**Artemisinin-napthoquine versus dihydroartemisinin-piperaquine in adult subjects with *Plasmodium vivax* infection**

Armedy Ronny Hasugian,  
Hadjar Siswantoro,  
Michael P. Fay,  
Emiliana Tjitra

1National Institute of Health Research and Development, Ministry of Health Republic of Indonesia, Jakarta, Indonesia  
2National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

**Abstract**

**Background:** This study was to compare the efficacy and safety between Artemisinin-Napthoquine (AN) as a single dose as well as an alternative drug, and Dihydroartemisinin-Piperaquine (DHP) as a three-day standard regimen on *P. vivax* infection.

**Methods:** This was an open randomized study performed during the period of April 2007- March 2008 in three Armed Forces Hospitals in Jayapura, Papua Province, and one private hospital in Maumere, East Nusa Tenggara Province. This study was a part from previously published study for any malaria infection. Efficacy was the absence of clinical and parasitological malaria until day 42, performed as Adequate Clinical and Parasitological Response (ACPR). Safety was performed based on adverse event in any day of follow up which never reported at day recruitment (d0).

**Results:** This study analyses 158 *P. vivax* cases. A total 80 subjects were treated with AN and 78 with DHP. The median Parasite Clearance Estimator (PCE) was 2.32 (range: 1.42 – 7.78; Interquartile Range (IQR): 1.99 – 2.82) hours in AN and 2.05 (range: 1.30 – 8.30; IQR: 1.82 – 2.46) hours in DHP group. The parasite clearance was complete by 64 hours. The ACPR was 100% (95% CI: 95.2-100) in the AN, and 100% (95% CI: 94.9-100) in the DHP. Both drugs have similar mild and tolerated adverse events.

**Conclusions:** Both drugs have similar efficacy and safety for the treatment of *P. vivax* in adults. Although AN has took longer PCE compared to DHP, 100% clearance was achieved in both groups in 64 hours.  

*Key word:* malaria, Artemisinin, napthoquine, dihydroartemisinin, vivax
Malaria, the old disease caused by *Plasmodium* species has been difficult to control until now. *P. falciparum* and *P. vivax* infection (55%; 45%) comprise the main malaria infections in Indonesia.\(^1\) Although *P. vivax* is usually associated with uncomplicated malaria, some cases may become severe.\(^1,3\) Malaria is a major health issue in the eastern part of the Indonesia. Annual Parasite Incidence (API) in Papua and East Nusa Tenggara was reported as 177 and 81 cases per 100000 people in 2007.\(^4\)

Dihydroartemisine-Piperaquine (DHP) which has been widely used since 2009 has become the new standard regimen of antimalarial therapy in Indonesia and has demonstrated better efficacy and safety against *P. vivax* in comparison with AAQ.\(^4,6\) DHP is a fixed once-daily dose taken for three days. The drug is well-tolerated and has better compliance than AAQ in Indonesia.\(^5\) Drug compliance is a complex issue for antimalarial regimens and can be associated with early treatment failure (e.g. Chloroquine).\(^7\) Although safe and efficacious treatment regimens of only three days are available compliance remains an issue.\(^8-10\) An alternative drug that could be taken in a single dose and directly observed could improve compliance and prevent treatment failure and relapse. Additionally relapses an important issue and difficult to distinguish from reinfection or recrudescence in *P. vivax* infection.

Artemisinin-Napthoquine (AN) is a alternative drug that can be given in a single dose and is reported to have better efficacy and safety for *P. falciparum*.\(^11,12\) Artesunate-Amodiaquine (AAQ) was the first ACT approved in Indonesia since 2004 but the efficacy for *Pvivax* is 52%.\(^3\) AN was developed in China in the1990s and is known to be more efficacious than artesinin or piperaquine monotherapy.\(^12\) The API decreased was shown in Papua and East Nusa Tenggara in 2011 after Artemisinin Combination Therapy (ACT) was adopted as a standard regimen.\(^6,13,14\)

In this report, we compared the efficacy and safety profile of DHP and AN in treating *P. vivax* malaria patients in Indonesian hospitals. We compared the clinical symptoms from day 0 to 42 days and the recurrence of parasitemia from day 7 until day 42.

**METHODS**

**Study Design**

This was an open-label multi-center randomized trial. phase 3 comparative study to determine efficacy and safety of a single dose AN vs DHP as a three-day standard regimen in adults with uncomplicated *P. vivax*. We evaluated 158 subjects infected with *P. vivax* alone. Inclusion criteria were previously reported.\(^15\) Subjects infected by *P.vivax* were required to have circulating asexual parasite levels ≥ 250 parasite/µl.

