Turkiye Parazitol Derg 2022;46(2):102-7
DOI: 10.4274/tpd.galenos.2021.54264

Observation of Malaria Treatment with Dihydroartemisinin-Piperaquine Combination at Primary Health Care

Birinci Basamak Sağlık Hizmetlerinde Dihidroartemisinin-Piperaquine Kombinasyonu ile Sıtma Tedavisinin Etkinliğinin Gözlenmesi

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Cite this article as: Siahaan L. Observation of Malaria Treatment with Dihydroartemisinin-Piperaquine Combination at Primary Health Care. Turkiye Parazitol Derg 2022;46(2):102-7.

ABSTRACT

Objective: Dihydroartemisinin-Piperaquine (DHP) combination is the first-line treatment for uncomplicated malaria in Indonesia and has been used since 2010. This study was conducted to determine the efficacy of DHP combination for uncomplicated malaria treatment in a community-based evaluation.

Methods: Recruitment was done by active or passive case detection. All uncomplicated malaria patients were treated with DHP once a day, for 3 days, administered orally (as is done in primary health care). Patients were followed up until day 28 post-treatment. The primary end point was a 28-day cure rate.

Results: In this study, 484 subjects were screened through active and passive cases detection. A total of 45 subjects infected by *P. vivax* and 2 subjects infected by *P. falciparum* agreed to participate through written informed consent. There was no difference between clinical malaria and asymptomatic malaria in all analyzed characteristics. One patient had a D3 parasite density greater than 25% D0, although no parasites were found on the following day (D4). This study found 46 patients (97.9%) who had adequate clinical and parasitological responses. No adverse event was reported during the follow up of this study.

Conclusion: DHP was effective, safe, and well tolerated in the treatment of uncomplicated malaria at primary health care.

Keywords: Dihydroartemisinin-Piperaquine, malaria, primary health care

ÖZ

Amaç: Dihidroartemisinin-Piperaquine (DHP) kombinasyonu, Endonezya'da komplike olmayan sıtma için birinci basamak tedavidir ve 2010 yılından beri kullanılmaktadır. Bu çalışma, toplum temelli bir değerlendirmede komplike olmayan sıtma tedavisi için DHP kombinasyonunun etkinliğini belirlemek için yapılmıştır.

Yöntemler: Çalışmaya katılım, aktif veya pasif olgu tespiti ile yapıldı. Komplike olmayan tüm sıtma hastaları günde bir kez üç gün boyunca ağızdan DHP ile tedavi edildi (birinci basamak sağlık hizmetinde yapıldığı gibi). Hastalar tedavi sonrası 28. güne kadar takip edildi. Birincil son nokta 28 günlük bir iyileşme oranıydı.

Bulgular: Bu çalışmada 484 denek aktif ve pasif olgu tespiti ile tarandı. *P. vivax* ile enfekte olan toplam 45 denek ve *P. falciparum* ile enfekte olan iki denek, yazılı bilgilendirilmiş onam ile katılmayı kabul etti. Analiz edilen tüm özelliklerde klinik sıtma ile asemptomatik sıtma arasında hiçbir fark yoktu. Bir hastanın D3 parazit yoğunluğu %25 D0'dan daha yüksek olmasına rağmen ertesi gün parazit bulunmadı (D4). Bu çalışmada, yeterli klinik ve parazitolojik yanıtlara sahip 46 hasta (%97,9) bulundu. Çalışmanın takibi sırasında herhangi bir advers olay bildirilmedi.

Sonuç: DHP, birinci basamak sağlık hizmetlerinde komplike olmayan sıtmanın tedavisinde etkili, güvenlidir ve iyi tolere edilmektedir.

Anahtar Kelimeler: Dihidroartemisinin-Piperaquine, sıtma, birinci basamak sağlık hizmetleri

Received/Geliş Tarihi: 03.02.2021 **Accepted/Kabul Tarihi:** 01.12.2021

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Türkiye PARAZİTOLOJİ Dergisi

INTRODUCTION

Malaria is still a public health problem in Indonesia. Actions to control and eliminate malaria need to be supported by evaluating the accuracy of the diagnosis and the efficacy of the antimalarials used. The use of artemisinin-based combination therapy (ACTs) has become the main choice in Indonesia. It is widely accepted that ACTs provides the best available treatment for uncomplicated malaria (1). ACTs can slow down the development of resistance. ACTs is also very fast in clearing plasmodium in the blood, and has a gametocide effect to inhibit the spread of malaria transmission (2).

