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PHARMACOKINETICS AND PHARMACODYNAMICS OF PRIMAQUINE TO PATIENTS WITH UNCOMPLICATED FALCIPARUM MALARIA IN HALMAHERA INDONESIA

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Key words:

Falciparum malaria, pharmacokinetic, Primaquine, Parasite Clearance, APCR

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ABSTRACT: Malaria remains one of deadly diseases in Indonesia which mainly occurred in Tobelo, North Halmahera. Genetic factor is one of significant factors where the gene acting in protein and enzyme coding influences the drug pharmacokinetics. However, no studies have been carried out on the pharmacokinetics of anti-malaria of primaquine in Indonesia. The purpose of this research is to know the kinetic profile of primaquine combination in the uncomplicated falciparum malaria, the relation of drug content and parasite clearance, and its pharmacological effects. Random clinical tests were conducted with experimental method to 12 patients RSUD Tobelo, North Halmahera from September to December, 2014. Blood samples were taken sequentially starting from day 0 to day 28, and then thick blood drop, liver function, kidney function, leucocyte, erythrocyte and hemoglobin were tested, The samples were then tested to measure the kinetic concentration of by using LCMS as well as analyzing the parameters of its pharmacokinetics. The results showed that the kinetic the primaquine kinetics synergized well and it was mutually complementing where the patients were cured without any side effects. The kinetic The primaquine kinetics included Ka = 2.63 hours, C_{max} = 3,1672 ng/ml, T_{max} = 1.08 ug/ml, t1/2 = 6.22 hours, AUC = 1,237.24 ng/hour/ml, VD = 67.99 liters, Cl = 20.78 liters/hour. Primaquine was able to clean the parasite and showed that there was a relation (P=0.041 < 0.05) between the drug content and significant parasite clearance. The pharmacological effect was APCR, with 100% of treatment. The malaria treatment as conducted in Papua still success.

INTRODUCTION: Malaria disease is one of deadly diseases in the world [1]. In 2008, it was estimated that 243 million infection cases resulted in nearly 863,000 deaths, which was cited as the highest number of death caused by malaria since it was discovered [1, 2].

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The malaria infections happen in various parts of the world, specifically in tropical and sub-tropical areas such as most regions in Asia (particularly in South East Asia), America (mainly Latin America) and sub-African Sahara.

In Indonesia, around 35% of its population lives in risk area of malaria and it is reported that more than 38,000 people a year have died because of severe malaria caused by *P. Falciparum* [3]. The malaria outbreak almost occurs each year in various endemic regions in Indonesia, such as East Nusa Tenggara, West Nusa Tenggara, Maluku, North Maluku, Central Borneo, Bangka Belitung, Riau

Island, Bengkulu, Jambi, Central Sulawesi, West Sulawesi (Regency of Mamuju and Mamasa), Gorontalo, and Nanggroe Aceh Darussalam. These areas are categorized as the red zones of malaria victims [4].

The failure of ACT therapy is shown by a prolonged clearance time. The prolonged parasite clearance period on the malaria patients marks the infection caused by resistant parasite strains [5]. A study in assessing the efficacy of artensunate-mefloquine between June 2007 and May 2008 was conducted in two different regions: Wang Pha, Thailand where the parasite was sensitive to ACT, and Pailin, Cambodia where parasite was believed to be more resistant [5]. The findings showed that there was a significant extension of parasite clearance period in Pailin than Wang Pha. Another research was conducted [6] in Province of Battambang, Cambodia, located near Pailin, in a smaller scale that included 60 patients. Both studies reveal two patients (3,3%) with longer parasite clearance although the metabolite artemisinin content within plasma was adequate.

Currently, the program of Indonesian government in its attempts to cure malaria is the implementation of primaquine. The malaria treatment by implementing, as conducted in Papua, still has a 7% of cumulative recrudescence risk of *P. falciparum*. In relation to this issue, the existing treatment therapy with primaquine is expected to suppress the previous number of cumulative recrudescence [7].

Hence, the treatment therapy as managed and programmed by the government in line with Permenkes [6] by co formulation of dihydroartemisinin, piperaquine, and primaquine has been applied in Halmahera. This combination application is based on the fact that, as reported by Internist Division of Local Public Hospital (RSUD) of Tobelo, in Halmahera, one of 5 (five) main diseases is malaria (The Report of RSUDT) [9]. The efficacy extent of primaquine application is simply the increasing number of cured malaria patients. Therefore, it is important to conduct pharmacokinetic treatment test on the primaquine as well as its pharmacological effects.

