e-ISSN : 2686-2506

Majalah Farmasetika, 5 (1) 2020, 39-48
https://doi.org/10.24198/mfarmasetika.v5i1.25927

Antimalaria Medicine and Its Mechanism : A Review

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(Submit 24/1/2020, Revisi 28/1/2020, Diterima 30/1/2020)

Abstract

Malaria is a deadly disease caused by Plasmodium infection that is spread by female Anopheles. Malaria is a serious and deadly disease due to Plasmodium infection which is spread by female Anopheles mosquitoes. Among the five Plasmodium species, the most common species attacking humans are the Plasmodium falciparum and Plasmodium vivax species. Decreased sensitivity resulting in continuous and inadequate treatment, causing parasitic mutations, other than that allegedly originating from resistant areas. The purpose of this paper is to find out some anti-malaria drugs and the mechanism of action used in Indonesia based on references from the current development of anti-malaria drugs. While the benefits are providing information about antimalarial drugs and the mechanism of action in the use of drugs in Indonesia for malaria. Treatment of malaria is classified into 3, namely: classification of malaria drugs based on the workings of drugs in the Plasmodium life cycle, classification of antimalarial drugs based on the chemical structure of the drug, and classification of antimalarial drugs based on the workplace of the drug in the Plasmodium subcellular organelle.

Keywords: Malaria, Plasmodium, antimalarial, mechanism

Outline

- Introduction
- Discussion
- Conclusion
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Introduction

Malaria is a serious and deadly disease caused by Plasmodium falciparum infection which is spread by Anopheles mosquitoes[1]. Malaria also remains an infectious disease, infecting millions of people, especially in the tropics. Among the five Plasmodium species, the most common species attacking humans are Plasmodium falciparum and Plasmodium vivax species[2]. Despite the increase in its impact, malaria will continue to affect human health. The updated forecasts show that 212 million cases occur by 2015, which caused 429,000 deaths, most occur in children under 5 in Africa[3].

Decreased sensitivity resulting in continuous and inadequate treatment, causing parasitic mutations, other than that allegedly originating from resistant areas. In the last thirty years, Plasmodium falciparum has been resistant to existing anti-malaria drugs. Antimalarial drug resistance has also occurred against Plasmodium vivax and has been reported from Papua New Guinea, India, Myanmar, and Indonesia so that malaria treatment must be adapted to the geographical conditions of each country[4].

Efforts to eradicate malaria were severely hampered due to the development of Plasmodium falciparum resistance to current antimalarial drugs such as chloroquine, sulfadoxine-pyrimethamine, amodiaquine, and kinin. The mechanism of resistance is due to genetic mutations that occur naturally in malaria parasites that provide benefits for the parasite to survive[5].

The purpose of this paper is to discuss some antimalaria drugs and the mechanism of action of drugs used in Indonesia based on references from the current development of antimalaria drugs.

Discussion

Malaria Life Cycle

The malaria life cycle consists of 2 cycles, namely the exogenous sexual phase (sporogony) in the body of the mosquito and the asexual (schizo) phase in the body of the intermediate/human host6.

Sexual Phase Exogenous (Sporogoni) in Mosquito Body

Mengingesti female Anopheles mosquito erythrocytes containing microgametes and macrogametes of patients. In the mosquito's body mating occurs between microgametes and macrogametes producing zygotes. This mating occurs in the mosquito stomach. The zygote develops into an ookinete, then enters the wall of the stomach of the mosquito to develop into an oocyst, after the oocysts mature and rupture, out of the sporozoite that moves to the mosquito's salivary gland and is ready to be transmitted to humans

Asexual Phase (Skizon) in the Body of Intermediary/Human Hospes

Hepatic Cells Cycle (Skizon Eksoritrositik)

When biting the humans, the sporozoites of Anopheles enter the bloodstream for 1/2 to 2 hours then head to the liver to multiply. This sporozoite quickly infects the liver cells and then develops into the exoerythrocytic schizont. The exoerythrocytic schizont contains up to 30,000 merozoites. Liver cells infected with exoerythrocytic schizont rupture and release mature merozoites into the bloodstream.

Erythrocytes Cycle (Skizon Eritrositik)

Merozoites are released from erythrocytes infects liver cells, then evolved into reform, then trophozoite, and eventually become schizonts. Erythrocytes containing schizont rupture and release merozoites to infect other erythrocytes.

