EISSN
INTERNATIONAL JOURNAL OF TECHNOLOGY, EDUCATION AND SOCIAL HUMANITIES
https://journal.bengkuluinstitute.com/index.php/IJoTES
IJoTES

Volume 2 Number 1 January- June 2024
https://journal.bengkuluinstitute.com/index.php/IJoTES

Article Review

Effect of the Anti-Malarial Drug Mefloquine on the Reproductive System of Plasmodium falciparum

Chusna Lailatul Muna[1*]; Dewi Putri Ayu Wifdaturrohmah[2)]

[1,2,]Tadris Science Study Program, Faculty of Tarbiyah, Institut Agama Islam Negeri Kediri, East Java, Indonesia
*E-mail correspondence: chusnalailatulmuna031@gmail.com

Abstract

This study aims to determine the effect of Mefloquine on the Plasmodium falciparum reproductive system. This research includes Pubmed literature research, using the library research method where information sources are obtained through articles, e-books and e-journals. The results obtained were 3 Pudmed articles. From the studies that have been carried out, it was concluded that Mefloquine has a significant influence on the Plasmodium falciparum reproductive system, seen from the disappearance of parasitemia and cured disease, proving that Mefloquine can significantly influence the Plasmodium falciparum reproductive system. To make it more effective, it can also be combined with other drugs such as the AS-MQ-PQ combination (Artemisinin, Mefloquine and Primaquine) which shows faster results.

Keywords: *Malaria, Mefloquine, Plasmodium falciparum and Reproduction System.*

INTRODUCTION

Almost half of the people around the world, about 3.2 billion people, are at risk of being infected with malaria. And every year it is estimated that about 1-3 million deaths from malaria and it is known that many children under 5 years old and pregnant women are victims. In Indonesia itself there are still provinces infected with malaria, especially the eastern part of Indonesia which is a malaria endemic area. (Agung Bagus S. Satyarsa, et al., 2020)

There are five species of the genus *Plasmodium* that cause malaria. The five species are *Plasmodium falciparum, Plasmodium ovale, Plasmodium knowlesi, Plasmodium vivax and Plasmodium malariae.* The parasites that cause malaria are different, so the type of malaria suffered is also different, if malaria is caused by *Plasmodium falciparum* it is called tropical malaria which causes many deaths, if malaria is caused by *Plasmodium vivax* it is called tertiana malaria, if malaria is caused by *Plasmodium malariae* it is called kuarta and others. (Khayriah, 2016)

In the 2013 Riskesdas data, it was recorded that 6.0% of malaria was caused by the *Plasmodium falcifarum* parasite. Indonesian provinces indicated as malaria areas are Papua, NTT (East Nusa Tenggara), West Papua, Central Sulawesi, and Maluku.

P. falcifarum not only has a high mortality and prevalence rate, but also a high morbidity and progression rate. The symptoms of *P. falcifarum* malaria are nonspecific such as headache, fatigue, muscle pain, joint pain, as well as dizziness, fever, chills, sweating, lack of appetite, and coughing. If *P. falcifarum* malaria is not treated properly, it will be fatal and even lethal. (Agung Bagus S. Satyarsa, et al., 2020)

One of the malaria medications is Mefloquine. Mefloquine is an anti-malarial drug that works by interfering with the life processes of malaria parasites in the human body. This drug belongs to the aminoquinoline antimalarial drug group that affects the life cycle of the malaria parasite.

The following is an explanation of mefloquine's mechanism of action:

1. Penetration into Malaria Parasites: Mefloquine must enter malaria parasite cells through a passive diffusion process to initiate its effects.
2. Interference with Hemoglobin: Once inside the parasite cell, mefloquine affects the hemoglobin molecule which is an oxygen transporting protein in red blood cells. Mefloquine interferes with the utilization of hemoglobin by the malaria parasite, inhibiting the growth and development of the parasite.
3. Effects on the Parasite Nervous System: Mefloquine also affects the nervous system of the malaria parasite by inhibiting important nerve pathways, interfering with the parasite's activity.
4. Interference with Parasite DNA: Mefloquine can damage the parasite's DNA, inhibiting the formation of new DNA necessary for parasite reproduction.
5. Effect on Parasite Life Phase: Mefloquine is effective against both the asexual and sexual phases of malaria parasites, slowing the growth and preventing the spread of parasites in the human body.