This research focuses on the pharmacokinetic test and pharmacological effects of primaquine in falciparum malaria disease in Halmahera.

MATERIALS AND METHODS:

Research Design:

This research is designed to assess the kinetic profile and efficacy of primaquine on falciparum malaria patients by conducting: (1) a sample selection from the population; (2) a measurement of basic variables; (3) a pre-treatment assessment; (4) a post-treatment assessment; (5) an evaluation of result variables based on therapy effectiveness, side effects, and treatment failure of the combination treatment.

Site and Time:

The research was conducted in RSUD Tobelo, North Halmahera from September to November, 2014. This site is chosen based on several considerations: (1) RSUD Tobelo, North Halamhera is located in malaria endemic region so that the hospital has sufficient number of patients suffering from malaria; (2) previous research findings show that Halmahera, North Maluku reveals higher endemicity; (3) the research site is researcher's work area so that the data collection required are free from bureaucracy issues. The kinetic test of drug profile, however, is performed in Laboratory DKI Jakarta.

Population and Sample:

The population aimed for this research was all in-patients suffering from falciparum malaria that were hospitalized in Internist Division of RSUD Tobelo. The total number of falciparum malaria patients from October to November, 2014 was 40 patients. Considering that the research was conducted from August to November, 2014 and the data collection was done in November, the population of this study, then, was the total number of in-patients hospitalized in Internist Division of RSUD Tobelo from September to November, 2014.

Referring to previous studies, it can be defined that there has been no precise regulation concerning the total number of sample for kinetic test, ranging between 7 and 24 samples. Hence, the sampling technique used in this study is consecutive sampling, i.e. patients who meet the research

criteria (inclusion and exclusion) were used as samples [8]. From a total of 40 patients, 21 patients met the inclusion and exclusion criteria. After sample data collection, six patients resigned with various reasons, such as family reasons and hesitation, leaving 15 patients to proceed to the experiment. However, after checking process and laboratory data management, three samples were found unfit for further experiment since the checking results showed that two patients had parasite lower than 2000/µl and one patient had mixed malaria (*P. falciparum* and *P.vivax*). This results in the final number of samples of 12 patients.

Instrument:

The instrument used LCMS used to measure drug concentration within plasma.

Patient's blood sample taking:

1. **Patient check**

2. **Written agreement**

3. **Drug distribution of dihydroartemisinin, piperaquine, and primaquine combination:**

Blood derived from a pin of finger's tip of each patient were taken for blood smear aimed for hemoglobin assessment. Patients, then, was given oral drug of dihydroartemisinin, piperaquine, and primaquine combination whose dose was stated around 25 mg/kg of total of dihydroartemisinin and 4 mg/kg of piperaquine on day 1, 2, and 3 and the primaquine on day 1.

4. **Patient's observation and evaluation:**

All patients were observed directly for 30 minutes. Patients who vomited was re-dosage with similar treatment and observed for the next 30 minutes. The research's doctor evaluated each subject and collected blood for thick and thin blood supply examination on day 0, 1, 2, 3, and 7. Patients having fever was given fever drug. In addition, patient with hemoglobin < 8 g/dl was given oral zinc tablet.[9]

Patients, then was asked to return on day 7, 14, and 28 and in the unscheduled day if they still feel sick. Physical and temperature examination were recorded, and special attention was given for disease record of patient, side effect, worse condition that could happen, and medication record of other ongoing disease treatment. On day 1 and 2, the research's drugs were under observation. The research doctor then conducted treatment for other disease suffered by the patients at the same time as malaria.

5. **Thick blood film examination**

6. **Thin blood film examination**

The supply of thick and thin blood is used for qualitative examination in order to decide whether or not malaria parasite (positive or negative), and plasmodium stadium (plasmodium falciparum, tropozoite, skizon, and gametocyte). Besides, the blood supply is used as well to quantitative investigation, which is deciding parasite density. The measurement of parasite density is conducted quantitatively in the thick blood supply [9, 10].

7. **Intervention distribution of dihydroartemisinin, piperaquine, and primaquine combination with standard dosage:**

After pre-treatment was conducted, the victims of falciparum malaria were given intervention of dihydroartemisinin, piperaquine, and primaquine combination with standard dosage and it continued with post-treatment such as serial assessment to know the kinetics of the combination in each subject. All feasible subjects had medical record and detailed demography filled when admitted. Physical and laboratory test (microscopy malaria, hematology, and blood chemical) were conducted in initial phase (on day 0, prior to treatment) [11]. Limited physical test was done during hospitalization (on day 1-2) and the following days (3, 7, 14, and 28). Hematology and blood chemical, thus, were inspected on day 0, 3, 7, and 28. Then, microscopy result was checked using cross check by trained and certified lab staff in RSUD Tobelo, and laborant of parasitology section of Faculty of Medical, Universitas Gadjah Mada, Yogyakarta.

