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Review Article

ANTI-MALARIAL DRUGS AND ITS FUTURE PROSPECTS

Santosh Kumar Singh and ∗Bijay Kumar
Molecular Biology Unit, Institute of Medical Sciences, Banaras Hindu University, Varansasi-221 005
∗Author for Correspondence: bijaysbt@gmail.com

ABSTRACT
Malaria infection is major concern against emergence of drug tolerant *Plasmodium* species. Drug resistance raised fair question to search for new anti-malarial drugs and look forward for innovative treatment strategy to combat deadly infection. Such drug must have certain features like specificity for the target, potency to eliminate blood stages of parasite and can prevent relapse of infection in liver after treatment. Current drug availability, uses and their mode of action can be useful for researcher and clinician to decide their job in social interest.

Keywords: *Malaria, Plasmodium, Anti-Malarial Drugs, Drug Resistance*

INTRODUCTION

Malaria is one of the deadly infectious diseases covering major part of the globe like Africa, Asia and America. It is caused by several species of *Plasmodium* in humans: *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium knowlesi* and *Plasmodium falciparum*. Most fatal form of infection is caused by *Plasmodium falciparum* and it causes severe complication in large population residing in Africa and South East Asia. If infected individual *with P. falciparum* left untreated, it may cause organ failure, block brain capillaries leading to coma (cerebral malaria) and ultimately may cause the death of the patient (W.H.O., 2014). Foremost lethality of *Plasmodium* is not only limited *P. falciparum*. There are many reports on lethal effect of *Plasmodium vivax* and *Plasmodium knowlesi* in humans (Gilles & Lucas, 1998). This review mainly emphasizes the current anti-malarial drugs and their mode of action.

Anti-malarial Drugs

Any compound sought to be as drug or drug like candidate that fulfills certain criteria, like specificity, safety, potency, doses and duration of treatment. An effective antimalarial drug eliminate all malaria parasite from erythrocytic stage and prevent their development to severe disease manifestation. Pharmacologically, anti-malarial drugs can be classified into eleven groups viz. (1) 4-Aminoquinolines, (2) Diaminopyrimidines, (3) 8-Aminoquinolines, (4) Quinoline-methanol, (5) Cinchona alkaloids, (6) Sesquiterpine lactones, (7) Amino alcohols, (8) Napthoquinones, (9) Tetracyclines, (10) Biguanides, and (11). Sulfonamides (Gilles & Lucas, 1998).

Aminoquinolines

All the drugs of this category primarily target the endolysosmal system of parasite. Most commonly used drug from this class is Chloroquine, that set gold standard for treatment. This drug was synthesized in 1940 in German laboratory. Initially chloroquine was not supposed to be safe for treatment but re-evaluation in 1943 found this drug safe for treatment (Coatney, 1963). Chloroquine belong to 4-aminoquinoline and is potentially active drug having blood schizonticidal property and effective against erythrocytic stages of all *plasmodial* strain. Chloroquine interferes with heame detoxification of the parasite that increase toxicity inside the cell and lead to death and elimination of the parasite. Cholorquine can be taken orally and quickly absorbed by gastrointestinal tract of the patient (Krishna & White, 1996). It frequently adheres to the plasma proteins, cellular component of the blood and various body tissues (Okonkwo et al, 1999; Salako et al, 1984). This provides great potential to the drug for killing parasite. Choloroquine long half-life 20-60 days is advantageous for treatment. Moreover, this drug is only active against uncomplicated form of malaria caused by *P. vivax*, *P. malariae*, *P. ovale* and *P. Knowlesi* (Krafts

et al, 2012). Resistance against the Chloroquine was reported in 1959 in South America and some region of South East Asia, afterwards many resistance cases were reported throughout world.

Diamino Pyrimidines

Pyrimethanmine inhibit the *Plasmodium falciparum* dihydrofolate reductase, this drug belongs to diamino pyrimidine class. It is quickly absorbed by gastrointestinal tract and profoundly distributed into spleen, liver, lungs and kidneys. It has half-life of approx 100 hours (Yuthavong, 2002). It works against pre-erythrocytic stage of parasite having schizonticide property. Resistance against pyrimethamine very frequently reported against *Plasmodium falciparum* from different parts of the world. These advocate clinicians not to use this drug alone for the treatment. Combination of pyrimethamine with sulphone / sulphonamide inhibitor is recommended for the treatment (Watkins et al, 1997).

