

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

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Received: October 1, 2015; Revised: October 14, 2015; Accepted: October 18, 2015

Abstrak

Latar belakang: Penelitian ini untuk membandingkan efikasi dan keamanan Artemisinin-Napthoquine (AN) dengan dosis tunggal dan obat pilihan ACT lain, dengan Dihydroartemisinin-Piperaquine (DHP) pada pengobatan *P.vivax*.

Metode: Penelitian ini adalah studi randomisasi terbuka dengan subyek direkrut mulai tahun 2007 – 2008 dari RS St Gabriel, Maumere dan RS Polisi, RS Angkatan Darat dan RS Angkatan Laut di Jayapura. Penelitian ini merupakan bagian dari penelitian utama yang sudah dipublikasi sebelumnya. Efikasi dinyatakan dengan ketiadaan klinis dan parasit malaria sampai dengan hari ke 42, disebut Adequate Clinical and Parasitological Response (ACPR). Keamanan dinyatakan sebagai kejadian sampingan yang ditemukan pada setiap kunjungan ulang yang tidak dilaporkan sebelumnya pada hari rekrutmen (h0).

Hasil: Total 158 subyek dianalisis. Sejumlah 80 subyek direkrut pada kelompok AN dan 78 dengan DHP. Median Parasite Clearance Estimator (PCE) yaitu 2,32 (kisaran: 1,42 – 7,78; IQR: 1,99 – 2,82) jam pada AN dan 2,05 (kisaran: 1,30 – 8,30; IQR: 1,82 – 2,46) jam pada DHP. Parasite clearance sudah terjadi dalam 64 jam. Adequate clinical parasitological response (ACPR) at day 42 was 100% (95% CI: 95,2-100) pada AN, dan 100% (95% CI: 94,9-100) pada DHP. Kejadian Sampingan ditemukan ringan dan dapat ditoleransi.

Kesimpulan: Kedua obat memiliki efikasi dan keamanan yang sebanding untuk pengobatan malaria vivaks dewasa. Walaupun pembersihan parasit AN lebih lama dibandingkan DHP, 100% pembersihan terjadi pada kedua kelompok pengobatan dalam 64 jam. (*Health Science Journal of Indonesia 2015;6:92-8*)

Kata kunci: malaria, Artemisinin, napthoquine ,dihydroartemisinin, vivax

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% Confidence Interval (CI): 95.2-100) in the AN, and 100% (95% CI: 94.9-100) in the DHP group. 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. (*Health Science Journal of Indonesia 2015;6:92-8*)

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

Dihydroartemisinin-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-Naphthoquine (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 *P. vivax* is 52%.⁵ AN was developed in China in the 1990s and is known to be more efficacious than artemisinin 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/ul.

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 Naphthoquine (equivalent with 156.6 mg of Phosphate 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 dihydroartemisinin piperaquine. Four tablets of Artemisinin-Naphthoquine (Arco™) were administered to the AN subjects by investigator on recruitment day (D0) only. Dihydroartemisinin-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 μ l leucocyte multiplied by 5000 μ l leucocyte.¹⁵ While

the gametocyte was calculated per 2000 ul leucocyte multiplied by 5000 μ l leucocyte. All subjects were hospitalized until day 3 to observe adverse events even though the parasitemia was cleared.

History taking, clinical examination and adverse events were all performed on the initial recruitment day 0 (d0), and on follow-up visits (d1, d2, d3, d7, d14, d21, d28, d35), and until the last day (d42) or days of recurrence.

Study outcomes and Data Analysis

Efficacy was defined according to the WHO 2009 as a Adequate Clinical and Parasitology Response (ACPR) protocol at D42, which is evaluated based on intention to treat (ITT) and Per Protocol (PP) analysis.¹⁸ ACPR is defined as the absence of clinical and parasitological malaria until day 42. The subject who unable to meet ACPR was considered either Early Treatment Failure (ETF), Late Clinical Failure (LCF), or Late Parasitological Failure (LPF).¹⁸ Subjects lost to follow up, withdrawal of consent and protocol violations were considered censored events until day 42 according WHO guideline 2009.¹⁸ 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.¹⁵

Safety was performed based on a occurrence of adverse events that happened until d42 during AN and DHP treatment. Any clinical symptom in anyway 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 at day of recruitment according to standard clinical malaria manifestation.¹⁸ Proportion of asexual parasitemia and gametocytes werecalculated for each eight-hour intervaluntil hour 72 (d72), gametocytes would be continued especially each seven-days interval until day 42(d42). Proportion of parasite clearance was measured for regression models of the log transformed parasite counts were fitted in order to estimate parasite clearance using the Parasite Clearance Estimator Tool (PCE) developed by the World Wide Antimalarial Resistance Network (WWARN).¹⁹