The artesunate-amodiaquine combination is an Artemisin derivative that was widely used in malaria endemic countries in early 2000s, including Indonesia. However, there have been many reports stating a decreased efficacy of the Artesunate-Amodiaquine combination. Thwing, in their study in South Kenya, found that 31.1% of the Artesunate-Amodiaquine combination treatment has failed (3). A related research in Timika also reported treatment failure by 22% (4). Artemisin combination side effects are often the reasons why patients did not adhere to the treatment process (5). The decrease in efficacy of the Artesunate-Amodiaquine combination has been followed up by changes in treatment patterns, replacing the drug combination with other artemisinin derivatives, namely the dihydroartemisinin-piperaquine (DHP) combination (1).

As the most reliable antimalarial combination at this time, the use of the DHP combination should receive serious attention. Hasugian found that the efficacy of the DHP combination treatment was still superior to the artesunate-amodiaquine combination (4). Similarly, Tjitra found that the efficacy of the DHP combination was still above 95% (6). Overall, although there have been reports of decreased efficacy, this DHP combination is still superior to other artemisinin derivatives. Therefore, routine monitoring of the therapeutic efficacy of ACTs is essential in making timely changes of treatment policy. It can also help to detect early changes in the parasite susceptibility to antimalarial drugs (1). This study was also conducted as an effort to achieve the elimination of malaria by 2030 in Indonesia.

METHODS

Study Design

This study was a prospective observation of the clinical and parasitological response to directly observed treatment for malaria. The World Health Organization (WHO) standard protocol for the assessment of the efficacy of antimalarial drugs for 28 days was modified according to existing conditions in public health services (7).

This was a part of a research to establish a diagnostic model for patients with asymptomatic malaria in hypo endemic area from 2015 to 2019. The therapy observation data was specifically collected from February 2018 to December 2018 in 2 Primary Health Care and 5 villages in the study area. The study was conducted in Batubara District, one of 13 malaria hypoendemic areas in North Sumatra Province. The study subjects were taken from the districts with the highest malaria prevalence, namely Tanjung Tiram and Labuhan Ruku Districts. This study was approved by the Health Research Ethical Committee, Medical Faculty, Universitas Sumatera Utara (decision number: 262/KOMET/FK USU/2015). Data collection was only done after obtaining medical approval after an explanation (informed consent) by the subject or the subject's parents.

Patient Selection

Subjects were people who live permanently around research location, selected by random sampling. They were obtained in two ways: Active case detection and passive case detection. Active case detection was carried out by visiting people who have a history of suffering from malaria in the last 2 years based on secondary data. Meanwhile, passive case detection was done by waiting for patients to visit the public health center. Subjects were collected by simple random method. Examination would be carried out after the subject received an explanation and gave an informed consent. The main criteria for subjects to be included in this study were: Subjects with age greater than 1 year and has written informed consent to participate in the study. Pregnant or lactating mothers and anyone with signs or symptoms of severe malaria were excluded from the study.

The diagnosis of malaria was established by performing microscopic examination by at least two trained microscopic experts. If differences in results are found, the final decision will be determined by the third examiner. All subjects were observed for 28 days. Follow-up microscopic examination was carried out on a fixed schedule on day 0, 1, 2, 3, 4, 7, 14, 21, 28, and every day the subject felt unwell. Thick and thin blood stains with Giemsa's stain were examined on the same day as the blood draw. The parasite density was calculated by counting the number of asexual parasites/gametocytes against the number of white blood cells (WBC) in thick blood films. Parasite density was expressed as the number of asexual parasites per microliter (μL) of blood. Density was calculated by dividing the number of asexual parasites by the number of WBCs counted, then multiplying by 5000 (assuming a WBC density of 5000 WBCs/μL). When the number of parasites was less than 10 per 200 WBCs in follow-up examination, counting was done against at least 500 WBCs. Blood slides were considered negative when the examination of 1000 WBCs did not reveal any asexual parasites.