8. **Evaluation of combination treatment's result:**

The research finding is evaluated with WHO's clinical response and parasitology standard[10]. If

there is parasitology and clinical failure, coartem or duo-cotexcin is given, or if there are severe disease symptoms, quinine intravenous is given. The patients who are asymptompatic and parasite free on day 28, with no early treatment failure (EFT), late clinical failure (LCF), or late parasitological failure (LPF) are classified as adequate clinical and parasitological response (ACPR).

9. Regular blood taking:

For gaining regular drug content, drug distribution was performed with the following dosage: 2-4 tablets of drug distribution to patient. This distribution refers to Permenkes RI, 2013. Drug distribution is by oral or with water. The distribution of drug's dosage refers [8] based on patient's weight:

Weight Category (W) ≥ 60kgis given four tablets of drug's dose.

Weight Category (W) of 41-60kg is given three tablets of drug's dose

Weight Category (W) ≤ 40kgis given two tablets of drug's dose

The blood sample taking in this research is as follows:

a) The blood sample taking on day 1 was started from 0 or prior to treatment. At the first day of blood sample taking was 5 ml at hour 0.25, 0.5, 0.75, 01, 1.25, 1.5, 2, 3, 6, 8, 12, 18, and 24.

b) The blood sample taking on day 2 was conducted post-treatment once at hour 1.5 of 5 ml (taking 14).

c) The blood sample taking on day 3 was performed post-treatment at hour 1 of 5 ml and hour 3 (taking 15 and 16).

d) The blood sample taking on day 7, 14, and 28 was done once which was 5 ml taken at 8 o'clock in the morning along with the supply taking of thick and thin blood drop.

Then, the sample was put in the vacutainer containing EDTA and centrifugalized for 15 minutes by 3,000 rpm and plasma, then, was moved to the tube and stored at 41ºC and analyzed in laboratory.

10. Recording laboratory result:

The record was conducted concerning whether other clinical symptoms that include in indicators of therapy effectiveness, side effect, and clinical refinement exist. Subjects who did not pass the treatment procedure, such as walking out or passing away, were considered failed and excluded from the analysis. In order to identify the artemisinin pharmacokinetics, maximum artemisinin concentration (C_{max}) and time to reach concentration (T_{max}) were taken directly from data of observed time concentration for each individual. Artemisinin elimination rate constant (k) was estimated for each individual with long-linear, ordinary-least-squares regression from three to five of terminal concentration-time-datum point. Terminal half-life ($t_{1/2}$) was counted as 1n2/k.

AUC from drug supply to the late sample where artemisinin concentration that could be counted (AUC_{0-t}) was measured with linear trapezoidal method to view declining phase of the curve. AUC from the late time of parasite quantification within the sample until unlimited (AUS_{t-00}) was estimated by dividing last predicted concentration with k. AUC from zero to unlimited time (AUC_{0-00}) was counted as total of $AUC_{0-t}$and(AUS_{t-00}). Oral clearance based on blood concentration (CL_s/F) for each subject was derived as dose divided with (AUS_{0-00}) [12]

11. Deciding primaquine content:

The deciding procedure of dihydroartemisinin, piperaquine, and primaquine of blood was conducted in health laboratory of DKI Province in the research comprises of: Analysis of primaquine content in the blood sample for analysis was taken in all patients serially. Then, blood sample was collected into sterile heparin-lithium, and plasma was separated and stored at 20ºC to avoid photodecomposition. Later on, the tube was wrapped with aluminum foil. For plasma sample (1.0 ml) containing standard internal was added with acetonitrile (2.0 ml). The mixture then was put in the vortex over 15 minutes. After being centrifugalized (200g; 5 minutes), liquid phase was moved to clean tube, where each of it was added

with 2.0 ml of ammonia. The mix was extracted with tumbling mechanical over 15 minutes with disetile-ether (5.0x2). After centrifugal process (1500g; 10 minutes) and separated, organic phase combination was vapored with nitrogen flow at 25ºC. The residual, thus, was reconstructed within methanol (100µl) and injected in HPLC, so that piperaquine and primaquine content was derived. Plasma was put into centrifugal tube + 100µl of internal standard of water methanol (50:50, v/v), well mixed + 100µl of ether-diclomethane mixture (60:40), mixed with water steam during 1 minute, and shivered over 10 minutes (240 time/minute), and centrifugalized at 3000 rpm over 10 minutes. The organic phase was reserved and put into tube test which was dried at 25ºC with nitrogen flow +150µl of mobile phase (methanol-water, 50-50), and put into residue within water steam. Then, 10µlwas taken to be analyzed with LCMS (liquid chromatography-mass spectrometry), content of varying time serial was derived.[13]

