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Use of Combination Therapy in Malaria Treatment and Prevention in Indonesia

Penggunaan Terapi Kombinasi Dalam Pengobatan dan Pencegahan Malaria di Indonesia

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ABSTRACT

Malaria is still a health problem in Indonesia. Treatment of Malaria often encounters obstacles. Resistance to various malaria drugs in some areas causes an increase in morbidity and mortality due to malaria. Rational use of malaria drugs that are still effective and available is essential. Therefore, this article will review the use of combination therapy in the treatment of Malaria in Indonesia. Using combination therapy increases the efficacy of treatment and slows down the occurrence of resistance to each component in the drug. From this article, it can be concluded that artemisinin-based combinations using artemisinin derivatives are still effective for use as combination therapy against malaria. This combination can be a fixed combination or co-administered. The drugs that can be combined are 4-aminoquinoline, antifolate, 4-quinoline-methanol, artemisinin and its derivatives, antibiotics, and atovaquone-proguanil. It is hoped that the combination of these drugs can still be used for an extended period of time, remain safe, effective, and affordable by the community.

Keywords: *treatment, malaria, combination therapy, a parasitic disease*

ABSTRAK

Malaria masih menjadi masalah kesehatan di Indonesia. Pengobatan terhadap malaria kerap kali menemukan kendala. Resistensi terhadap berbagai obat malaria di beberapa daerah menyebabkan peningkatan angka morbiditas dan mortalitas akibat penyakit malaria. Penggunaan obat malaria secara rasional yang masih efektif dan tersedia merupakan hal yang penting. Untuk itu, artikel ini akan meninjau penggunaan terapi kombinasi dalam pengobatan malaria di Indonesia. Tujuan penggunaan terapi kombinasi adalah untuk meningkatkan efikasi pengobatan dan memperlambat terjadinya resistensi setiap komponen dalam obat tersebut. Dari artikel ini, dapat disimpulkan bahwa kombinasi berbasis artemisinin yang menggunakan derivat artemisinin masih efektif untuk digunakan sebagai terapi kombinasi terhadap malaria. Kombinasi ini dapat berupa fixed combination maupun co-administered. Adapun obat yang dapat dikombinasikan yaitu golongan 4-aminokuinolin, golongan obat antifolat, 4 quinoline-methanol, artemisinin dan derivatnya, antibiotik, serta atovakuon-proguanil. Kombinasi antara obat-obat tersebut diharapkan masih dapat digunakan dalam jangka waktu yang cukup lama, tetap aman, efektif dan terjangkau oleh masyarakat.

Kata kunci: *pengobatan, malaria, terapi kombinasi, penyakit parasit.*

INTRODUCTION

Malaria caused by Plasmodium falciparum is still found in Indonesia, especially in the eastern region. Patients with falciparum malaria can be severe and have a poor prognosis, such as cerebral malaria and even death. Resistance to various malaria drugs in some areas causes an increase in morbidity and mortality due to malaria. Therefore, rational use of malaria drugs that are still effective and available is essential. Thus, it is hoped that these drugs can still be used for an extended period, remain safe, effective, and affordable by the community. Therefore, many studies are conducted to review existing combinations or to develop new combinations of malaria drugs. (Beales, 2009)

In Indonesia, Malaria is found to be widespread on all islands with varying degrees and severity of infection. According to the latest data, almost half of Indonesia's population lives in malaria-endemic areas (more than 90 million people or about 46% of Indonesia's total population). It is estimated that there are 30 million cases of malaria every year. From the 2019 Household Health Survey (SKRT) data, the prevalence of malaria is around 850.2 per 100,000 population, with a mortality rate of 11 per 100,000 for men and 8 per 100,000 for women. In Java and Bali, malaria endemicity is spread in 37 areas. For Central Java and West Java, malaria cases are a re-emerging disease. For outside Java and Bali, 70 million of them are in areas that have a risk of malaria, with 30 millions of them are in Eastern Indonesia. (Ahmadi, 2019) This article aims to review the use of combination therapy in the treatment of Malaria in Indonesia.

COMBINATION THERAPY IN MALARIA

The combination of malaria drugs is the simultaneous administration of two or more blood schizontoside drugs with a different action or biochemical targets. The Artemisinin-based combination is a combination that uses an artemisinin derivative as one of the components of the combination drug. Combination therapy can be in the form of a fixed combination where all components are formulated in the same tablet or capsule, or each component in the form of different tablets or capsules is administered simultaneously (co-administered). Due to this definition, the use of chloroquine and chlorpheniramine or primaquine is not included in combination therapy. (White, 2010)

Malaria drugs in the form of fixed-dose products are synergistic, but each component is not antimalarial when used alone; for example, sulfadoxine-pyrimethamine and chlorproguanil-dapsone are also not included in combination drugs. Using combination therapy increases the efficacy of treatment and slows down the occurrence of resistance to each component in the drug. The same concept is also applied in treating leprosy, tuberculosis, malignancy, and more recently to diseases caused by viruses. (Nomura, 2011)

Combining drugs will slow the development of resistance based on the assumption that resistance occurs due to parasitic mutations. When a combination drug with a different mode of action is given, the probability of simultaneous mutation in that combination is the percentage of mutations for each drug multiplied by the number of parasites exposed to that drug. For example, a mutation occurs at every 1:10 nuclear division. The probability of resistance to both drugs becomes 1:103, while the number of asexual stage parasites that are usually found in acute infection is 1:102 so that in combination drug administration, the process of resistance occurs will be slowed down. (Syafrudin, 2012)