The study received ethical approval by the Ethics Commission of the National Institute of Health Research and Development, Ministry of Health, Indonesia with no. LB.03.02/2/449/2007, and The Bureau of Food and Drug Control Republic of Indonesia with no. PO.01.01.3.1.1682

RESULTS

A total of 158 subjects were included in the study with 80 subjects treated with AN and 78 with 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: 1.82 – 2.46) hours with median PC50 2.00 (range: 0.07 – 14.88) 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 ACPR 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 ACPR were by exact binomial method for PP analysis or beta product confidence procedure for ITT analysis and were equivalent because there was 100% response.²⁰

Table 1. Several baseline characteristics of subjects

| Characteristic | Artemisinin+Napthoquine (n=80) | DihydroArtemisinin+Piperaquine (n=78) | P |
|---|-----------------------------------|--|-------|
| Number of subject | | | |
| Males (%) | 91.3 | 82.1 | 0.142 |
| History of Fever (%) | 97.5 | 98.7 | 1.000 |
| Fever ≥ 37.5 °C (%) | 56.3 | 55.1 | 1.000 |
| Laboratory | | | |
| Geometric mean (95%CI) parasitemiain par/ul | 4769 (3751 – 6002) | 4628 (3640 – 6002) | 0.874 |
| Geometric mean (95%CI) gametocytemiain par/ul | 40 (30 – 54) | 33 (25 – 44) | 0.303 |
| Gametocytemia (%) | 88.8 | 92.3 | 0.623 |
| Median (range) haemoglobin in g/dl | 13 (7.3 – 23.1) | 13 (7.5 – 16.4) | 0.523 |
| Anemia group (Hb<11 g/dl) (%) | 13.8 | 17.9 | 0.518 |
| Median (range) age in years | 23 (16 – 62) | 23 (16 -64) | 0.490 |
| Median (range) body weight in Kg | 60 (39 – 81) | 58.5 (41 -75) | 0.153 |

Table 2. Several clinical manifestation characteristics of subjects

| Clinical Symptom | Artemisinin+Napthoquine | Artemisinin+Piperaquine | P |
|-------------------|-------------------------|-------------------------|-------|
| Diarrhea | 3.8 | 0.0 | 0.245 |
| Palpitations | 7.5 | 3.8 | 0.517 |
| Cough | 7.5 | 10.3 | 0.742 |
| Abdominal pain | 10.0 | 10.3 | 1.000 |
| Anorexia | 12.5 | 14.1 | 0.950 |
| Sleep disturbance | 13.8 | 11.5 | 0.858 |
| Unwell | 21.3 | 25.6 | 0.643 |
| Sweating | 21.3 | 29.5 | 0.314 |
| Vomiting | 22.5 | 6.4 | 0.008 |
| Myalgia | 23.8 | 37.2 | 0.096 |
| Fatigue | 23.8 | 19.2 | 0.619 |
| Dizzy | 41.3 | 34.6 | 0.487 |
| Rigors/chills | 52.5 | 50.0 | 0.877 |
| Headache | 53.8 | 51.3 | 0.880 |
| Nausea | 58.8 | 51.3 | 0.433 |

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*.^{11,15} 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.²¹ 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.^{21,22} The submicroscopic parasitemia study might be required in the future to detect the gametocytopenia 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.^{5,11,12,23} Artemisinin derivative was a fast acting drug including dihydroartemisinin and artemisinin. However dihydroartemisinin showed higher activity and had parasite clearance time faster compare artemisinin.^{23,24} 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