Work procedure:

The work procedure of this research can be explained as follows:

a) Sample transportation procedure that was from Tobelo to Maluku and heading to Jakarta, and the sample was stored in the cool-box during 8 hours to arrive in the health laboratory of Province of DKI Jakarta.

b) Content test and sample examination by using LCMS (liquid chromatography-mass spectrometry) was in line with what had given by health laboratory of Province of DKI Jakarta.[11,12]

Data analysis:

Descriptive statistical analysis by using graphs and tables is used to describe the treatment profile of primaquine combination in the falciparum malaria patients by using parameters such as Ka (absorption rate), T_{max} (time to reach peak content), $t_{1/2}$ (time which half-life of drug is eliminated), VD (distribution volume), CL (clearance), C_{max}(peak content), and AUC (area under the curve). Correlation test analysis is used to prove the relation of drug content that is C_{max} (peak content) with parasite clearance from primaquine combination[11, 12].

RESULTS:

Characteristic of research's subject:

The data shows that the total of male and female sample in this research is same (six people). Viewed from age factor, the more dominant age is between 18-25 years old. It indicates that young age is vulnerable to malaria infection in the research site. Based on weight, the more dominant infected by malaria is the weight of 41-60 kg. In addition, based on blood type, in general, the blood type of the research's sample is O.

TABLE 1: CHARACTERISTICS OF RESPONDENTS SUFFERING FROM MALARIA AS RESEARCH SAMPLE IN RSUD TOBELO, NORTH HALMAHERA (n=12)

Remark	Total	Percentage (%)
Gender:		
1. Male	6	50.00
2. Female	6	50.00
Total	**12**	**100**
Age:		
1. 18 – 25 Years	10	83.34
2. 26 – 35 Years	2	16.66
Total	**12**	**100**
Body Weight:		
1. ≤ 40 kg	2	16.66
2. 41 – 60 kg	7	58.34
3. ≥ 60 kg	3	25.00
Total	**12**	**100**
Blood Group :		
1. O	8	66.66
2. A	3	25.00
3. B	1	8.33
4. AB	0	**100**
Total	**12**	

TABLE 2: DRUG DISTRIBUTION TO THE PATIENT BASED ON FALCIPARUM MALARIA PATIENT'S WEIGHT IN RSUD TOBELO

No	BB > 60kg	41 – 60kg	≤ 40 Kg		Dosage DHP and Primaquine								
				DHP +	0 D			1-D			2-D		
				Primakuin	4tb	3tb	2tb	4tb	3tb	2tb	4tb	3tb	2tb
1	63			4 DHP + 3 Prm	√			√			√		
2	62			4 DHP + 3 Prm	√			√			√		
3		59		3 DHP + 2 Prm		√			√			√	
4		45		3 DHP + 2 Prm		√			√			√	
5		45		3 DHP + 2 Prm		√			√			√	
6	62			4 DHP + 3 Prm	√			√			√		
7		56		3 DHP + 2 Prm		√			√			√	
8		-	39	2 DHP + 2 Prm			√			√			√
9		55		3 DHP + 2 Prm		√			√			√	
10		-	40	2 DHP + 2 Prm			√			√			√
11		55		3 DHP + 2 Prm		√			√			√	
12		50	-	3 DHP + 2 Prm		√			√			√	
Jlh	3	7	2		3	7	2	3	7	2	3	7	2

Note:
W : Weight
kg : kilogram
Prm : primaquine
tb : Tablet : total : Day

Malaria examination on research's sample and its treatment:

a. Malaria investigation in the patients:

The investigation findings show that 12 research's samples were positive suffering from falciparum malaria. Meanwhile, the examination result of thick blood film can be noticed from the total of parasite within the patient's blood and plasmodium stadium such as ring and gamete (crescent) [10, 11]. According to measurement results, the highest thick parasite film was at subject number 5 with 128.749/µL, followed by subject number 12 with 104.154/µL, and subject number 2 with 73.692/µL.