The hemoglobin level is measured by the dipstick method [Easy Touch GHb meter, Lot HB15414B4T: Control: (N) 12-15 g/mL]. Axillary temperature was measured by digital thermometer. Condition of fever is defined by axillary temperature ≥37.5 °C. Meanwhile, other characteristics were obtained through interviews and observation.

A fixed-dose DHP regimen was given to subjects with uncomplicated malaria. One tablet of DHP (D-ARTEPP™ from Guillin Pharmaceutical Co. Ltd), consisted of 40 mg dihydroartemisinin and 320 mg piperaquine. DHP dosage was 2-4 mg/kg body weight/day dihydroartemisinin and 16-32 mg/kg body weight/day piperaquine, given for 3 days orally, in single dose per day on day 0, 1, and 2. All DHP doses were administered under supervision by a nurse or midwife designated by the principal investigator. Side effects are defined as signs and symptoms that occur after treatment has been initiated. Serious side effects are defined as death, life-threatening reactions, events requiring hospitalization or resulting in disability, or medical events requiring intervention.

The primary endpoint of this study was the treatment efficacy by day 28. The outcomes were evaluated with reference to the classification system suggested by the WHO, as follows:

Early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) and adequate clinical and parasitological response.

Statistical Analysis

Categorical variables were presented as absolute and proportions (%). Quantitative variables were presented as means and standard deviations. Chi-square test was used to analyze significant differences of proportion, and t-test was used for differences in numerical values. Statistical analyses were conducted using SPSS 20 for Windows and checked before analysis.

RESULTS

The baseline characteristics of enrolled study was summarized in Table 1. Among 484 subjects who were admitted as subjects of this study, 47 (9.7%) tested positive for malaria by microscopy, 45 (95.7%) tested positive by *Plasmodium vivax* and 2 (4.3%) tested positive by *Plasmodium falciparum*. All patients were successfully received followed up treatments with no drop-outs. There was no difference in sex (p>0.05) between the two groups. Subjects in the Malaria (+) group were younger, even though the age difference with Malaria (-) group was small (p>0.05). There was also no difference in fever (p>0.05), although difference between two groups' mean axillary temperatures were apparent (p<0.05). Meanwhile, there was a difference in the mean hemoglobin, where malaria patients appeared to have lower hemoglobin level. All patients who had fever at day 0 were not feverish anymore after taking DHP in the next day (D1). There were no adverse reactions or severe malaria.

The baseline characteristics of patients was summarized in Table 2. There were 24 patients without fever (asymptomatic malaria) and 23 patients with fever (clinical malaria). However, there was no characteristics difference between the two groups. There was no significant difference in all variables analyzed in the two groups (p>0.05).

The mean parasitic density on D0 started to decrease on D1 until D3, in both of clinical malaria and asymptomatic malaria. The decreased also occurred in gametocyte. There were no significant differences of parasitic density and gametocytes in all malaria patients (p>0.05). During D4, D7, D14, D21 and D28, there were no parasites found in the blood smears in all patients. The mean hemoglobin was higher in asymptomatic malaria than clinical malaria, although there was no significant difference (p>0.05).

The efficacy of the DHP combination in this study was shown in Table 3. There were 3 patients who had the same parasite density at D2 as D0, namely 2 patients with clinical malaria and 1 asymptomatic malaria. However, none of the patients

Table 1. Baseline characteristics of study's population

Variables	Malaria (+) (n=47)	Malaria (-) (n=437)	p
Spesies : *Plasmodium vivax : Plasmodium falciparum*, (%)	45 (95.7) : 2 (4.3)	0	-
Sex : Male : Female, %	42.6 : 57.4	48.3 : 51.7	0.455
Fever : Yes : No, %	48.9 : 51.1	60.0 : 40.0	0.145
Mean age ± SD (range), years	18.74±12.804 (4-60)	21.72±14.878 (1-72)	0.141
Mean axillary temperature ± SD (range), °C	37.55±0.529 (36.9-38.5)	37.29±0.745 (36.2-38.4)	0.004
Mean haemoglobin ± SD (range), g/dL	12.09±0.852 (10.3-13.2)	13.05±0.674 (10.1-14.0)	0.000