**Study Setting**

The study was performed during the period of April 2007- March 2008 in three Armed Forces Hospitals in Jayapura, Papua Province and one private hospital in Maumere, Sikka District, East Nusa Tenggara Province. All of the subject were uncomplicated *P. vivax* cases but all of them were hospitalized because AN was a new drug therefore the subjects received DHP had the same treatment as AN. In Papua province, chloroquine resistance, cross-resistant amodiaquine, and low AAQ efficacy and safety for *P.vivax* had been previously reported.\(^3,5,16,17\)

**Study Drugs**

The AN was manufactured by Kunming Pharmaceutical Corporation as Arco™. One tablet contains 250 mg of Artemisinin and 100 mg of Napthoquine(equivalent with 156.6 mg ofPhosphate Naphthoquine). The drug was compared with DHP. Duo-Cotecxin™ produced by Beijing Holley Cotex Pharmaceutical Co.Ltd; one tablet contains 40 mg and 320 mg of dihydrotetemisin piperaquine. Four tablets of Artemisinine-Napthoquine (Arco™) were administered to the AN subjects by investigator on recruitment day (D0) only. Dihydroartemisin-piperaquine (Duo-Cotecxin™) was given to DHP subjects by investigator in one dose a day for three days; one dose was 3 tablets for people with body weight of 35-60 kg or 4 tablets for body weight of >60 kg. Primaquine with 0.5 mg per kg body weight was given to all subject when recurrence occurred or on the last day of the study (Day 42). All drug treatments on all subjects were directly observed.

**Study Procedure**

As detailed previously,\(^15\) parasite asexual and gametocyte count was measured on day 0 at hour 0 (h0) then measured at eight-hour intervals for the first three days (at 8, 16, 24, 32, 40, 48, 56, 64, and 72 hours). Measuring the parasite was conducted on follow up schedule at day 7, 14, 21, 28, 35 and 42. The blood blot slide was taken and read by trained microscopist. The asexual parasite count was calculated based on total parasite per 200 µl leucocyte multiplied by 5000 µl leucocyte. While
Parasitological Failure (LPF), Failure (ETF), Late Clinical Failure (LCF) or Late meet ACPR was considered either Early Treatment malaria until day 42. The subject who unable to is
up, withdrawal of consent and protocol violations were considered censored events until day 42 according WHO guideline 2009. Subjects lost to follow, withdrawal of consent and protocol violations were considered censored events until day 42 according WHO guideline 2009. ITT is defined as analysis on all the subjects who were recruited and take at least one dose of the study drug; while PP is defined as analysis on all subject who finished the study regimen. The protocol violation was defined as all the subject who unable to meet inclusion and exclusion criteria including the new infection with different species.

Safety was performed based on a occurrence of adverse events that happened until d42 during AN and DHP treatment. Any clinical symptom in anyday of follow-up which never reported at day recruitment(d0) was considered as an adverse event.

Other parameters measured such as proportion of clinical symptom, parasite clearance time and gametocyte clearances were analyzed by chi-square test and t-test or mann-whitney test. Proportion of clinical symptom was define as any clinical symptom was define as any clinical symptom, parasite clearance time and Other parameters measured such as proportion of asexual recruitment(d0) was considered as an adverse event. AN and DHP treatment. Any clinical symptom in adverse events that happened until d42 during AN and DHP (figure 1). In the AN group two cases (2.5%) were analysed as protocol violations, one due to the ingestion of other antimalarial drugs on the d28, and the other because of failure classified as Late Parasitological Failure (LPF) with a different species (P. falciparum) on d32. In DHP group two cases (2.6%) were analysed as withdrawn consent on d0 and d4 and two cases (2.6%) as protocol violations with LPF of different species (P. falciparum) on day 35. Additionally, three cases in the AN group and four cases in the DHP group were lost to follow-up (LTFU). Primaquine was given to all subject.

The baseline characteristics of the two study groups were similar such as sex and fever (table 1). The clinical symptom characteristics at day of admission were similar (table 2). History of vomiting was reported in more than 20 % of the subjects in AN group compared to DHP (22.5% vs 6.4%, p = 0.008).

The proportion of parasitemia at eight-hour intervals from 0 until 72 hours can be found in figure 1. The median parasite clearance estimator (PCE) was 2.32 (range: 1.42 – 7.78 ; IQR: 1.99 – 2.82) hours with median PC50 2.98 (range: 0.11 – 11.59) hours and median PC90 8.41 (range: 4.22 – 24.32) hours after AN treatment. While the median PCE after DP treatment was 2.05 (range: 1.30 – 8.30 ; IQR: 1.99 – 2.82) hours with median PC50 2.98 (range: 0.11 – 11.59) hours and median PC90 6.22 (range: 3.23 -22.58) hours. Gametocyte clearance was not evidence until 72 hours after treatment for both of drugs (figure 2). All subjects obtained gametocyte clearance on day 21 in the AN group and on day 7 in the DHP group.