The administration of mefloquine is tailored to the type of malaria parasite and the medical condition of the individual. Use of this drug should be in accordance with the prescribed dosage and with careful medical monitoring to maximize effectiveness and reduce the risk of side effects. It is important to use mefloquine as directed by the doctor and avoid inappropriate use.

In Colombia, malaria is a serious public health problem. In 2009, a total of 79,909 cases were reported. In the period 2000-2006, first-line therapy for uncomplicated cases of falciparum malaria was the combination amodiaquine-sulfadoxine/pyrimethamine (AQ-SP), with the addition of a single dose of primaquine (PQ) (0.75 mg/kg) on the fourth day of treatment. After June 2006, health authorities recommended therapy with artemisinin-mefloccine (AS-MQ) or artemether-lumefantrine (AM-LF) and continued with more specific studies outlined in the results. (Arango EM, et al., 2012) Of the many people in the world infected with malaria, the purpose of this study is to determine the effect of Mefloquine on the reproductive system of *Plasmodium falciparum.*

RESEARCH METHODS

This research, using the method of literature review or *lybrary research.* Where the author collects data and analyzes and draws conclusions from the information sources obtained. References in this study were obtained from Pubmed literature. This research also comes from articles, e-books, and e-journals, which are related to the effect of the malaria drug Mefloquine on the development of the Plasmodium reproductive system, especially *Plasmodium falciparum*.

RESULTS AND DISCUSSION

Based on Pubmed literature, there are 3 articles that discuss the effect of the anti-malarial drug Mefloquine on the reproductive system of *Plasmodium falciparum*. Tropical malaria caused by *P.falciparum* appears after an incubation period of 7-14 days after being bitten by anopheles mosquitoes. Malaria caused by *P.falciparum* can be a serious and potentially life-threatening disease if not treated quickly. There are symptoms that appear in malaria caused by *P.falciparum* according to how severe the disease is, including the following: (Emanuel Ileatan Lewar, n.d., 2016)

a. High Fever: Fever is the main symptom of malaria. The body temperature may rise suddenly and reach high numbers.
b. Dizziness and Headache: Patients often experience severe dizziness and headache accompanied by discomfort.
c. Muscle and Joint Pain: People with malaria tend to feel pain in the muscles and joints, making physical activity difficult.
d. Nausea and Vomiting: Nausea and vomiting may occur along with fever.

EISSN
INTERNATIONAL JOURNAL OF TECHNOLOGY, EDUCATION AND SOCIAL HUMANITIES
https://journal.bengkuluinstitute.com/index.php/IJoTES
IJoTES
Volume 2 Number 1 January- June 2024
https://journal.bengkuluinstitute.com/index.php/IJoTES

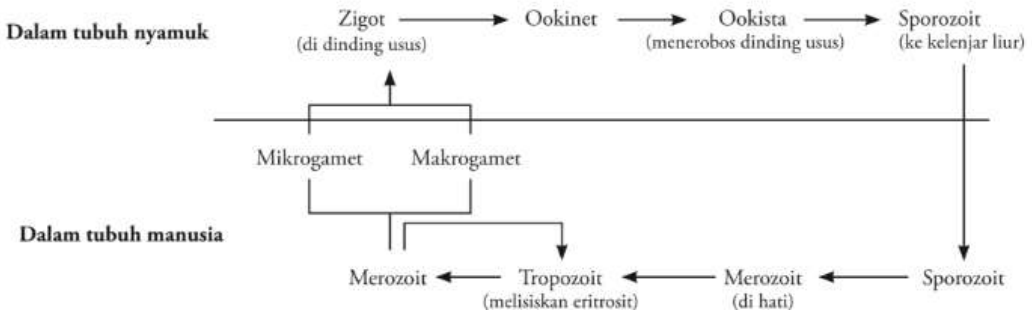
e. Chills: Patients often experience chills, especially when the body temperature rises.
f. Abdominal Pain: Pain in the abdominal region may occur, often accompanied by indigestion.
g. Weakness and Fatigue: Patients may feel very weak and tired.
h. Anemia: Plasmodium falciparum can cause damage to red blood cells, which can lead to anemia (a condition of lack of red blood cells).
i. Splenomegaly: If the infection is not addressed, the spleen may enlarge in response to the increased number of parasites in the blood.
j. Impaired Consciousness and Coma: In severe cases, especially in children or adults with weak immunity, Plasmodium falciparum can cause impaired consciousness and coma.
k. Impaired Kidney and Liver Function: Severe malaria can affect vital organs such as the kidneys and liver.
l. Respiratory distress: In very severe cases, falciparum malaria can cause serious respiratory distress.