SD: Standard deviation

Table 2. Baseline characteristics of malaria's patients

Variables	Clinical malaria (n=23)	Asymptomatic malaria (n=24)	p
Sex : Male, female, %	43.5 : 56.5	41.7 : 58.3	0.900
Fever : Yes : No, %	52.2 : 47.8	45.8 : 54.2	0.664
Mean age ± SD (range), years	16.87±11.833 (4-19)	20.54±13.676 (8-60)	0.331
Mean axillary temperature ± SD (range), °C	37.62±0.457 (37.9-38.5)	37.48±0.594 (36.9-37.4)	0.389
Mean haemoglobin ± SD (range), g/dL	12.06±0.926 (10.3-12.0)	12.13±0.794 (10.7-13.2)	0.786
Mean asexual parasite density ± SD (range) on day 0, per µL	2740.87±1768.116 (2160-6320)	2440.00±1370.598 (480-5600)	0.517
Mean asexual parasite density ± SD (range) on day 1, per µL	1206.09±876.925 (880-3480)	1055.42±629.327 (200-2240)	0.501
Mean asexual parasite density ± SD (range) on day 2, per µL	1172.17±1094.012 (80-3560)	996.67±937.706 (0-2120)	0.557
Mean asexual parasite density ± SD (range) on day 3, per µL	64.35±109.038 (0-360)	60.00±130.284 (0-440)	0.902
Mean gametocyte density ± SD (range) on day 0, per µL	442.17±214.835 (140-800)	487.08±250.191 (0-880)	0.513
Mean gametocyte density ± SD (range) on day 1, per µL	73.04±37.951 (40-120)	77.50±46.555 (0-220)	0.721
Mean gametocyte density ± SD (range) on day 2, per µL	6.96±15.502 (0-40)	6.67±15.228 (0-40)	0.949
Mean gametocyte density ± SD (range) on day 3, per µL	0	0	-

SD: Standard deviation

had a higher parasite density at D2 than in D0. However, it was found that many patients had a higher density of parasite D2 than D1.

Meanwhile, it was found that one patient had a parasite density greater at D3 than 25% D0 density. Technically, this indicates early failure of treatment. At that time, the patient was unwilling to start second-line treatment. Interestingly, on the 4th day of blood tests, parasites were no longer found. the same results were obtained at the next examination. Up to follow-up on day 28, there was no finding of treatment failure, neither LCF nor LPF.

DISCUSSION

The main issue at the moment is malaria elimination. Efforts that have been made include improving the quality of diagnosis and evaluating the efficacy of treatment. The efficacy of antimalarials is assessed by the reduced density of plasmodium in the blood after antimalarial administration accompanied by the disappearance of clinical signs and symptoms of malaria. Decrease in drug efficacy can occur due to resistance. Antimalarial resistance occurs due to inadequate use of drugs, either due to insufficient doses or due to incomplete treatment. Early detection of decreased drug efficacy can prevent drug resistance.

DHP is the foremost ACT for uncomplicated malaria in many countries, including Indonesia. Dihydroartemisinin is one of the highly active artemisinin derivatives and the main *in vivo* metabolite of artesunate or artemeter. Piperaquine is bisquinoline which maintains activity against chloroquine resistant *Plasmodium*. Both drugs are very active against the asexual stage of *Plasmodium* (8). In general, therapeutic efficacy studies on DHP have shown good results for malaria infection, as well as the post-treatment prophylactic effect of delaying reinfection (4,9,10).

This study did not find any differences in the characteristics of both the malaria and non-malaria groups, as well as in the clinical malaria and asymptomatic malaria groups. Hemoglobin levels in malaria patients appear to be lower. This is consistent with the pathogenesis of malaria, although there was no significant difference in hemoglobin levels between clinical malaria and asymptomatic malaria groups. Body temperature above 37.5 °C can still be used as an initial screening for malaria ($p<0.05$), although this variable cannot differentiate between clinical malaria patients and asymptomatic malaria ($p>0.05$). This suggests that microscopic examination is the standard for the diagnosis of malaria.

