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**SPECIAL ARTICLE**

## COMBINATION TREATMENT THE BEST MANAGEMENT OF MALARIA IN INDONESIA

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### ABSTRACT

Malaria is still one of deadly diseases worldwide since half of its population risks on the malaria. In 2008, the infection caused 863.000 deaths globally. In Indonesia, about 35% of people lives here and 38,000 people was reported died each year because of the plasmodium falciparum malaria. Genetic factor then is one of significant drug distributions where the gene acting in protein and enzyme coding influences the drug namely absorption, distribution, metabolism, and elimination (ADME).

The purpose of this research is to know the profile of combination pharmacokinetic of DHA, piperaquine and primaquine in the falciparum malaria without complicated, relation of drug content, Cmax (peak content) and parasite clearance with DHA (Dehydroartemisinin), piperaquine and primaquine combination and its pharmacology effect that is therapy, side effect, and therapy failure on falciparum malaria without complicated in Halmahera.

The research conducts randomly clinical test with experimental method in order to know pharmacokinetic combination of DHA, piperaquine, primaquine and its pharmacology effect to falciparum malaria before and after distribution of ACT therapy (Artemycine Combination Therapy) toward 12 patients of falciparum malaria.

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## INTRODUCTION

Malaria is still one of deadly diseases worldwide since half of its population risks on the malaria. In 2008, the infection caused 863.000 deaths globally. In Indonesia, about 35% of people lives here and 38,000 people was reported died each year because of the plasmodium falciparum malaria. The invasion of plasmodium on erythrocyte was the central process of initial malaria pathogenesis. Genetic factor then is one of significant drug distributions where the gene acting in protein and enzyme coding influences the drug namely absorption, distribution, metabolism, and elimination (ADME).<sup>1,2</sup>

The some malaria treatment programs that have been carried out previously by the WHO as the use of chloroquine and the Roll Back Malaria program. The failure of this program, encouraging shifts toward malaria therapy to the era of artemisinin-based combination therapy (artemisinin based combination therapy ACT). The success of ACT therapy is one of them can be seen from a WHO report in 2010 that the application of the therapy there was a decrease of malaria globally. Although ACT therapy is reported to have a fairly high success rate, but there is a fact which is quite surprising that several studies specifically conducted in Thailand Cambodia showed that the ACT therapy also experienced a significant failure rate. ACT treatment failure is also indicated by time clearance elongated. Parasite clearance time are elongated in patients indicate the presence of infection by the malaria parasite resistant strains.<sup>3</sup>

The ACT treatment failure has prompted the WHO to carry out improvements to the treatment with a combination of the active metabolite dihydroartemisinin from artemisinin and its derivatives. Indonesian government's program in the treatment of malaria these days is the application of a combination of DHP (dihydroartemisinin + piperazine) by adding primaquine. The success rate of DHP and primaquine combined application of the new limited number of patients were cured of malaria is increasing. Accordingly, it is important to test the pharmacokinetics of treatment with a combination dihydroartemisinin, piperazine and primaquine and pharmacological effects. The testing is important because during the test the pharmacokinetics in Indonesia has never been anti-malaria combination drug. The Pharmacokinetics DHA, piperazine and Primaquine has never been examined in Indonesia.<sup>4</sup>

## METHODS

The profile pharmacokinetic combination dehydroartemisinin, piperazine and primaquine in 12 patients with falciparum malaria without synergize well or do not contradict each other in the blood of patients with uncomplicated falciparum malaria. This is indicated by the parameters used that combination dehydroartemisinin, piperazine and primaquine are complementary to each other so that patients experienced healing without showing any significant side effects. Dehydroartemisinin cinetic profiles of the mean velocity of absorption seen dehydroartemisinin (DHA) was 2,24 hours. The mean Cmax was 495,80 ng / ml, the mean Tmax of 1,25 hours, a mean  $t_{1/2}$  0,81 hours, the mean AUC 559,18 ng h / ml, the mean volume of distribution of 1.193,60 liters, and the mean is 582 Cl , 12 liters / hour. Pharmacokinetic profiles piperazine seen from the mean speed of drug absorption piperazine was 2,63 hours. The mean Cmax was 1.576,05 ng / ml, the mean Tmax of 1,50 hours, a mean  $t_{1/2}$  7.37 hours, the mean AUC 3.312.39 ng h / ml, the mean volume of distribution of 1.481,53 liters, Cl average is 371,15liters / hour. Primaquine pharmacokinetic profile seen from the mean speed of absorption of the drug primaquine was 2,63 hours. The mean Cmax was 330,06 ng / ml, the mean Tmax of 1.25 hours, the mean  $t_{1/2}$  6,22 hours, the mean AUC 1.237,24 h ng / ml, the mean volume of distribution of 67,99 liters and Cl average is 20,78 liter / hour.