In contrast, the lowest was at subject number 3 with 2.427/µL. The examination results of thick blood supply revealed that ring-shaped parasites were found in the research's blood sample number 12 in H_0. Based on the examination results of thin and thick blood supply, the therapy or treatment of primaquine combination was then administered.

b. Treatment and Sample Taking:

The patients, then, was orally given the combination of primaquine. The total of tablet given to the patientsis [9, 10, 11]. The drug distributed to the patients was 2-4 tablets. The dosage was based on Permenkes RI, 2013. Moreover, drug distribution of primaquine to the research sample's patients caused dizziness, headache, and vomit to three patients. On day 1, subject 4 and 5 felt dizzy and headache. On day 2, subject 4 vomited and felt nauseous, and on day 3 subject 3 and 4 dazed. In total, there were nine subjects including subject 1, 2, 6, 7, 8, 9, 10, 11, and 12 who had not felt any clinical symptoms from the drug distribution of primaquine. Only three patients felt the clinical complaints, comprising of subject 3, 4, and 5 that were given 3 tablets.

From the data above, subject number 4 starting from day 1 to 3 had clinical complaint, such as daze, headache, and vomit. Meanwhile, subject

number 3 complained on day 3 of the drug distribution. Related with the patient who vomited, the patient received a re-dosage with similar treatment and observed for the next 30 minutes. By this treatment, the patient was no longer having complaints so that the examination could be continued to the end.

Patients involved in the research whose hemoglobin was<8g/dl would be treated with oral zinc tablet. However, all samples in this research had HB>8g/dl between 11.1-16.0 g/dl so that the early treatment was not necessary. According to patient's blood check on day 1, the number of leucocyte, RBC, platelet, GOT, GPT, bilirubin totalmurenum, and creatinine were identified.

The parasite depiction within twelve patient's blood that are the research's sample during the treatment with primaquine can be explained that on day H_0 (the day one as patient came to hospital) parasite was found within their blood. It was seen from the thick and thin blood supply.

Kinetics and Pharmacologic primaquine:

Based on the test results, the following issues can be summed up: (1) kinetic profile of primaquine, (2) the relation of drug content and parasite clearance from dihydroartemisinin, piperaquine, and primaquine combination, and (3) pharmacological effect and efficacy of primaquine.

a. Kinetic profile of primaquine in uncomplicated falciparum malaria patients. Combination of primaquine distributed to uncomplicated falciparum malaria patients is aimed to know drug effectiveness inside patient's body. Prior to review the result of primaquine firstly the kinetic profile of each primaquineis explained.

Primaquine in 12 patients:

Primaquine is one of effective 8-aminoquinoline substances against gametocyte in all plasmodium species. This drug is active on blood schizon of *P. falciparum, P. vivax.* However, if it is used in a high dose, it should be aware and. It is effective on network schizon of *P. falciparum* and *P. vivax* (Permenkes RI, Number 5, 2013). Primaquine is easily absorbed by oral technique. The peak of plasma concentration happened 1-3 hours with half-time is about 5 hours. It is also quickly metabolized in the liver and small amount of it is exercised through urine. There are two major metabolites, 5-hydroxiprimaquine and 5-hydroxy-dimethyl-primaquine formation. Both are anti malaria and causes methemoglobin formation.

The drug concentration of primaquine on plasma (C_p) viewed since the blood sample taking of falciparum malaria patient at hour 0.25 can be explained that the lowest drug concentration of primaquine on plasma (C_p) was the subject number 6 (1.47 ng/mL), while the highest was the subject number 11 (38.18 ng/mL). The highest drug concentration of primaquine on plasma (C_p) occurred at hour 1.00 that was the subject number 5 (484.82ng/mL). At hour 24, the declining and lowest drug concentration of primaquine on plasma (C_p) was on the subject number 6 and 7 (1.86 ng/mL).

If it is seen from the mean of drug concentration of primaquine on plasma (C_p) of 12 falciparum malaria patients, it can be noticed that the blood sample taking at hour 0.254 shows the mean of drug concentration of primaquine on plasma (C_p) was 10.61ng/mL. The highest peak of drug concentration of primaquine on plasma (C_p) occurred at hour 1.00 after primaquine was distribute to the patient by the mean of 279.80 ng/mL, and it decreased at hour 24 by the mean of 7.77 ng/mL. This data illustrates that the blood sample taking started from hour 0.25 to 24 was from the lower point to higher and it continued to decline subsequently. The strongest reaction of drug concentration of primaquine on plasma (C_p) was at hour 1.00 or following the drug distribution. The drug concentration of primaquine on plasma (C_p) is illustrated in **Fig. 1**.