Malaria Symptoms And Parasite Mechanisms In Infecting Eritrosits

Symptoms of Malaria

Clinical manifestations of malaria depends on the immunity of patients and the high transmission of malaria infection, while the lightness or heaviness of infection will be affected by Plasmodium species, age, area of origin of the infection, state of health, nutrition consumed, the alleged genetic constitution, as well as chemoprophylaxis and treatment earlier[6].

Paroxysmal

A condition where the attack occurs very often and in a short time, such as cold, headache, diarrhea, vomiting, nausea, anorexia, chills, cramps, stiffness, fever for 48 hours, fever at body temperature ≥37,5 °C, hepatomegaly, splenomegaly7.

Clinical manifestations of symptoms of severe malaria

A condition where the attack is more severe, such as respiratory distress, severe anemia, collapse, hyperpyrexia, persistent vomiting, hypoglycemia, hypotension, coma, convulsions, hemoglobinuria6,7.

The Mechanism of Plasmodium falciparum in Infecting Erythrocytes

The occurrence of Plasmodium falciparum infection in humans occurs when sporozoite is released from the salivary gland of female Anopheles mosquitoes (containing malaria parasites). It then enters the blood cells and liver tissue. The life cycle of the malaria parasite forms the tissue sizone stage in liver cells (exoerytrocyther stage). After liver cells rupture, then release merozoites that enter the erythrocytes to form the sizone stage in erythrocytes (erythrocyte stage). The shape of the young troposite until the mature sizone causes the erythrocytes to break out and out of merozoites. Most Merozoites reenter the erythrocytes and a small portion form male gametocytes.

The cycle of female Anopheles mosquitoes. Female Anopheles is infected by female malaria mosquitoes and continue their life cycle in the mosquito body (sporogony stage). Inside the mosquito's stomach, there is a marriage between gamete cells called zygotes. The zygote will turn into an ookinete, and turn into an oocyst in mosquito's stomach. The mature form will break and secretes sporozoites that enter the mosquito's salivary gland[8].

Antimalaria Medicines And Mechanism of Its Work

Classification of Malaria Drugs Based on How the Drug Works on the Plasmodium Life Cycle

Blood Schizontoside Antimalarial Medicine

It is the one who attacks the *Plasmodia* that live in the blood. This type of antimalarial is for prevention and ending clinical attacks[6], such as primaquine[9], artemisinin, dihydroartemisinin[10], chloroquine, mepacrine, amodiaquine, mefloquine, quinine, quinidine, halofantrine and tetracycline, fluoroquinolone, and erythromycin, erythromycin, erythrome[11,12].

Chloroquine is one of the autophagy inhibitors antimalarial drugs[12,13]. Chloroquine, a 4-aminoquinoline drug, is widely used throughout the world where malaria is endemic. It has been the most effective and cheapest antimalarial for several decades, and still recommended to treat *Plasmodium vivax* infections. Indeed, chloroquine has a quick onset reaction, with low toxicity[12,14].

The mechanism of chloroquine is the inhibition of the formation of β-43 hematin in the vacuole of the parasite[12,14]. The mechanism of action of this drug is unclear because it is alkaline drug can achieve high concentrations in food vacuoles from parasites and increase its pH. Chloroquine suppresses the enzyme heme-polymerase from the parasite which functions to change the heme toxin into non-toxic hemozoin that results from the accumulation of toxic heme in the body of the parasite. Chloroquine also inhibits the process of nucleic acid biosynthesis[4].

Mefloquine is a methanol quinoline, having a similar structure with quinine. This is a strong and long-acting blood schizontocide, and effective in killing malaria parasites including *Plasmodium falciparum* which is resistant to chloroquine, and quinine[12,14].

Tissue Antimalarial Medication

It is the one that kills *Plasmodia* in the exoerythrocytic phase in the liver, preventing the invasion of *Plasmodia* in blood cells[6], such as pyrimethamine and primaquine. This group of drugs can prevent relapse in *Plasmodium vivax* infection[15].

Pyrimethamine is a weak base drug with water solubility ~40 µg/ml at 25°C. Pyrimethamine has pKa 7 at 20°C and logP 2.7. Even though the base is weak, pyrimethamine release at gastric pH (~1-2) does not reach 100% even after 3 hours[16].

Primaquine (PMQ), 8-aminoquinoline, is antimalarial drugs that have the advantage of preventing recurrence in *Plasmodium vivax* and *Plasmodium ovale*, and including powerful drugs against gametocytes from *Plasmodium falciparum* infection. The disadvantage of PMQ is the acute hemolytic toxicity to people having glucose-6-phosphate dehydrogenase (G6PD) deficiency[17]. The mechanism of action of this drug is not yet clear, it is suspected that this drug works by producing reactive oxygen or competing with electron transport in parasitic bodies. Primakuin is well absorbed after oral administration and is rapidly metabolized. Half time ± 6 hours. Metabolites from primaquine are oxidative substances and can cause hemolysis in sensitive patients[4].