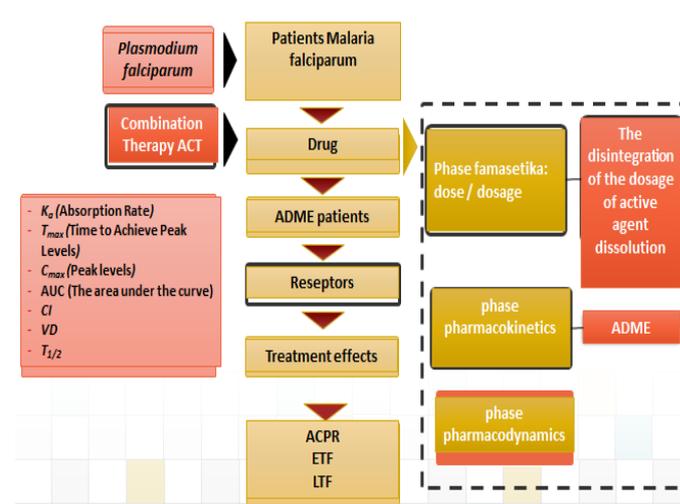


Figure 1. Flow Treatment of Malaria.

After administration of the combination drug dehydroartemisinin, piperazine and primaquine showed that the levels of drugs given to patients through a combination dehydroartemisinin, piperazine and primaquine able to clean clearance of parasites in the

blood of patients with falciparum malaria only in the first and second day of treatment. It shows the relationship between the levels of the drug in combination dehydroartemisinin, piperazine and primaquine with clearance of the parasite in the blood of patients with falciparum malaria. The more appropriate levels of drugs administered to the patient, the more speed up or shorten cleaning time clearance of the parasite from the blood of patients with falciparum malaria.<sup>5</sup>

## RESULTS

The results showed that the dose or concentration of drug administered to the patient is able to clean clearance Parasit on the first day of treatment. Based on the results of diagnostics performed to 12 samples of research, it appears that on the day of the first administration of the combination drug dehydroartemisinin, piperazine and primaquine patient's body temperature is quite high at between 370C - 380C more. But on the second day and the subsequent administration of the combination drug dehydroartemisinin, piperazine and primaquine body temperature of 12 samples of research have shown that the average normal temperature of 360C. This indicates that administration of the combination drug dehydroartemisinin, piperazine and primaquine are also able to lower the body temperature of patients who previously quite high.

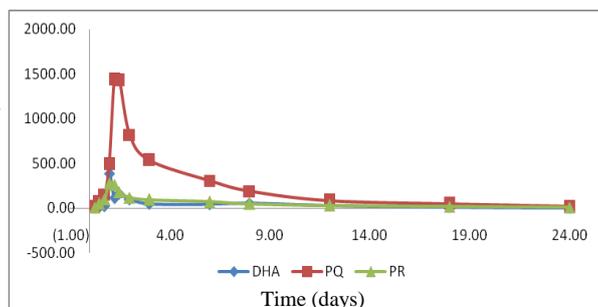
Judging from liver function (GOT, GPT), bilirubin, kidney function (urea and creatinine) 12 patients prior to drug administration dehydroartemisinin, piperazine and primaquine including normal. After administration of the combination drug, it is known that liver function (GOT, GPT), bilirubin, kidney function (urea and creatinine) 12 patients are also in a state of normal limits. This indicates that a combination drug treatment dehydroartemisinin, piperazine and primaquine no negative effects on the functions of vital organs of the body. Thus, it can be said that the combination drug therapy dehydroartemisinin, piperazine and primaquine will not cause negative effects.

Judging from the pharmacological effects of the combination drug delivery dehydroartemisinin, piperazine and primaquine classified as fast or be between 1-7 days. The therapeutic effect of the combination drug delivery dehydroartemisinin, piperazine and primaquine achieve high cure rates in patients with uncomplicated falciparum malaria. That is,

overall patient stated that as many as 12 people recovering from falciparum malaria after therapy or treatment with a combination of dehydroartemisinin, piperazine and primaquine.

The combination dehydroartemisinin, piperazine and primaquine as done in this study is a combination consisting of 40 mg of dihydro-artemisinin and 320 mg piperazine phosphate in the form of fixed dose (single dose), primaquine 15 mg, taken once daily for three days (Hasugian et al., 2007). Dihydroartemisinin and piperazine (DHP) is an important new treatment for drug-resistant malaria. Primaquine is a compound 8 aminokuinolin highly effective against the gametocytes of all species of plasmodium.<sup>6</sup>

The Dehydroartemisinin combination drug therapies, piperazine and primaquine in malaria patients can provide significant pharmacological effects, in the hope of a cure rate of patients with malaria reached 95% and with low side effects. Dihydroartemisinin-piperazine, primaquine are combinations containing artemisinin others that have good efficacy. This study shows that patients with falciparum malaria cure rate reached 100 percent. A total of 12 research subjects declared fully recovered from malaria falciparum. That is, the results of this study showed better results compared to the results of several previous studies such as 164 those in Vietnam Thailand and Burma where nearly 100% cure rate in patients with P. falciparum infection. A study of 334 patients with malaria in Timika, Papua (Indonesia) directing that the incidence of recurrent infection (recrudescence Rate) on day 42 after the administration of DHP in patients with P. falciparum is much lower (2.8%) compared to patients therapy artesunate-amodiaquine (AAQ) 13%,  $p = 0.001$  Mehlotra et al., 2006). The same thing was found in P. vivax infection (recurrence rate of 6.7% in the treated group versus 30% in the DHP AAQ group [ $p < 0.001$ ] (Imperuma and Allen, 2007).<sup>7</sup>



**Figure 2.** The mean concentration of Drug Combinations Dehydroartemisinin (DHA), piperazine (PQ), and Primaquine (PR) First Day in Plasma (Cp).