Figure 1 demonstrates that drug concentration of primaquine on plasma (C_p) in each patient happened on the subject number 5, at hour 1.00 or one hour after primaquine drug distribution. Similarly, the mean of the highest peak of drug concentration of primaquine on plasma (C_p) occurred at hour 1.00.

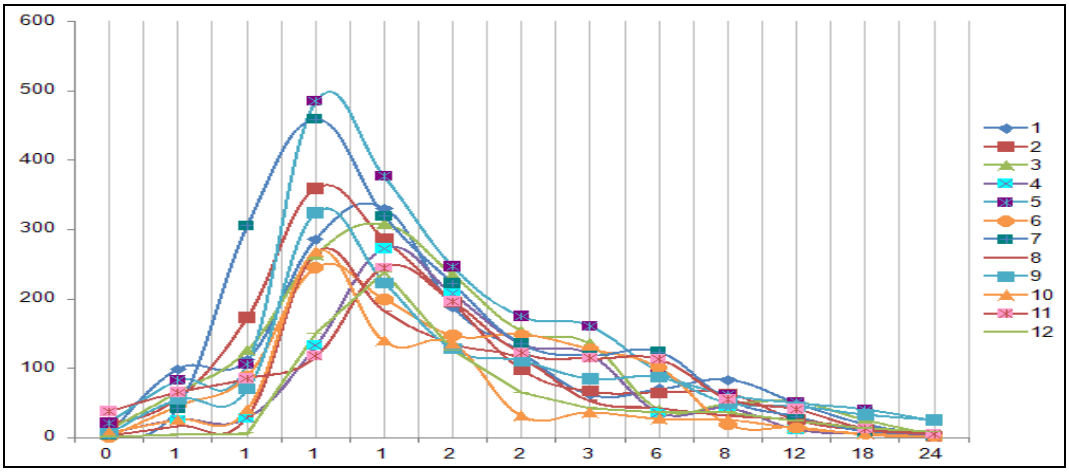

FIG.1: DRUG CONCENTRATION OF PRIMAQUINE ON PLASMA (C_P) ON FALCIPARUM MALARIA PATIENT

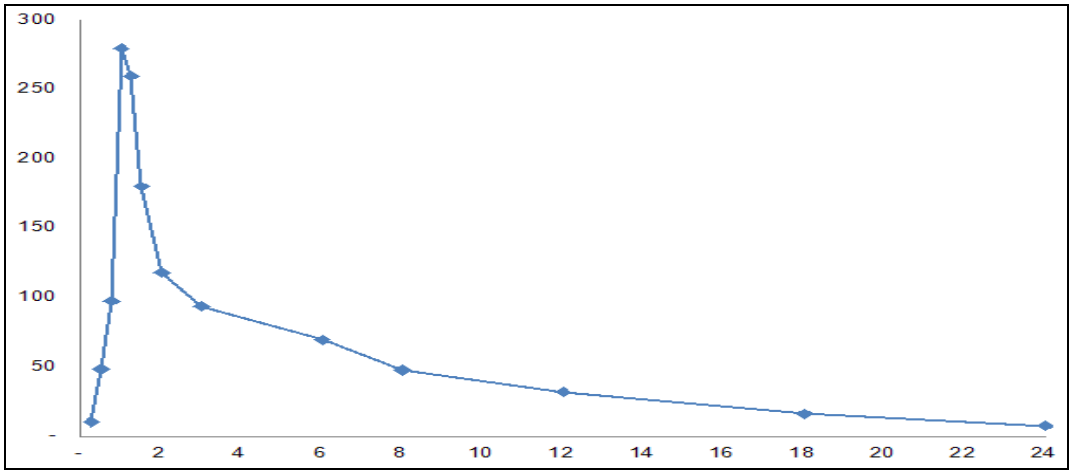

FIG. 2: MEAN OF DRUG CONCENTRATION OF PRIMAQUINE ON PLASMA (C_P) AT DAY ONE OF DRUG DISTRIBUTION

The drug concentration of primaquine on plasma (C_p) reached its ultimate point on day 1 mainly at hour 1.00 shown by the mean of the highest drug concentration of primaquine on plasma (C_p) at that hour. On day 2-28, it can be said that drug concentration of primaquine on plasma (C_p) was regularly lower. This data means that drug concentration of primaquine until day 28, generally, was not found anymore. It shows that the drug concentration of primaquine on plasma (C_p) from the blood of total of patient (11 patients) was not established, excluding the subject number 11. the drug concentration of primaquine on plasma (C_p) on day 2-28 in detail is explained in **Fig. 3**.