Several studies have reported the side effects of the drugs, which are nausea, diarrhea, and vomiting. Other side effects reported are anemia, dizziness, coughing and difficulty of sleeping (11-13). Although there is no evidence of cardiotoxicity, piperaquine can make the QT interval lengthen (14-16). This combination should also get serious attention when given to patients with age over 70 years, body weight <5 kg, and liver and kidney disorders (15,16).

This study actually also observed at adverse events, adherence, fever clearance time and parasite clearance time as indicators of treatment. Adverse events were assessed by direct interview. Adverse events were defined as a condition of any unfavorable, unintended sign, symptom, syndrome or disease that develops or worsens concomitant with the use of study medicines, regardless of whether it is related to the study medicines. But throughout the observations in this study, there were no adverse events of the drugs that bothered the patients, so all patients were adherent to taking medication according to the rules. The same results were obtained in several other studies (17-20).

By 24 hours after treatment, all of the patients were afebrile. Therefore, the time needed to relieve fever is around 24 hours. Other studies have also found a fast fever-reducing effect on DHP (6,17,18). Measurement of parasite clearance time cannot be done because the patient was only willing to draw blood once a day. Even the calculation of parasite density every day cannot be done exactly per 24 hours. However, asexual parasites were no longer seen in 2 patients (4.3%) in D2, 13 patients (27.7%) in D3 and 32 patients (68%) in D4, respectively. Meanwhile, gametocytes were no longer seen in 2 patients (4.3%) in D2, 13 patients (27.7%) in D3 and 32 patients (68%) in D4, respectively.

This study found an interesting phenomenon, namely fluctuation in parasite density after treatment. Parasitic density is expected to decrease gradually from the start of treatment (D0) until all parasites are gone on the third day after treatment (D3). However, this study found the same parasite density in D2 as D0 in 3 patients (3/47; 6.38%). It was even found that 20 people (20/47; 42.55%) had a greater parasite density in D2 compared to D1. Parasite was still found in D3 in 16 people (16/47; 34.04%).

This result is different from several other studies which found that asexual parasite disappearance in some patients started in D1 and disappeared completely in D3 (17,21). However, these

Table 3. Outcomes of malaria's patients treated with DHP

Characteristics	Clinical malaria (n=23)	Asymptomatic malaria (n=24)
Early treatment failure, ratio	**1/47**	
Asexual parasite density on day 0< day 1, ratio	0	0
Asexual parasite density on day 0= day 2, ratio	2/23	1/24
Asexual parasite density on day 0< day 2, ratio	0	0
Asexual parasite density on day 1< day 2, ratio	13/23	7/24
Asexual parasite density on day 3>0 per µL, ratio	11/23	5/24
Asexual parasite density on day 3≥25% of count on day 0, ratio	0	**1/24**
Late clinical failure, ratio	0	
Late parasitological failure, ratio	0	
Adequate clinical and parasitological response rate, ratio	**46/47**	

results differ from the decrease in the number of sexual parasites (gametocytes), where gametocytes begin to disappear in D3 (21) and have not even shown a decrease up to D7 (17).

In this study, a once per day, 3-dose treatment of DHP was a simple, highly efficacious, and generally well-tolerated treatment for uncomplicated malaria, even one of them had a density greater than 25% density at D0. Results of this study clearly indicate that DHP is still highly effective (46/47 or 97.87%).

The treatment efficacy in this study was still good, even the efficacy was still above 95%. The same results were found in several studies (6,8,18,19,22-26). Some studies have even stated that giving this combination of drugs can reduce recurrence by up to 42 days (24,27). The results of this study can also provide an idea that the level of patient compliance in the treatment process is still good. This is important to note because patient adherence to treatment greatly affects the efficacy of the drug (24).

CONLUSION

This study found one patient who was categorized as ETF, who needs serious attention. This information reflects a possible decrease in the ability of antimalarials to eliminate parasites in the patient's blood. This can be seen from the fluctuation of parasite density after antimalarial administration. A decrease in the ability of these drugs can indicate an early sign of drug resistance. For this reason, an effort is needed to determine what risk factors affect the density fluctuation of the parasite so the drug resistance process can be prevented.