Gametocide Antimalarial Medication

It is killing the stage of gametocytes in the blood[6], gametocide works by destroying the sexual form of all species of *Plasmodium* malaria in the blood so as to prevent the transmission of parasites to the body of mosquitoes like Primakuin[4].

Antimalarial Drug Sporontocide

Inhibiting the development of further gametocytes in the body of mosquitoes that suck human blood, so that there is no transmission, such as the drug groups primaquine and proguanil[15]. Proguanil is one of the antimalarial prophylactic drugs usually taken simultaneously with other antimalarial drugs, namely atovaquone or chloroquine. The cytochrome P450 enzyme converted in the liver, into 4-chlorophenyl-1-biguanide (CPB) and active metabolite cycloguanil (CG). Proguanil is a phenylbiguanide group and has a striking structural similarity to the 5-hydroxytryptamine 3 (5-HT3) receptor widely known as agonistmeta-chlorophenyl biguanide (Mcpbg)[18].

Classification of Antimalarial Drugs Based on the Structure of Drug Chemistry[15]

Table 1: Antimalaria Classification Drug

Antimalarial Drug Classification	Drug Name
Aryl aminoalkohol	Kuinolon metanol kinina & meflokuin dan phenanten metanol halofantrin
4-aminokuinolon	Klorokuin dan amodiakuin
Sulfanes	Di aminophenil sulfone & sulfadoksin, sulfalene dan kontrimoksasol
Biguanida	Proguanil/ klorguanida dan klrorproguanil
8-aminokuinolon	Primakuin
Antibiotik	Tetrasiklin, doksisiklin, clindamisin
Obat antimalaria peroxide	Artemisinin Artemisinin Artemether Dihydroartemisinin Arteether Artesunate Artelinic acid
Diaminopirimidin	Pirimetamin
Alkaloids cinchona	Kinina

Classification of Antimalarial Drugs Based on Medication Workplace in Subcellular Organelles Plasmodium

Group 4-aminocinolin Drug

The 4-aminoquinoline chloroquine drug (Figure 1) has been widely used in malaria treatment. Chloroquine expected to be trapped in parasitic vacuoles, where chloroquine inhibits the biocrystallization of β-hematin.

This is a result of the nature of the vacuole, where chloroquine becomes 'trapped' in the form of an impermeable membrane that is definitely protected. Chloroquine then complexes with heme free, leading to the heme accumulation and ultimately, parasitic death[19].

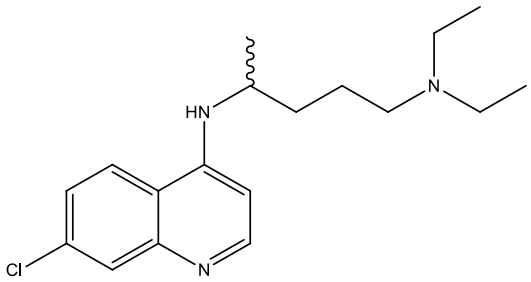

Fig.1 Chloroquine[19].

Antibiotic

Doxycycline and tetracycline have simple antimalarial activity against *Plasmodium vivax* or *Plasmodium falciparum*. Doxycycline has now replaced tetracycline for use in combination with quinine against *Plasmodium falciparum* because of its therapeutic advantages of twice-daily doses and low costs (US $ 3.14/100 generic capsules in Indonesia)[20].

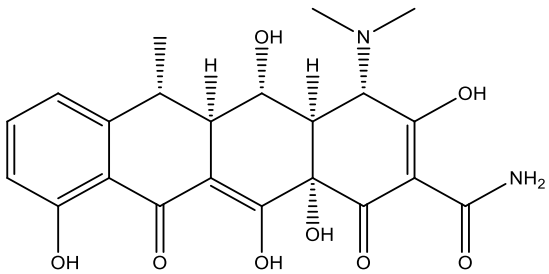

Fig. 2 Doxycycline[21]

Antimalarial Drug Sulfadoxine and Pyrimethamine

Sulfadoxine and pyrimethamine are blood schyzontocides that work slowly and are more effectively active against *Plasmodium falciparum* than *Plasmodium vivax*. They inhibit dihydrofolate reductase from *Plasmodia*, which is important in etrahydrofolate biosynthesis. Sulfadoxine-pyrimethamine is also called the group of anti-folate drugs because it works by blocking the two pathways of the formation of folate in the body of the parasite. Sulfadoxine inhibits the use of *para-aminobenzoic acid* (PABA) by inhibiting the enzyme *dihydropteroate synthase* (DHPS). Pyrimethamine inhibits the *enzyme dihydrofolate reductase* (DHFR) from Plasmodium thereby blocking the synthesis of thymine and purines which are important ingredients for DNA synthesis and cell multiplication[4].