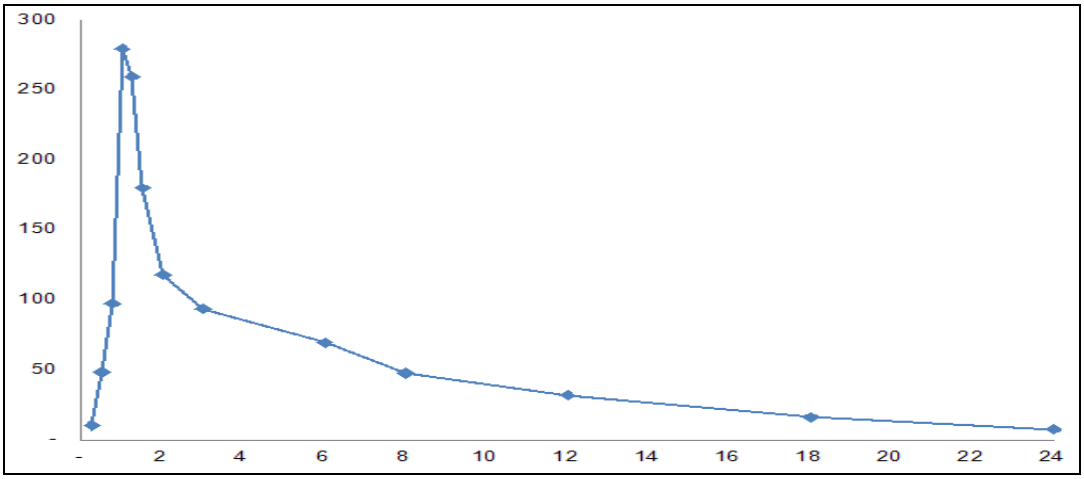

FIG. 3: MEAN OF DRUG CONCENTRATION OF PRIMAQUINE ON PLASMA (C_P) AT DAY 2-28

Based on drug concentration of primaquine on plasma (C_p) in each falciparum malaria patients, it can be stated that on day 2-28 the highest point of drug concentration of primaquine on plasma (C_p)happened on day 3 that was on the subject number 10 (389.15 ng/mL). It happened because there was an increase caused by polymorphism. It was shown by the mean of the drug concentration of primaquine on plasma (C_p) was 143.71 ng/mL. At day 2-28, drug concentration of primaquine on plasma (C_p) was still active inside the plasma, yet its mean was lower at 24.57 ng/mL on day 28.

However, the peak level of drug concentration of primaquine on plasma (C_p) happened at hour 1.00 or one hour after drug distribution. It was stated by the mean of drug concentration of primaquine on plasma at (C_p) of 279.80 ng/mL. While on day 2-28, in general, the drug concentration of primaquine on plasma (C_p) was not active anymore. The fact was that the primaquine was not detected in 11 patients' blood, but the primaquine was found in the subject number 11 on day 28.

TABLE 3: COMPARISON OF PHARMACOKINETIC PROFILE, PRIMAQUINE IN HALMAHERA AND OTHER COUNTRIES [11, 14]

No.	Parameter (PQ)	Halmahera 2015 (n=12)	WHO 2010	Vietnam 2009 Male	Vietnam 2009 Female
1	Ka (hour / minute)	2.63	-	-	-
2	C_{max} (ng/mL)	123.84	167 – 980	122 (101 – 140)	213 (153-227)
3	T_{max} (jam)	2.01	2.0 – 6.1	7 (2-10)	9 (10-29)
4	T ½ (jam)	6.22	6.1 – 21.8	6.1 (3.5 – 7.0)	6.8 (5.5 – 90)
5	AUC (ng jam/ml)	1,237.24	12.737	907 (749-1017)	1910 (1558-21681)
6	VD (liter)	67.99	-	4.59 (3.47-6.45)	3.42 (2.74-387)
7	Cl (l/jam)	20.78	0.6	0.55 (0.48-0.68)	0.31 (0.27 – 0.44)