Observation of drug efficacy is one part of many efforts needed to break the chain of malaria transmission. One of the inhibitors of the malaria elimination process is the occurrence of antimalarial resistance. Observation of early signs of drug resistance in primary care, is the answer for malaria elimination.

ACKNOWLEDGMENTS

This research was funded by Ministry of Research, Technology and Higher Education through Research Institute, Universitas Sumatera Utara. We thank the health workers in health care services in Batubara district, and also to the holders of the malaria program in Batubara district, North Sumatera. We also thank all the participants in this study.

*Ethcis

Ethics Committee Approval: This study was approved by the Health Research Ethical Committee, Medical Faculty, Universitas Sumatera Utara (decision number: 262/KOMET/FK USU/2015).

Informed Consent: Each participant was clearly informed about the objective of the study, and verbal permission from the head of each household was obtained.

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

REFERENCES

1. World Health Organization. Guidelines for The Treatment of Malaria. Geneva. 2015.
2. World Health Organization. Antimalarial Drug Combination Therapy. Report of a WHO Technical Consultation. World Health Organization. Geneva. 2001.
3. Thwing JI, Odero CO, Odhiambo FO, Otieno KO, Kariuki S, Ord R, et al. In-vivo efficacy of amodiaquine-artesunate in children with uncomplicated Plasmodium falciparum malaria in western Kenya. Trop Med Int Health 2009; 14: 294-300.
4. Hasugian AR, Purba HL, Kenangalem E, Wuwung RM, Ebsworth EP, Maristela R, et al. Dihydroartemisinin-piperaquine versus artesunate-amodiaquine: superior efficacy and posttreatment prophylaxis against multidrug-resistant Plasmodium falciparum and Plasmodium vivax malaria. Clin Infect Dis 2007; 44: 1067-74.
5. Siahaan L, Yuniarti T, Juliani I, Darmawan P. PerbandinganBeberapaKombinasi Artesunate Pada Pengobatan Malaria Falciparum TanpaKomplikasi. Simposium Nasional Parasitologi Dan PenyakitTropis. Denpasar, 25-26 Agustus 2007.
6. Tjitra E, Delima D, Hasugian AR, Siswantoro H, Avriana R, Sampurno OD. Efficacy and safety of dihydroartemisinin-piperaquine in Indonesia children infected with uncomplicated Plasmodium falciparum and Plasmodium vivax, Paediatrica Indonesiana 2011; 51: 351-60.
7. World Health Organization. Monitoring Antimalarial Drug Resistance. Report of a WHO Consultation. Geneva 2001: 9-21.
8. Ashley EA, McGready R, Hutagalung R, Phaiphun L, Slight T, Proux S, et al. A randomized, controlled study of a simple, once-daily regimen of dihydroartemisinin-piperaquine for the treatment of uncomplicated, multidrug-resistant falciparum malaria. Clin Infect Dis 2005; 41: 425-32.
9. Ratcliff A, Siswantoro H, Kenangalem E, Maristela R, Wuwung RM, Laihad F, et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. Lancet 2007; 369: 757-65.
10. Pasaribu AP, Chokejindachai W, Sirivichayakul C, Tanomsing N, Chavez I, Tjitra E, et al. A randomized comparison of dihydroartemisinin-piperaquine and artesunate-amodiaquine combined with primaquine for radical treatment of vivax malaria in Sumatera, Indonesia. J Infect Dis 2018; 208: 1906-13.
11. Krudsood S, Looareesuwan S, Tangpukdee N, Wilairatana P, Phumratanaprapin W, Leowattana W, et al. New fixed-dose artesunate-mefloquine formulation against multidrug-resistant Plasmodium falciparum in adults: a comparative phase IIb safety and pharmacokinetic study with standard-dose nonfixed artesunate plus mefloquine. Antimicrob Agents Chemother 2010; 54: 3730-7.
12. Mwesigwa J, Parikh S, McGee B, German P, Drysdale T, Kalyango JN, et al. Pharmacokinetics of artemether-lumefantrine and artesunate-amodiaquine in children in Kampala, Uganda. Antimicrob Agents Chemother 2010; 54: 52-9.
13. Sirivichayakul C, Sabchareon A, Pengsaa K, Thaiarporn I, Chaivisuth A, Na-Bangchang K, et al. Comparative study of the effectiveness and pharmacokinetics of two rectal artesunate/oral mefloquine combination regimens for the treatment of uncomplicated childhood falciparum malaria. Ann Trop Paediatr 2007; 27: 17-24.
14. Stepniewska K, Taylor W, Sirima SB, Ouedraogo EB, Ouedraogo A, Gansané A, et al. Population pharmacokinetics of artesunate and amodiaquine in African children. Malar J 2009; 8: 200.
15. German PI, Aweeka FT. Clinical pharmacology of artemisinin-based combination therapies. Clin Pharmacokinet 2008; 47: 91-102.
16. Karunajeewa H, Lim C, Hung TY, Ilett KF, Denis MB, Socheat D, et al. Safety evaluation of fixed combination piperaquine plus dihydroartemisinin (Artekin) in Cambodian children and adults with malaria. Br J Clin Pharmacol 2004; 57: 93-9.
17. Wang Y, Yang Z, Yuan L, Zhou G, Parker D, Lee MC, et al. Clinical Efficacy of Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated Plasmodium falciparum Malaria at the China-Myanmar Border. Am J Trop Med Hyg 2015; 93: 577-83.
18. Zwang J, Ashley EA, Karema C, D'Alessandro U, Smithuis F, Dorsey G, et al. Safety and efficacy of dihydroartemisinin-piperaquine in falciparum malaria: a prospective multi-centre individual patient data analysis. PLoS One 2009; 4: e6358.
19. Myint HY, Ashley EA, Day NP, Nosten F, White NJ. Efficacy and safety of