In Colombia, malaria is a serious public health problem. In 2009, a total of 79,909 cases were reported. In the period 2000-2006, first-line therapy for uncomplicated cases of falciparum malaria was amodiaquine-sulfadoxine/pyrimethamine (AQ-SP), with the addition of a single dose of primaquine (0.75 mg/kg) on the fourth day of treatment. After June 2006, health authorities recommended therapy with artemisinin-meflocine (AS-MQ) or artemeter-lumefantrine (AM-LF). (Gomes, A. R. Q., n.d.) Several studies in Colombia have verified therapeutic efficacy exceeding 96% for the former regime (AQ-SP) and artemisinin-based combination therapy (ACT). (Arango EM, et al., 2012)

However, the effect of antimalarial treatment on P. falciparum gametocytemia in Colombia has rarely been evaluated. There are only four studies comparing microscopic gametocythemia after treatment in the period 2002-2010: two studies considered chloroquine and/or SP; one evaluated the AQ-SP combination, the AQ-AS combination, and the AS-SP combination and one evaluated the AS-MQ combination and the AS-MQ-PQ combination. These studies verified that microscopic gametocytemia was not affected by therapy without AS or PQ. Administration of AS therapy resulted in lower gametocytemia, although gametocytes remained for 2-3 weeks after treatment. Moreover, the addition of PQ after 24 hours of MQ-AS treatment resulted in one week faster elimination of gametocytes compared to MQ-AS treatment without PQ.

This result agrees with the study of Tangpukdee N and other experts who showed that the use of Mefloquine given together with artesunate can eliminate fever and asexual parasitemia after 7 days of treatment. This study also observed the reaction of patients with malaria and the results showed a cure on day 7. (Tangpukdee et al., 2008)

Usually, primaquine is given after blood schizone therapy is completed (day 4), but its efficacy against gametocytemia has not been studied based on the timing of administration. Co-administration of PQ with blood schizonts is known to increase efficacy against asexual parasites, without increasing the risk of toxicity. Therefore, delaying PQ administration in clinical practice is not justified, as this may prolong the period of gametocytemia and inhibit the transmission-blocking effect. (Arango EM, et al., 2012)



Reproductive System of *Plasmodium falciparum*: (Operation, G. 2017)

Plasmodium falciparum has a complex life cycle involving two main hosts, humans and Anopheles mosquitoes. (Mau, S.Si, M,Sc & Mulatsih, 2017) In the reproductive system of this parasite, there are several important stages:

a. Asexual Cycle (Schizont): The parasite enters human red blood cells, multiplies, and replicates in this phase. This stage is when malaria symptoms such as fever and anemia occur. From research that has been conducted by experts shows that the use of Mefloquine given together with artesunate can eliminate fever and asexual parasitemia after 7 days of treatment. This study also observed the reactions of patients with malaria and the results showed a cure on day 7. (Tangpukdee et al., 2008)
b. Sexual Cycle (Gametocytes): During infection, a portion of the parasite turns into gametocytes, which are the sexualized form of the parasite. Gametocytes are the stage that can be transmitted through Anopheles mosquitoes as they draw blood. (Banyal et al., 2016)
c. Mating in the Mosquito Body: After the mosquito draws blood containing gametocytes, male gametocytes (microgametocytes) and female gametocytes (macrogametocytes) mate in the mosquito's body, producing sporozoites, a form of the parasite that can infect humans when the infected mosquito bites back. (Dayat & Banyal, 2018a)

The reproductive system of *Plasmodium falciparum* plays an important role in the life cycle and transmission of the disease. Since gametocytes are the stage that can be transmitted to others, antimalarial drugs must also be effective against this stage to control the spread of the disease. Therefore, drug resistance developing in the asexual or sexual stages can have a serious impact on malaria control efforts.