DRUG OF CHOICE BASED ON CHEMICAL STRUCTURE

Malaria drugs for treatment and prevention are divided into seven types, namely the 4-aminoquinoline group (chloroquine and

amodiaquine), the antifolate drug class, 4-quinoline-methanol (quinine), artemisinin and its derivatives, antibiotics (doxycycline, tetracycline, clindamycin), and atovaquone-proguanil. (WHO, 2013)

Chloroquine (CQ)

Chloroquine (CQ) has blood schizontocidal activity against all infections caused by *P. malariae, P. ovale, P. falciparum, and P. vivax,* which are still sensitive to chloroquine. Chloroquine is also gametocytocidal against *P.malariae, P.ovale, and P.vivax*. This drug as a drug of the first choice against P. falciparum infection is now minimal. In some places, chloroquine is used in combination with sulfadoxine-pyrimethamine (SP) because of the antipyretic and anti-inflammatory effects of chloroquine and its effectiveness against *P. vivax* infections. The combination of CQ-SP has been used as the drug of choice against *P. falciparum* in East Timor, Ethiopia, and Papua New Guinea because it is more effective than SP monotherapy alone. (Murphy, 2014)

Amodiaquine

Amodiaquine is a drug that has a structure and activity similar to that of chloroquine, including antipyretic and anti-inflammatory effects. Amodiaquine is still quite effective in areas with low-grade chloroquine-resistant P. falciparum. It is unknown whether increasing the dose of amodiaquine to more than 25 mg/kg can increase the drug's effectiveness or cause drug toxicity. In the mid-1980s, adverse drug reactions were reported with prophylactic use of amodiaquine. In 1990, amodiaquine was no longer recommended as prophylaxis. However, amodiaquine is still used for treatment. The possibility of cross-resistance between amodiaquine and chloroquine has been reported in Africa. Amodiaquine is safe enough for use by pregnant women infected with malaria. (Olliaro, 2015)

Antifolate Drug Class

The combination of antifolate drugs works specifically on parasitic enzymes, namely dihydrofolate reductase and dihydropteroate synthase. This drug is no longer recommended as prophylaxis. Sulfadoxine-pyrimethamine is a drug with blood schizonticidal activity only against P. falciparum but does not have a gametocytocidal effect. This drug does not cross-react with chloroquine, amodiaquine, mefloquine, quinine, halofantrine and artemisinin derivatives. Because it can still be used in areas that are only resistant to chloroquine. The addition of folic acid in patients treated with sulfadoxine-pyrimethamine is not recommended because it can inhibit the action of sulfadoxine. It is recommended that folic acid be given one week after treatment with sulfadoxine-pyrimethamine. (Staedke, 2016)

4-quinoline-methanol (Kina)

Quinine is an effective malaria drug against P. falciparum which is resistant to chloroquine and sulfadoxine-pyrimethamine. In patients with uncomplicated falciparum malaria, quinine is usually given in combination with doxycycline, tetracycline, or clindamycin. Intramuscular injection of quinine is only given to patients who cannot tolerate oral quinine (continuous vomiting). As soon as there is no vomiting, treatment with quinine is continued orally. In patients with severe Malaria or Malaria with complications, quinine is given by infusion in 5% dextrose. Quinine is a malaria drug that is safe for pregnant women because it does not cause uterine contractions and fetal distress. (Basco, 2017)

Artemisinin and its Derivates

Artemisinin (qinghaosu) is a malaria drug isolated from the Artemisia annua plant. It is a sesquiterpene lactone group with peroxide bonds. This drug has the fastest blood schizonticide effect compared to other malaria drugs. It can be used in patients with severe malaria and malaria patients without complications. Artemisinin has no hypnozoites effect, although it has been reported to exhibit a gametocidal effect. Artemisinin is usually used for patients with P. falciparum who are

resistant to various malaria drugs and also in patients with complications. This drug is not recommended to be used for parasitic infections P.ovale, P.malariae, and P.vivax as long as these three species can still be treated with other malaria drugs. (Darlow, 2018)

Primaquine

Primaquine is an eight aminoquinolin class of drugs against the four species of plasmodium gametocytocidal and hipnozoitisida against P. vivax and P. ovale. It is the only drug on the market that can be used to prevent relapse. Other derivatives, namely bulaquine and tafenoquine, are still under study. Preferably before giving primaquine, measurement of the G6PD enzyme in patients to avoid hemolytic anemia. The use of primaquine for prophylaxis is still under research. Primaquine should not be given to pregnant women because of the risk of hemolysis in the fetus, which is usually relatively G6PD deficient. In children younger than one year, primaquine should not be given for the same reason. Side effects can include nausea, vomiting, pain, and stomach cramps. This can be avoided by encouraging the patient to eat before taking the drug. (Baird, 2009)

Doxycycline

As with tetracycline, the combination of quinine with doxycycline can be used for P. falciparum strains that are becoming resistant to quinine. However, monotherapy with doxycycline is not recommended for treating malaria patients because of its very slow action. In contrast to tetracycline, doxycycline can be used for chemoprophylaxis. To avoid the occurrence of esophageal ulceration, patients should eat before taking medication. Doxycycline should not be given to pregnant women and children younger than eight years. Other side effects are phototoxic reactions, depression of bone formation, tooth discoloration, and permanent gum hypoplasia. (Fryauff, 2010)

CONCLUSION

Based on the explanation above, it can be concluded that artemisinin-based combinations using artemisinin derivatives are still effective for use as combination therapy against malaria. This combination can be a fixed combination or co-administered. The drugs that can be combined are 4-aminoquinoline, antifolate, 4-quinoline-methanol, artemisinin and its derivatives, antibiotics, and atovaquone-proguanil. It is hoped that the combination of these drugs can still be used for an extended period of time, remain safe, effective, and affordable by the community.

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