## DISCUSSION

*P. falciparum* associated with hazards, it takes a combination treatment that can provide a high pharmacological effect in the form of cure malaria. This drug combination therapy is the answer to malaria drugs such as chloroquine are widely used previously. Combination therapy such as combination dihydroartemisinin, piperazine and primaquine therapy is so far considered to be effective against resistant malaria drug therapy. Treatment failure due to parasite resistance to malaria drugs given characterized by persistence or reemergence of asexual parasites in the peripheral blood (recrudescences) which can be with or without clinical symptoms of malaria. If this situation is not resolved, recrudescences time will become shorter or faster detectable parasitaemia which means the severity of the degree of parasite resistance. Treatment failure or delay in recovery at the beginning of treatment will increase the gametocyte carriage which is the source (reservoir) transmission. This allows more and more people are infected with malaria, and even the occurrence of Extraordinary Events (KLB) as happens in some areas in Indonesia in particular which is a malaria endemic regions such as North Halmahera. The same thing can be compared with the results Mynt et al. (2007) in which 2,600 patients with malaria, with a combination of drugs and piperazine dihydroartemisinin achieving cure rates of 95% with low side effects. Research conducted Ashley et al. (2005) showed that the application of the combination dihydroartemisinin and piperazine against 499 respondents, with a confidence level of 95%, the result amounted to 95.7% of patients infected with *P. falciparum* malaria who experience healing. By using a combination of dihydroartemisinin, piperazine and primaquine as in this study, it appears that all of the patients, or 100 percent healed. This shows that treatment with the combination treatment dihydroartemisinin, piperazine and primaquine against *falciparum* malaria is a combination that is suitable and able to complete the combination treatment as determined Mynt et al. (2007) and Ashley et al. (2005) which only uses a combination dihydroartemisinin and piperazine. Thus, it can be explained that the combination dihydroartemisinin, piperazine and primaquine can be the first choice for the treatment of uncomplicated *falciparum* malaria.<sup>8,9</sup>

Dihydroartemisinin combination drug, piperazine and primaquine in this study also showed mild side effects. This indicates that the combination can be fused to each other between each other. That is, that

the combination treatment for *falciparum* malaria as in this study has an accuracy or a high level match. In doing this drug combination, should be considered a type of medicine will be combined. Mixing drugs incompatible with other drugs, will result in inactivation of the drug. Treatment of uncomplicated *falciparum* malaria with a combination dihydroartemisinin, piperazine and primaquine proven all three drugs are mutually fused to one another so that it can be used as a cure *falciparum* malaria drugs enhance existing malaria.<sup>10,11</sup>

Other findings was that the treatment of uncomplicated *falciparum* malaria with a combination dihydroartemisinin, piperazine and primaquine can shorten the treatment period compared to the period before the treatment of *falciparum* malaria. This is indicated by the results of the examination gametocytes or parasites in the blood of patients with *falciparum* malaria that on day 2, all the parasites in the blood of patients has become negative. Results of this study indicate that using dihydroartemisinin combination drug, piperazine and primaquine.

This study shows that the treatment of *falciparum* malaria with a combination dihydroartemisinin, piperazine and primaquine turns providing low side effects in the form of dizziness, headaches and vomiting. The number of patients experiencing the complaint by just 4 people or by 26.6 percent. The results showed that treatment with a combination dihydroartemisinin, piperazine and primaquine is better than the previous use of drugs that tend to cause more side effects vary.

## CONCLUSION

The results showed that the volume of distribution and clearance are two factors which are very different from the results of research conducted by the WHO and other countries. It can be influenced in part by genes of different factors.<sup>3,5</sup>

Based on the results, it can be delivered some of the suggestions for improvement and development of existing research came among others: first, to determine the effectiveness of the combination dihydroartemisinin, piperazine, primaquine in the treatment of *falciparum* malaria, necessary to distinguish between ABO blood group in patients with *falciparum* malaria. Secondly, it is necessary to conduct further research on the side effects of medication combinations dihydroartemisinin, piperazine, primaquine 4 patients experienced side effects so that they can find a solution that is right.

Thirdly, it is necessary to do further research to find out how the most appropriate time span needed for the treatment of falciparum malaria with a combination dehydroartemisinin, piperazine, primaquine. Fourthly, it is necessary to investigate whether the combination dehydroartemisinin, piperazine, primaquine may be given to falciparum malaria with complications. Fifth, research must be done in other areas with different ethnic communities and the conditions of malaria endemic regions are different so that can know the effectiveness of the treatment of falciparum malaria with a combination dehydroartemisinin, piperazine, primaquine. Sixth, there should be further studies of genes and polymorphisms in combination therapy DHA, piperazine da primaquine.

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