DISCUSSION

Mefloquine, as an anti-malarial drug, has an impact on the sexual reproductive phase or gametocytes of *Plasmodium falciparum*. *Plasmodium falciparum* is the parasite that causes the most dangerous malaria for humans. Mefloquine can affect the function of *Plasmodium falciparum* sexual reproductive cells, including the formation and development of reproductive cells such as microgametocytes and macrogametocytes. It can be observed that Mefloquine can show the results of eliminating parasites on day 7 after treatment.

Mefloquine can affect various stages of the *Plasmodium falciparum* life cycle, including the asexual stage in the human body and the sexual stage in the mosquito. By interfering with these various stages, Mefloquine helps to inhibit the development of the parasite and prevent the spread of infection.

Inhibition of Gametocyte Formation and Maturation

Mefloquine interferes with the formation and maturation of gametocytes, the phase of the parasite that develops into sexually reproductive cells. This reduces the number of mature gametocytes and may inhibit the parasite's sexual reproduction.

EISSN
INTERNATIONAL JOURNAL OF TECHNOLOGY, EDUCATION AND SOCIAL HUMANITIES
https://journal.bengkuluinstitute.com/index.php/IJoTES
IJoTES
Volume 2 Number 1 January- June 2024
https://journal.bengkuluinstitute.com/index.php/IJoTES

By inhibiting the formation and maturation of gametocytes, Mefloquine can reduce the number of parasites that can be transmitted through the Anopheles mosquito vector. This is important in efforts to control the spread of malaria, as gametocytes are the form of the parasite that can be transmitted from humans to mosquitoes and then spread to others through the bites of infected mosquitoes.

However, it is important to note that Mefloquine's effect on the reproductive system of *Plasmodium falciparum* does not completely stop the parasite's reproductive cycle. Therefore, the use of Mefloquine should still be combined with other preventive measures, such as the use of insecticide-treated bed nets and mosquito vector control, to ensure effective control of malaria.

The use of Mefloquine in patients with malaria can eliminate parasitemia and fever on the 10th day after treatment. Mefloquine is more effective when taken with the combination of AS-MQ-PQ (Artemisinin, Mefloquine and Primaquine), the drug will work 7 days faster with this combination. (Ankalgi et al., 2020)

Clinical outcomes and parasite elimination effectiveness of AS-MQ (with or without PQ) reached 100%, with all patients having no parasitemia and no fever by the third day of treatment. The use of PQ improved gametocyte elimination, with 92% of patients receiving PQ having no gametocytes on day 3, compared to 78.3% of patients receiving only AS-MQ. Furthermore, the use of the AS-MQ-PQ treatment scheme resulted in the elimination of circulating gametocytes on average one week faster than the scheme without PQ. (Nosten, F., 2000)

For the treatment of *P. falciparum* malaria, this study recommends the use of AS-MQ based on its good therapeutic efficacy. However, further assessment is needed regarding the benefits of adding PQ to this treatment regimen. (Vásquez AM, et al., 2009)

Inhibition to Gametocyte Proliferation

Mefloquine can inhibit the ability of gametocytes to multiply after being transmitted to vector mosquitoes. This reduces the possibility of transmitting malaria to other people through mosquitoes.

In addition to inhibiting gametocyte formation, Mefloquine can also interfere with the ability of gametocytes to multiply in human blood. (Martins AC, et al., 2021) This reduces the number of gametocytes that can be produced by the parasite and ultimately reduces the potential for transmission of the parasite to mosquitoes when mosquitoes suck blood from an infected person.