The APCR of both drugs on d42 based on ITT and PP analysis was 100% (95% CI: 95.2 –100) for AN and 100%, 95% CI: 94.9 – 100 for DHP. There was no ETF, LCF or LPF with P. vivax following recurrence cases in both treatment arm. Confidence intervals measures for APCR were by exact binomial method for PP analysis or beta product confidence procedure for ITT analysis and were equivalent because there was 100% response.
A few adverse events were reported during this study. The most commonly reported adverse events in the AN group were nausea 6.3% (5/80), abdominal pain 5% (4/80), fatigue 3.8% (3/80), cough 3.8% (3/80), dizzy 7.5% (6/80), sleep disturbance 6.3% (5/80) and rigors 5% (4/80). The most common adverse events reported in the DHP group were fatigue 9.1% (7/77). cough 2.6% (2/77), dizzy 3.9% (3/77), vomiting 7.8% (6/77) and abdominal pain 2.6% (2/77).

**DISCUSSION**

Our study shows AN and DHP had similar efficacy with 100 percent ACPR in all subjects with *P. vivax* at day 42. This demonstrated that both drugs have essentially fulfilled the WHO criteria in that the percentage of efficacy is higher than 95%. Both drugs also show similar safety profile.

This study is consistent with other AN and DHP studies and confirmed that AN as a single drug can be a potential alternative for treating infection with *P. vivax*. In our study the recurrence of *P. Vivax* was not found. Gametocytemia was found in more than 80 percent of patients at baseline which is characteristic of the sexual stage of *P. vivax* infection. Both drugs can eliminate the gametocyte but gametocytemia was found in a few cases after 72 hours of treatment so the transmission could potentially continue. Prolonged gametocytemia in *P. falciparum* and *P. vivax* treatment could be one of many signs of recurrent parasitemia although in this study we observed no recurrence. The submicroscopic parasitemia study might be required in the future to detect the gametocytenia level at the end of the treatment study. Because of this the primaquine was needed in the early treatment with ACTs. Primaquine can diminish asexual stage for all of Plasmodium species in humans.

The median PCE, PC50 and PC90 of DHP were faster than AN. The data conformed another study of an artemisinin derivative. Artemisinin derivative was a fast acting drug including dihydroarteminin and artemisinin. However dihydroarteminin showed higher activity and had parasite clearance time faster compare artemisinin. The parasitemia was clear at 64 hours for all subjects in both treatment. This shows that AN as a single-dose and DHP as a three-dose daily drugs have a similar anti-parasitic potential. Artemisinin derivatives can eliminate the parasitemia immediately, but if administered alone as...
monotherapy, it must be given for 5 – 7 days because of rapid drug elimination. This disadvantage exists even with a small parasitemia count, but it can be overcome by co-administration of Naphthoquine, which results in adequate parasite clearance time and protection from early recurrence. Moreover, artemisinin resistance for P. vivax has not been reported yet in Indonesia.

The adverse events were categorized as mild in this study for both treatments. This is consistent with the other studies. All adverse events were related to the drugs. Both drugs were tolerated well, despite high numbers of cases in the AN group reporting vomiting at baseline. This shows that both drugs did not given any severe effect.

The limitations of our study were a small sample size and inclusion of only adults. This study was a part of main study for all malaria cases, and was giving us information related the efficacy and safety of AN for treatment P. vivax infection. The inclusion of only adults was related with AN as a new drug, so the children study for AN was needed to use this drug as an alternative of malaria treatment widely. The study had more male subjects than females because we conducted the study at four hospitals and three were armed forces hospitals, which primarily serve men. Eventhough, there was no different cases between men and women for malaria vivax infection.
In conclusion, both drugs had similar efficacy and safety profiles for the treatment of vivax malaria in adult subjects in hospitals in Indonesia and fulfills WHO criteria. AN took longer to clear the parasitemia than DHP but parasite clearance was complete in all patients by 64 hours. Further evaluation studies are still needed at Primary Health Care centers, especially for efficacy and safety for children. This study supports the recommendation of AN as an alternative drug for *P. vivax* malaria.

**Acknowledgment**

We thank the Police Department Hospital, Army Hospital, and Navy Hospital in Jayapura, and St. Gabriel Hospital in Maumere. We are also grateful to the NIHRD team. We also thank Dr. Nancy Touchette (National Institutes of Health, USA), Prof Inge Sutanto (Faculty of Medicine, Universitas Indonesia), and Dr. Aprilianto Eddy Wiria, PhD (Departement of Parasitology Leiden University Medical Centre) for reviewing this manuscript.