8-Amino Quinolines

Primaquine belongs to 8-aminoquinolines and used for the treatment of infection caused by *P. vivax* and *P. ovale*. It is also active against liver stage of *Plasmodium falciparum* (Baird & Hoffman, 2004; Watkins et al, 1997). It gets metabolized in the cellular milieu to 6-methoxyprimaquine-8-aminoquinoline, hydroxyprimaquine and carboxyprimaquine (Vale et al, 2009). It is effective gametocytocidial compound and potentially active against matured gametocytes of *Plasmodium falciparum*. Use of this drug at early stage can control the spread of malarial parasite by blocking their transmission (Eziefula et al, 2014). It must not be used in G6PD deficient patient as it may cause the life threatening hemolysis disease. Even though it is uniformly distributed in the blood plasma within 2 hours, its short half-life (6 hours) lead to the emergence of resistant strains. The relapse of *Plasmodium vivax* infection reported in south pacific region is clear indication of drug resistance (Collins & Jeffery, 1996).

Quinoline-Methanol

Mefloquine is popular drug of quinoline–methanol class. It is potently active against intra-erythrocytic stage of *Plasmodium* infection. Schizonticide action of this drug is through the formation of the toxic mefloquine-ferriprotoporphyrin-IX complex (Foley & Tilley, 1998). It is equally effective against *Plasmodium vivax* and *Plasmodium falciparum*. Resistance against mefloquine was reported in 1982 at Thialand and South Eatern regions of Asia (Karwacki et al, 1989). Later, it was advised to all clinician to follow combination therapy to handle the spread of mefloquine resistant strain. Most of the combination therapy uses mefloquine / artemether or mefloquine / artesunate (Nosten et al, 1994; Price et al, 1995). Combination of artemisnine with mefloquine is very effective in the treatment of mefloquine resistant strain *Plasmodium falciparum* infection, as this combination of drug extends the half-life of mefloquine in the patients (Grellepois et al, 2005).

Cinchona Alkaloids

Cinchona alkaloids are in use from the ancient time for the treatment of malaria. Quinine is first drug of choice against malaria and this drug belongs to the arylamino alcohol class. Several other alkaloids, cinchona like quinidine, cinchonine and cinchonidine are effective against malaria infection. Quinine remains the drug of first choice for the treatment of malaria in African continent and other endemic region of the world and found to be very effective against uncomplicated form of malarial infection. Most of the cinchona alkaloids (quinine, quinidine, cinchonidine and cinchonine) interfere with haeme detoxification process of the parasite. Quinine potentially kills the sexual stages of the *P. vivax*, *P.malariae* and *P.ovale* but was not found effective against mature gametocytes of *P. falciparum*. It blocks the development of parasite to trophozoite (Wesche & Black, 1990). Tolerance / resistance for quinine in *Plasmodium falciparum* infection was reported at French Guiena and Brazil (Demar & Carme, 2004). Molecular detection has revealed that Pfmdr1 gene mutation is one of the major cause for quinine resistances.

Sesquiterpine Lactones

Artemisnin is compound derived from plant Qinghao (*Artemisia annua*), found very effective in destroying both asexual and sexual stage of parasite. (Thapar et al, 2002) This belongs to sesquiterpine lactone category of compounds. There are many semi-synthetic derivatives of artemisnin like dihydroartemisnin, water soluble hemi-succinate (artesunate), reduced lactol, the oil-soluble methyl ether

(artemether and erteether) (Bray et al, 2005; Daily, 2006; Kokwaro et al, 2007). Endoperoxide bridge of artemisinin plays major role in drug activity. There is dispute in opinion for artemisinin target and mode of action, some research have concluded that Fe^{2+} activated form preferentially disrupt the parasite Ca^{2+} transporter (PfATP6) and lead to the death of parasite (Eckstein-Ludwig et al, 2003).

1. Artemether

It is optional drug for the treatment of severe malaria if artesunate is not available. It is second choice of because it not easily soluble in water and only intramuscular dosages are available due to oil soluble nature of artemether. It is recommended in combination of lumefantrine for treatment of uncomplicated malaria caused by all species of *Plasmodium*. It is specifically active against *Plasmodium* ring stage followed by early schizonts. It also limit the malaria transmission by killing the gametocytes at erythrocytic stage of progression (Golenser et al, 2006). It is lipid soluble compound available as oil based oral or intramuscular injection dosages (Karbwang et al, 1997). Oral artemether is quickly absorbed from gastrointestinal tract and attain plasma protein peak in 2 hours. Once it reaches the liver, metabolized into dihydroartemisnin and eliminate the all species *Plasmodium*. The half-life of artemether range from 0.9 to 5.12 hours (Ashley et al, 2007).

2. Artesunate

Initial treatment of severe malaria usually done with artesunate. It is hemisuccinate analogue of dihydroatemisnin. It is recommended in combination with amodaquine, pyrimethamine, sulfadoxine and mefloquine. It is very effective in killing and elimination of all species of *Plasmodium* during acute uncomplicated malaria. It is potentially active in killing erythrocytic stage of parasite along with gametocytes. It is ineffective against merozoites, sporozoites and liver schizonts. It is highly hydrophilic in nature, effective in all form of dosage like oral, intramuscular, rectal and intravenous. Artesunate, after absorption in human body, metabolically converted into its active form dihydroartemisnin by easterases with the help of CYP2A6 enzymes (Batty et al, 1998).