Prevention of Parasite Transmission

By reducing the number and reproductive ability of gametocytes, mefloquine helps inhibit the transmission of parasites from humans to Anopheles mosquitoes and vice versa. Ookinetes are the early forms of Plasmodium falciparum parasites that are involved in the invasion process of Anopheles mosquitoes when the parasite passes from humans to mosquitoes. (Dayat & Banyal, 2018b) This invasion is an important stage in the life cycle of the malaria parasite, where the parasite will transform into ookinetes and then move into the intestinal tissue of the mosquito to multiply and spread into the mosquito's body.

Anti-malarial drugs play an important role in inhibiting ookinetes at the stage of invasion into Anopheles mosquitoes, thereby preventing the spread of malaria. By inhibiting ookinetes, anti-malarial drugs help reduce the transmission of parasites from humans to Anopheles mosquitoes, thus playing an important role in overall malaria control. (Dinata, A., 2018) It is important to use anti-malarial drugs according to the correct dosage and medical instructions to maximize their effectiveness in inhibiting ookinetes and preventing the spread of malaria. (Adnyanal, 2014)

Drug Resistance and Reproductive System of *Plasmodium falciparum*

Drug resistance in *Plasmodium falciparum, the* parasite that causes the highly dangerous malaria, refers to a condition in which the parasite shows a decreased level of sensitivity or even loses response to drugs that are usually effective in treating malaria infections. (Price RN, 2004) The phenomenon of drug resistance is a serious problem in malaria control efforts because it can reduce the effectiveness of treatment and increase the severity of the disease. The following is an explanation of drug resistance and the reproductive system of *Plasmodium falciparum*:

1. Genetic Mutation: *Plasmodium falciparum* has the ability to undergo genetic changes naturally. Some of these changes can lead to drug resistance. For example, genetic mutations in the parasite can change the target structure of the drug, making the drug no longer effective.
2. Adaptive Parasite Selection: Use of antimalarial drugs at inappropriate doses or use not according to the doctor's instructions can create selection pressure on parasites. Parasites that have mutations that confer immunity to the drug will be more likely to survive and reproduce, while susceptible parasites will die. As a result, a population of drug-resistant parasites may develop.
3. Resistance Gene Transfer (Nindela, 2015) : Drug-resistant parasites can also transfer resistance genes to other parasites through sexual interbreeding within vector mosquitoes that draw blood from infected humans. This can lead to a wider spread of drug resistance.

CONCLUSIONS

Malaria is caused by parasites of the genus Plasmodium, there are *5* species that cause malaria, one of which is *Plasmodium falciparum.* Mefloquine, as an anti-malarial drug, has an impact on the reproductive system of *Plasmodium falciparum*, namely ;

1. Effects on Sexual Reproductive Cell Function
2. Inhibition of Gametocyte Formation and Maturation
3. Inhibition to Gametocyte Proliferation
4. Prevention of Parasite Transmission

Mefloquine has a significant effect on the reproductive system of *Plasmodium falciparum* seen from the lost parasitemia and cured disease proves that Mefloquine can significantly affect the reproductive system of *Plasmodium falciparum*. To be more effective it can be combined with other drugs such as the combination of AS-MQ-PQ (Artemisinin, Mefloquine and Primaquine) showing faster results.

ACKNOWLEDGMENTS

We would like to thank Mr. Ibrahim Bin Sa'id, M. Si., Ph. D for his guidance and advice in making this research. This research provides useful insights in efforts to overcome the very dangerous malaria disease. Hopefully the information presented can be a useful guide for the wider community in general.

LITERATURE

Adnyanal, N. W. D. (2014). *Malaria incidence related to the residential environment in West Sumba Regency, Nusa Tenggara Timur Province*.

Agung Bagus S. Satyarsa, Feliani Sanjaya, Ni Made Gitari. (2020). *Potential of Liposome Nanoparticle-Based Anti-PfRH5 Antibody Vaccine as an Advanced Preventive Modality in Plasmodium falciparum Malaria*. Indonesian Clinical Pharmacy Journal.

