parasitological confirmation of the disease before commencing treatment when possible. This saves cost from unnecessary treatment and reduces false claims of ineffectiveness of some antimalarial drugs. Monotherapy for treatment of malaria should be discouraged as much as possible as this is a sure way of keeping most of the currently available antimalarial drugs effective by preventing development of resistant strains of parasites to them since

only few antimalarial drugs are being developed.

Conflict of Interest

The authors declare no competing interests.

REFERENCES

1. National Antimalarial Treatment Policy. Federal Ministry of Health. National Malaria and Vector Control Division. Abuja-Nigeria. February 2005. Available online at apps.who.int/medicinedocs/documents/s18401en/s18401en.pdf (Accessed on 10th June 2014)
2. World Health Organisation. Overview of malaria treatment, 2016. Available at, http://www.who.int/malaria/areas/treatment/overview/en/. Accessed 13th December 2016.
3. Kakkilaya BS. History of Malaria. Available at, http://www.malariasite.com. Accessed 20th November 2016.
4. Centers for Disease Control and Prevention, Center for Global Health, Division of Parasitic Diseases and Malaria. CDC and Malaria, available at www.cdc.gov/malaria. Accessed 8th January 2017.
5. WHO. WHO. Malaria Control: WHO Technical Updates Global Technical Strategy for Malaria 2016–2030, 2015. Available at, www.who.int/malaria/publications/atoz/9789241564991/en/. Accessed 20th February 2017.
6. Centre for Disease Control. The History of Malaria, an Ancient Disease. available at, http://www.cdc.gov/malaria/about/history/. Accessed 19th January 2017.
7. Cox F. History of the discovery of the malaria parasites and their vectors. Parasites & Vectors 2010; 3:5. DOI: 10.1186/1756-3305-3-5
8. Phillips RS. Current Status of Malaria and Potential for Control. Clinical Microbiology Reviews. 2001; 14(1): 208-226.
9. Nobel laureates in Medicine. Available at, http://nobelprize.org/medicine/laureates/1902. Accessed 4th June 2016.
10. Nobel prize. Available at, http://nobelprize.org/medicine/laureates/1907/laveran-lecture.html. Accessed 4th June 2016.
11. Richard C, Kamini NM . Evolutionary and Historical Aspects of the Burden of Malaria. Clinical Microbiology Reviews, Oct. 2002; 15: 564–594.
12. World Health Organization. Assessment and Monitoring of Antimalarial Drug Efficacy for the Treatment of Uncomplicated Falciparum Malaria. World Health Organization; Geneva, Switzerland 2003.
13. WHO (2001). Antimalarial Drug Combination Therapy: Report of a WHO Technical Consultation. WHO/CDS/RBM/2001.35.
14. Vasee SM, Michael FG, Andrian VS. Malaria vaccine developments. Lancet. 2004; 363: 150-156
15. Bruce-Chwatt LJ. Classification of antimalarial drugs in relation to different stages in the life-cycle of the parasite: commentary on a diagram. Bulletin of the World Health Organization. 1962; 27(2): 287-290. Available at. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2555808/pdf/bullwho00307-0096.pdf
16. Srinivas. Antimalarial Drugs. Available at, http://www.malariasite.com/malaria-drugs/. Accessed 9th January 2017.
17. White NJ. The treatment of malaria. N Engl J Med. 1996; 335 (11): 800-806.
18. Piero LO and Walter RJT. Antimalarial compounds: From bench to bedside. The Journal of Experimental Biology 2003; 206: 3753-3759.
19. Bloland PB, Ettling M, Meek S. Combination Therapy for malaria in Africa: Hype or myth. Bulletin of the World health Organization 2000; 78:1378-88.
20. Olumese P. Antimalarial combination therapy in Africa. African Health (Supplement on malaria-September 2001) Available at, http://www.who.int/malaria/cms. Accessed 10th Aug 2015).
21. Plowe CV, Monitoring antimalarial drug resistance: making the most of the tool at hand. The Journal of experimental biology. 2003; 206: 3745-3752.
22. Falade CO, Ogundele AO, Yusuf BO, Ademowo OG, Ladipo SM. High efficacy of two artemisinin based combination (artemether-lumefantrine and artesunate plus amodiaquine) for acute uncomplicated malaria in Ibadan, Nigeria. Trop Med Int Health 2008; 13(5): 635-43.
23. Mutabingwa TK. Artemisinin-based combination therapies (ACTs): best hope for malaria treatment but inaccesible to the needy! Acta Trop. 2005; 95(3): 305-15.
24. Snow RN, Craig M, Deichmann U, Marsh K. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. Bull World Health Organ. 1999; 77: 624–40.
25. White NJ. Preventing antimalarial drug resistance through combinations. Drug Resistance Updates 1998, 1: 3-9.
26. WHO/Roll back malaria. Position of WHO roll back malaria department on malaria treatment policy Nov. 2001. Available at, www.rbm.who.int/. Accessed 2en Decemeber 2016.
27. Sowunmi A. A randomized comparison of chloroquine, amodiaquine and their combination with pyrimethamine-sulfadoxine in the treatment of acute, uncomplicated, *Plasmodium falciparum* malaria in children. Ann Trop Med Parasitol. 2002; 96(3): 227-38.
28. Sowunmi A, Ayede AI, Falade AG, Ndikum VN, Sowunmi CO, Adedeji AA, Happi TC, Oduola AM. Randomized comparison of chloroquine and amodiaquine in the treatment of acute, uncomplicated, *Plasmodium falciparum* malaria in children. Ann Trop Med Parasitol. 2001; 95(6): 549-58.
29. WHO. Antimalarial Drug Combination Therapy: Report of a WHO Technical Consultation, 2001. WHO/CDS/RBM/2001.35.
30. Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant *falciparum* malaria: A review. J Postgrad Med. 2004; 50: 40-44.
31. White NJ. Assessment of the pharmacodynamic

properties of antimalarial drugs In Vivo. Antimicrobial Agents and Chemotherapy. 1997; 41(7): 1413-1422.

32. Sowunmi A, Fehintola FA, Adedeji AA, Gbotosho GO, Tambo E, Fateye BA, Happi TC, Oduola AM. Open randomized study of artesunate-amodiaquine vs. chloroquine-pyrimethamine-sulfadoxine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Nigerian children. Trop Med Int Health. 2005; 10(11): 1161-1170.
33. Eckstein-Ludwig U, Webb RJ, Van Goethem ID, *et al*. Artemisinins target the SERCA of *Plasmodium falciparum*. Nature. 2003; 424: 957-961.
34. Brewer TG, Grate SJ, Peggins JO, *et al*. Fatal neurotoxicity of arteether and artemether. Am J Trop Med Hyg 1994; 51: 251-259.
35. Moore KA, Simpson JA, Paw MK, Pimanpanarak, Wiladphaingern MJ, Rijken MJ, Jittamala P, White NJ, Fowkes FJI, Nosten F, McGready R. Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study. Lancent Infect Dis. 2016; http://dx.doi.org/10.1016/S1473-3099(15)00547-2
36. Schantz-Dunn J, Nour NM. Malaria and Pregnancy: A Global Health Perspective. Rev Obstet Gynecol. 2009; 2(3):1 86-192. doi: 10.3909/riog0091`