3. Dihydroartemisinin

Severe malarial cases caused by *P.knowlesi*, *P. vivax* , *P. ovale*, *P.malariae* and *P. falciparum* are commonly treated with dihydroatemisnin derivatives. This drug used in follow up treatment of severe forms of malarial infection. It is recommended in combination of piperaquine (Price et al, 2007).

Amino Alcohol

Lumefantrine is schizontocidal drug; it belongs to aryl amino alcohol class. It is used in combination with artemether for the treatment of malaria. It blocks the haeme detoxification within food vacuole that lead to toxic heme formation inside erythrocyte. It is very effective erythrocytic schizonticide compounds for the treatment drug resistant *P. falciparum*. It is lipophilic in nature and always recommended to be used with fatty food for quick absorption by gastrointestinal tract. Half -life of lumefantrine ranges 3-6 days after administration, has strong curative potential (Murambiwa et al, 2011). It is metabolized in the liver to its active form desbutyl-lumefantrine (Wong et al, 2011).

Napthoquinones

Atovaquone belongs to hydroxyl-napthaquinone class of drug and effective in killing / elimination of all stages of *Plasmodium* species. It also blocks the oocyst development in *Anopheles* mosquito (Houin et al, 1983). Ubiquinone analog of napthoquinones block the transport of vital parasite enzymes that participate in mitochondrial based cytochrome electron transport system that eventually interfere in mitochondrial membrane potential and lead to death of the parasite (Baggish & Hill, 2002).

Atovaquone is lipophilic in nature; so always recommended to be taken with fatty food like milk or lipid reach diet (Deye et al, 2012; Pudney et al, 1999). It strongly binds with plasma protein and reaches peak plasma concentration within 5-6 hours. It has very short half-life of 1-5 days. Resistance to atovaquone from single point mutation in *cytb* gene was reported and that lead to the relapse of malaria after treatment (Thapar et al, 2002).

Tetracyclines

Doxycycline derived from oxytetracycline, is a member of tetracycline family. It is used in cases

where resistance to chloroquine observed. It is recommended to use with quinine to treat resistant *P. falciparum* cases of malaria. It is a broad spectrum antibiotic, having better pharmacokinetic properties such as longer half-life, good absorption and safety as compared to tetracycline. It inhibits protein synthesis through disruption of the normal function of apicoplast in malarial parasites (Dahl et al, 2006). It is distributed in body fluids and tissues. It undergoes enterohepatic circulation, thus the clearance is slowed down. Excretion is extensively by the process of chelation in the gastrointestinal tract and to a lesser extent through renal elimination. The elimination half-life is around 8.8 to 22.4 hours (Dahl et al, 2006; Gilles & Lucas, 1998)

Biguanides

The proguanil and chloroproguanil belongs to biguanide group. In liver, both the drugs are metabolized to cycloguanil and chlorcycloguanil respectively. Proguanil is used for prophylaxis and chlorproguanil is used in combinational therapy. These drugs act on pre-erythrocytic phase, erythrocytic phase and prevent the sporozoite formation in mosquitoes. It is highly safe and affordable. Biguanides inhibits the dihydrofolate reductase-thymidylate synthase of *P. falciparum* and prevent the conversion of dihydrofolate to tetrahydrofolate (White, 1992).

Sulfonamides

Sulfonamides are no more effective antimalarials. Sulfadoxine is one of the member of the category sulphonamides. It is recommended along with pyrimethamine and it is used to prevent the transmission of moderate to high intensity malaria. This combination is active against erythrocytic phase of *plasmodium falciparum.* Sulfadoxine-pyrimethamine combination is prescribed with artesunate for effective treatment of acute uncomplicated malaria (Likwela et al, 2012).

CONCLUSION

Malaria is common life threatening disease of poor people, living in underdeveloped region of the world. Current trend of disease diagnosis and treatment are of high standard. WHO is making all its effort to bring access of drug and hospital facility to patient in outreach part, but unable to reach complete eradication or control of disease spread due to challenging geographical and climatic conditions. Poor drug regimen in these countries leads to the emergence of the drug resistant parasite. Most of the drugs used for treatment are potentially active against blood stages of parasite. Few drugs are primarily available that kills liver stage and stop the relapse of infection. There is urgent need to look for the drug molecules that can block the multiplication of parasite in mosquitoes and potentially block the liver stages in humans to avoid the relapse of disease.

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Conflict of interest

The authors declare that they have no conflict of interest.

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