dihydroartemisinin-piperaquine. Trans R Soc Trop Med Hyg 2007; 101: 858-66.

20. Janssens B, van Herp M, Goubert L, Chan S, Uong S, Nong S, et al. A randomized open study to assess the efficacy and tolerability of dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Cambodia. Trop Med Int Health 2007; 12: 251-9.
21. Lidia K, Deo DA, Pakan PD, Riwu M. Evaluation of therapeutic efficacy and safety of Dihydroartemisinin-Piperaquine in uncomplicated Plasmodium falcifarummonoinfection in Timor Tengah Selatan district, Nusa Tenggara Timur, Indonesia. Southeast Asian J Trop Med Public Health 2018; 49: 733-40.
22. Wang Q, Zhang Z, Yu W, Lu C, Li G, Pan Z, et al. Surveillance of the Efficacy of Artemisinin-Piperaquine in the Treatment of Uncomplicated *Plasmodium falciparum* Malaria Among Children Under 5 Years of Age in Est-Mono District, Togo, in 2017. Front Pharmacol 2020; 11: 784.
23. Chotsiri P, Zongo I, Milligan P, Compaore YD, Somé AF, Chandramohan D, et al. Optimal dosing of dihydroartemisinin-piperaquine for seasonal malaria chemoprevention in young children. Nat Commun 2019; 10: 480.
24. Nambozi M, Van Geertruyden JP, Hachizovu S, Chaponda M, Mukwamataba D, Mulenga M, et al. Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Zambian children. Malar J 2011; 10: 50.
25. Karema C, Fanello CI, van Overmeir C, van Geertruyden JP, van Doren W, Ngamije D, et al. Safety and efficacy of dihydroartemisinin/piperaquine (Artekin) for the treatment of uncomplicated Plasmodium falciparum malaria in Rwandan children. Trans R Soc Trop Med Hyg 2006; 100: 1105-11.
26. Tangpukdee N, Krudsood S, Thanachartwet W, Chalermrut K, Pengruksa C, Srivilairit S, et al. An open randomized clinical trial of Artekin vs artesunate-mefloquine in the treatment of acute uncomplicated falciparum malaria. Southeast Asian J Trop Med Public Health 2005; 36: 1085-91.
27. Commons RJ, Simpson JA, Thriemer K, Abreha T, Adam I, Anstey NM, et al. The efficacy of dihydroartemisinin-piperaquine and artemether-lumefantrine with and without primaquine on Plasmodium vivax recurrence: A systematic review and individual patient data meta-analysis. PLoS Med 2019; 16: e1002928.