The half-life of Sulfadoxine and Pyrimethamine is ~169 hours and ~111 hours α/β-Arteether is a CYP3A4/5 substrate, whereas sulfadoxine-pyrimethamine has no interaction with CYP3A4/5[22].

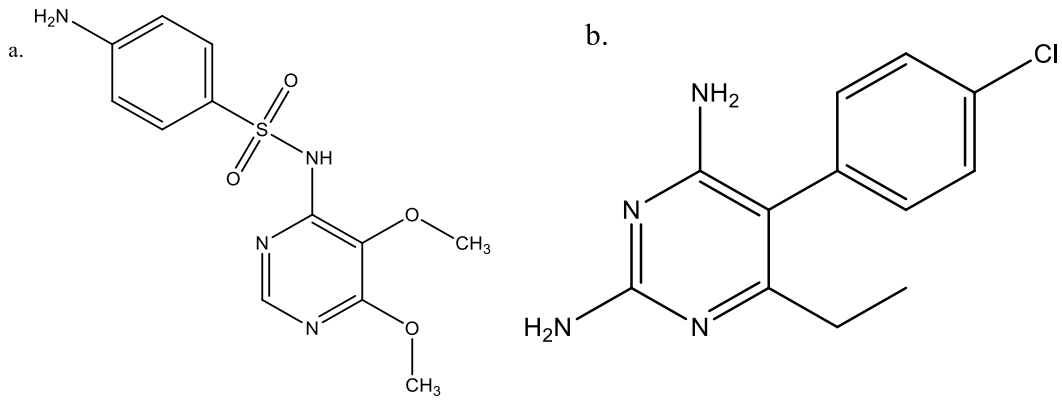

Fig. 3 a. Sulfadoxine dan b. Pyrimethamine[23]

Drug Generation From Artemisinin

Artemisinin is a sesquiterpene molecule contained sesquiterpen molecules including hydrogen, carbon, and oxygen but does not have a nitrogen atom and has advantages in the treatment of several drug-resistant strains of *Plasmodium falciparum* (MDR). Artemisinin has an antimalarial working mechanism that is different from other antimalarial drugs such as quinine, chloroquine, etc[12].

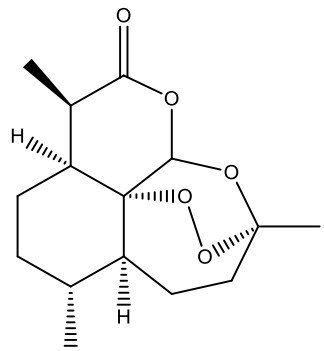

Fig. 4 Artemisinin[24]

Mechanism of working artemisinin: The structure of artemisinin is not like other antimalarial structures which have different working mechanisms. The mechanism of action of this drug is based on the presence of endoperoxide is needed for antimalarial activity. Because peroxide is known as reactive oxygen source species such as hydroxyl radicals and superoxide, the free radicals intensively involved in its mechanism of action. In the mechanism of action of artemisinin derivatives, free radicals showed an important role.

Meshnick and collaborators (1991) proved that artemisinin was intensively interacted with intra-parasitic heme. They also proved that heme or intra-parasitic iron could function of activating parasites of artemisinin into toxic free radicals. Malaria parasites are rich in iron-heme, which originates from host hemoglobin proteolysis. This result was the main reason for an explanation of artemisinin as selective parasites killer[25].

Conclusion

The group of malaria medicines consists of 3, namely: classification of malaria drugs based on the workings of the drug in the *Plasmodium* life cycle, classification of antimalarial drugs based on the chemical structure of the drug, and classification of antimalarial drugs based on the drug workplace on the subcellular organelles *Plasmodium*. It is known that chloroquine, pyrimethamine, primaquine, proguanil, doxycycline, tetracycline, sulfadoxine, and artemisia are drugs used in the treatment of malaria.

Acknowledgement

Thank you to Dr. rer. nat. Anis Yohana Chaerunisaa, M. Si., Apt. and Prof. Dr. Anas Subarnas, M. S., Apt. As a mentor who has provided comments and suggestions for the preparation of this paper.

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