**REFERENCES**

1. World Malaria Report. Geneva: World Health Organization; 2013.
2. Gething PW, Elyazar IR, Moyes CL, et al. A long neglected world malaria map: *Plasmodium vivax* endemicity in 2010. PLoS neglected tropical diseases. 2012;6:e1814. Epub 2012/09/13.
3. Tjitra E, Anstey NM, Sugiaiarto P, et al. Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Medicine. 2008;5:e128. Epub 2008/06/20.
4. Health Profile Indonesia. Jakarta: Departement of Health Republic of Indonesia; 2007. Indonesian.
5. Hasugian AR, Purba HL, Kenangalem E, et al. Dihydroartemisinin-piperaquine versus artesunate-amodiaquine: superior efficacy and posttreatment prophylaxis against multidrug-resistant *Plasmodium falciparum* and *Plasmodium vivax* malaria. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007;44:1067-74. Epub 2007/03/17.
6. Health Data Profile Indonesia. Jakarta: CDC. Ministry of Health Republic of Indonesia; 2011. Indonesian.
7. Bloland PB. Drug resistance malaria. World Health Organization. 2001.
8. Congpuong K, Buamombai P, Banmaurou I, et al. Compliance with a three-day course of artesunate-mefloquine combination and baseline anti-malarial treatment in an area of Thailand with highly multidrug resistant falciparum malaria. Malaria journal. 2010;9:43. Epub 2010/02/06.
9. Thanh NX, Trung TN, Phong NC, et al. The efficacy and tolerability of artemisinin-piperaquine (Artequick(R)) versus artesunate-amodiaquine (Coarsucam) for the treatment of uncomplicated Plasmodium falciparum malaria in south-central Vietnam. Malaria journal. 2012;11:217. Epub 2012/06/30.
10. Yeka A, Tibenderana J, Achan J, et al. Talisuna AO. Efficacy of quinine, arteether-lumefantrine and dihydroartemisinin-piperaquine as rescue treatment for uncomplicated malaria in Ugandan children. PLoS one. 2013;8(1):e53772. Epub 2013/01/26.
11. Hombhanje FW, Linge D, Saweri A, et al. Artemisinin-naphthoquine combination (ARCO) therapy for uncomplicated falciparum malaria in adults of Papua New Guinea: a preliminary report on safety and efficacy. Malaria journal. 2009;8:196. Epub 2009/08/13.
12. Wang J-y, Cao W-c, Shan C-q, et al. Naphthoquine phosphate and its combination with artemisinine. Acta Trop. 2004;89:375-81.
13. Guidelines treatment of malaria cases in Indonesia. Jakarta: General Directorate of Communicable Disease and Environment Health. Ministry of Health Republic of Indonesia; 2009.
14. Guideline Treatment of Malaria. Second Edition. World Health Organization 2010. 2010.
15. Tjitra E, Hasugian AR, Siswantoro H, et al. Efficacy and safety of artemisinin-naphthoquine versus dihydroartemisinin-piperaquine in adult patients with uncomplicated malaria: a multi-centre study in Indonesia. Malaria journal. 2012;11:153. Epub 2012/05/05.
16. Ratcliff A, Siswantoro H, Kenangalem E, Wuwung M, Brockman A, Edstein MD, et al. Therapeutic response of multidrug-resistant *Plasmodium falciparum* and *P. vivax* to chloroquine and sulfadoxine-pyrimethamine in southern Papua, Indonesia. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007;101:351-9. Epub 2006/10/10.
17. Tjitra E. Improving the diagnosis and treatment of malaria in eastern Indonesia. Darwin, Australia: Northern Territory University; 2001.
18. Methods for surveillance of antimalarial drug efficacy. World Health Organization. 2009.
19. Parasite Clearance Estimator [cited 2014 Dec 14]. Available from: https://www.wwarn.org/research/parasite-clearance-estimator.
20. Fay MP, Brittain EH, Proschan MA. Pointwise confidence intervals for a survival distribution with small samples or heavy censoring. Biostatistics. 2013;14:723-36. Epub 2013/05/02.
21. Douglas NM, Anstey NM, Angus BJ, et al. Artemisinin combination therapy for vivax malaria. The Lancet Infectious Diseases. 2010;10:405-16.
22. Price RN, Douglas NM, Anstey NM, et al. *Plasmodium vivax* treatments: what are we looking for? Current opinion in infectious diseases. 2011;24:578-85. Epub 2011/10/12.
23. Wernsdorfer WH, Wernsdorfer G, Prajakwong S, et al. Activity correlation between artemisinin and dihydroartemisinin in fresh isolates of *Plasmodium falciparum* from Thailand. Tropenmed Parasitol. 2000;22:87-94.
24. Trung TN, Van Phuc D. A randomized, controlled trial of artemisinin-piperaquine vs dihydroartemisinin-piperaquine phosphate in treatment of falciparum malaria. Chinese journal of integrative medicine. 2009;15:189-92.