DISCUSSION: Primaquine is depicted by the drug concentration of plasma (Cp) and based on parameters of pharmacokinetic test. The highest point of concentration with in plasma concentration (Cp) happened at hour 1 or one hour after drug distribution [11, 12, 14]. The lowest drug concentration occurred at hour 0.25in subject number 12 (0,50 ng/mL). This data indicates that the drug distribution of) to the malaria patients is relatively

fast, i.e. one hour after drug distribution. The speed of drug concentration within plasma (Cp) provides better effect to the malaria patients. In the following examination day (day 2-28), it was seen that starting from day 7 the concentration was not found in the patient's plasma (Cp) and on day 14-18 it was not detected anymore. This shows that is one of effective treatment combinations to cure malaria since it gives clinical or laboratory refinement showing the disappearance of parasite and gametocyte in the patient's blood.[11, 14-17]

Meanwhile, the highest point of concentration within the patient's plasma (Cp) happened at hour 1,25 or one hour after drug distribution. It shows that is slower than where it was also shown in the drug distribution in following days (day 2-28). The concentration was still existing in those days. Apparently, the concentration peak of both was almost at the same hour. In detail, was at 1.25 hour. It means that both combinations complete each other.

Similarly, primaquine also showed a similarity with both. The highest concentration of primaquine within the patient's plasma (Cp) was at hour 1.00 that happened subject number 5 (484, 82 ng/mL) and the lowest was at hour 24 in subject number 6 and 7 (1, 86 ng/mL). It shows the same concentration peak of primaquine, which occurred at hour 1.00 or one hour after drug distribution.

Thus, from the similarity of those three drug combination of primaquine in terms of the concentration peak, which happened at hour 1.00 – 1,25, these drugs are the reference combination for curing malaria as conducted in Halmahera. They have similar peak concentration at the same hour so that these drugs within the patient's plasma (Cp) react faster, which may help the patients recover more quickly.

The kinetic profile of primaquine can be seen from the mean of drug absorption acceleration (Ka) of

2.63 hours. As a result, the mean of those drugs was between 2 – 3 hours. Though there was a slight difference, the absorption acceleration of three drugs was similar. It means that the effect for the patient's malaria becomes effective in the treatment.[11, 14, 18, 19] According to the C_{max} (peak concentration), the peak concentration of primaquine was 123.84 ng/mL. It shows that there was a of peak concentration of primaquine. The difference means that these drugs provide better therapy within the patient's plasma (Cp) suffering from malaria.

Further, based on the mean of T_{max}(time to reach peak concentration), primaquine was 2.01 hours. It shows that these drugs have the same T_{max} where it indicates that drug concentration in the systemic circulation reaches the same peak of 2,01 – 2,77 hours.

For the $t_{1/2}$ (half-time of drug to show time required in changing total of drug within the body as half of previous amount), the research reveals that the mean of $t_{1/2}$ elimination primaquine was 6.22 hours. In short, longest $t_{1/2}$ while primaquine the shortest.

In the AUC (area under the curve), primaquine was 1.2374,24 ng hour/mL. This result shows that the AUC mean of piperaquine in the systemic circulation was primaquine and the AUC mean of was primaquine.

Based on the pharmacokinetic test of VD (volume distribution), the VD mean, was, primaquine was 67,99 liters. It demonstrates that these drugs have different VD from each other and indicates that the distribution of piperaquine within the patient's body liquid required or resulted larger volume and primaquine required smaller volume than primaquine.

Then, in terms of Cl (clearance) parameter, the mean of clearance of, primaquine was 20.78 liters/hour. It shows that these drugs had different ability to clear the drug within blood volume where had the highest mean of clearance within blood and primaquine had the lowest.

In summary, the kinetic profile of primaquine from 12 falciparum malaria patients synergizes perfectly and complements each other within the patient's blood of uncomplicated falciparum malaria so that the patients were cured without any side effect. The drug concentration distributed to the patients through the combination of primaquine is able to clear the parasite within the blood of falciparum malaria patients. It demonstrates that there is a relation of drug combination of primaquine with the parasite clearance within the blood of falciparum malaria patients. The more adjustable the drug is given to the patient, the faster or shorter the parasite clearance is. It is also shown by the significant measurement value of $p = 0.041 < 0.05$. Therefore, there is a significant relation in terms of the C_{max} with the parasite clearance of primaquine combination. The effect of primaquine combination is APCR (adequate clinical and parasitological response). The rate of treatment success is 100% >95%. After the drug distribution of primaquine combination, the parasite within the patient's blood on day one was already negative with the exception of patient number 1. Then, on day 2, all patients' blood was clear from the parasite. This means that the treatment length is one day shorter than the treatment standard of three days.[14, 18-20]

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