Ankalgi, A. D., Sharma, S., Sharma, R., Devi, A., Jindal, S., & Goyal, K. (2020). Development and validation of novel method for simultaneous estimation of Atovaquone and Mefloquine hydrochloride in bulk drug using RP-HPLC. *Journal of Applied Pharmaceutical Research,8* (3), 48-54. https://doi.org/10.18231/j.joapr.2020.v.8.i.3.48.54

Arango EM, Upegui YA, Carmona-Fonseca J. (2012). *Efficacy of different primaquine-based antimalarial regimens against Plasmodium falciparum gametocytemia.*

Banyal, N. A., Surianti, S., & Dayat, A. R. (2016). Classification of Plasmodium Images Causing Malaria Disease in Human Red Blood Cells Using Multi Class Support Vector Machine (SVM) Method. *ILKOM Scientific Journal,8* (2), 111-118. https://doi.org/10.33096/ilkom.v8i2.54.111-118

Dayat, A. R., & Banyal, N. A. (2018a). *Classification of Malaria-Causing Plasmodium Breeding in Human Red Blood Cells Using Support Vector Machine (Svm) in Jayapura City-Papua*. *10*.

Dayat, Abd. R., & Banyal, N. A. (2018b). Classification of Plasmodium Breeding Causes Malaria Disease in Human Red Blood Cells Using Support Vector Machine (Svm) in Jayapura City-Papua. *Ilkom Scientific Journal,10* (1), 28-32. Https://Doi.Org/10.33096/Ilkom.V10i1.196.28-32

Dinata, A. (2018). *Befriending Mosquitoes: The Surefire Way to Overcome Mosquito-Sourced Diseases. Arda Publishing House.*

Emanuel Ileatan Lewar. (2016). *Malaria Nursing Care with a Nursing Process Approach at the Melolo Health Center, East Sumba Regency*.

Gomes, A. R. Q., Cunha, N., Varela, E. L. P., Brígido, H. P. C., Vale, V. V., Dolabela, M. F., ... & Percário, S. (n.d.). *Oxidative stress in malaria: Potential benefits of antioxidant therapy.*

Khayriah, F. (2016). *Percentage of Malaria in Tarusan Health Center in 2016*.

Martins AC, Paoliello MMB, Docea AO, Santamaria A, Tinkov AA, Skalny AV, Aschner M. (2021). *Review of the mechanism underlying mefloquine-induced neurotoxicity.*

Mau, S.Si, M,Sc, F., & Mulatsih, M. (2017). Changes in Lymphocyte Counts in Patients with Falciparum and Vivax Malaria. *Health Research Bulletin,45* (2), 97-102. https://doi.org/10.22435/bpk.v45i2.6288.97-102

Nindela, R. (2015). *Plasmodium falciparum Merozoite Surface Protein-1 (MSP-1) and Merozoite Surface Protein-2 (MSP-2) as Malaria Vaccine Candidates*. *1*.

Nosten, F., Van Vugt, M., Price, R., Luxemburger, C., Thway, K. L., Brockman, A., ... & White, N. J. (2000). *Effects_of_artesunate-mefloquine_combination_on_in.pdf*.

Price RN, Uhlemann AC, Brockman A, McGready R, Ashley E, Phaipun L, Patel R, Laing K, Looareesuwan S, White NJ, Nosten F, Krishna S. (2004). *Mefloquine resistance in Plasmodium falciparum and increased pfmdr1 gene copy number.*

Tangpukdee, N., Krudsood, S., Srivilairit, S., Phophak, N., Chonsawat, P., Yanpanich, W., Kano, S., & Wilairatana, P. (2008). Gametocyte Clearance in Uncomplicated and Severe Plasmodium falciparum Malaria after Artesunate-Mefloquine Treatment in Thailand. *The Korean Journal of Parasitology,46* (2), 65. https://doi.org/10.3347/kjp.2008.46.2.65

Vásquez AM, Sanín F, Alvarez LG, Tobón A, Ríos A, Blair S. (2009). *Estudio piloto de la efficacia y de los efectos sobre los gametocitos del esquema artesunate-mefloquina-primaquina para la malaria por Plasmodium falciparum [Therapeutic efficacy of a regimen of artesunate-mefloquine-primaquine treatment for Plasmodium falciparum malaria and treatment effects on gametocytic development]*.