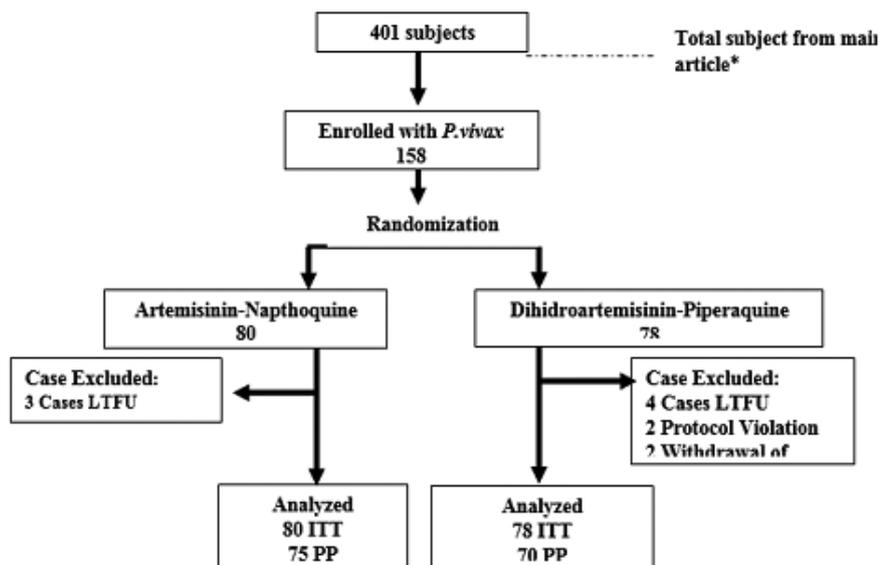


Figure 1. Subject flow diagram

Pv = Plasmodium vivax; LTFU= lost to follow up; PP= per protocol;
 * = Reference number 15

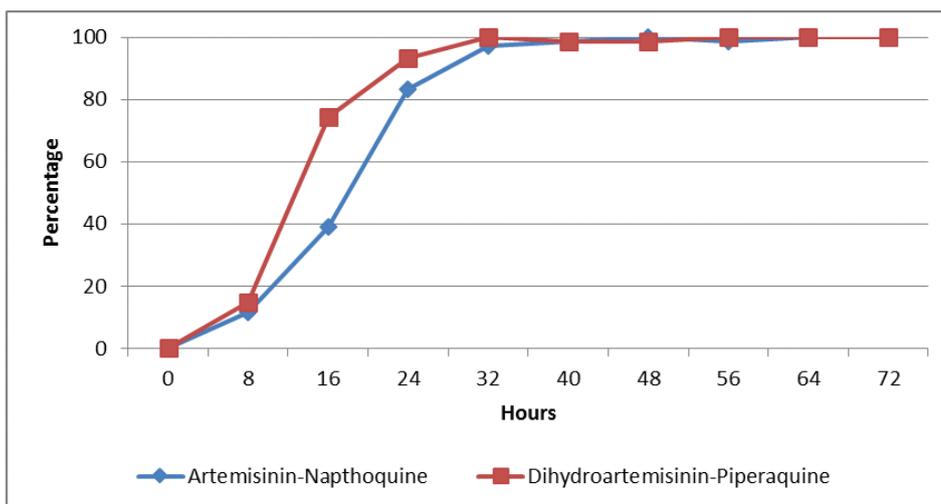


Figure 2. Proportion of asexual parasitemia in hours

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 Napthoquine, 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.^{5,11,15} 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,¹⁵ 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.

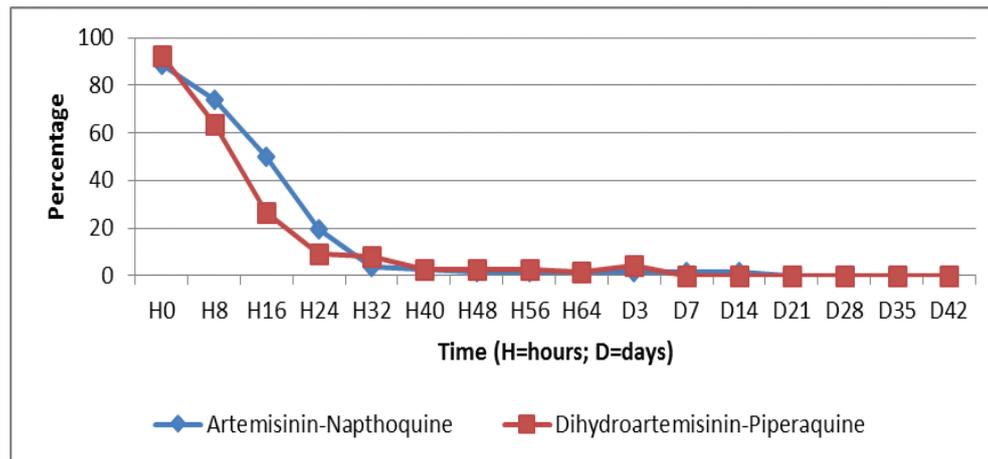


Figure 3. Proportion of Gametocytemia clearance in follow up event

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.

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