Efficacy of Artemisinin-Naphtoquine and Dihydroartemisinin-Piperaquine for uncomplicated malaria patient at primary health care

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Abstrak

Latar belakang: *Hasil uji klinik terdahulu terhadap artemisinin-naftokuin (ANT) dosis sekali minum pada pengobatan pasien dewasa dengan malaria tanpa komplikasi menunjukkan aman, dapat ditoleransi, dan sangat efektif. Data tambahan dibutuhkan untuk verifikasi keamanan dan efikasi dari kelompok umur lainnya sebelum obat baru ini dapat digunakan secara luas di Puskesmas di Indonesia.*

Metode: *Pada penelitian ini, kami menggunakan modifikasi pedoman uji klinis WHO 2009. Studi kuasi-eksperimental ini membandingkan dua paralel grup, subjek dengan ANT di 5 puskesmas rawat inap, dan subjek dengan obat kontrol dihidroartemisinin-piperakuin (DHP) minum obatnya di 5 puskesmas rawat jalan.*

Hasil: *Dari total 182 subjek yang direkrut, 168 kasus malaria yang dianalisis dalam uji klinik ini. Mereka adalah 71 kasus dalam ANT grup dan 97 kasus dalam DHP grup. Karakteristik subjek yang mendapat ANT dan DHP saat rekrutmen adalah Sama kecuali proporsi subjek dengan suhu aksila ≥37.5^{0}C, dan proporsi subjek dengan anemia (Hb <11 g/dl) di ANT grup lebih tinggi dibanding DHP grup (61.8% vs 23.8%, and 83.1% vs 48.5%). Subjek ANT grup juga lebih rendah proporsi parasite asexualnya pada hari ke-3 dibanding DHP grup (1.4% vs 10.3%). Efikasi terapetik ANT dan DHP adalah 95.1% (95% CI: 88.8-99.1) dan 91.9% (95% CI:84.3-96.0) pada hari 42. Kedua obat memiliki kejadian sampingan ringan.*

Kesimpulan: *Penggunaan ANT adalah aman dan memiliki efikasi yang sama dengan DHP untuk pengobatan pasien dewasa dan anak dengan malaria tanpa komplikasi di Puskesmas.* ***(Health Science Indones 2014;2:101-5)***

Kata kunci: *semua umur, malaria, artemisinin-naftokuin, dihidroartemisinin-piperakuin, puskesmas.*

Abstract

Background: Our previous study of single dose artemisinin-naphthoquine (ANT) in adult majority male patients showed it as a safe, tolerable, and very effective treatment for uncomplicated malaria. More data is required to verify safety and efficacy from other age groups before this new drug could be widely used in Primary Health Care (PHC)s in Indonesia.

Methods: For this study, we modified the 2009 WHO guidelines for clinical trials. This quasi-experimental study compared two parallel groups, subjects given ANT at 5 PHCs with inpatient facilities, and subjects given the control drug dihydroartemisinin-piperaquine (DHP) administered to subjects at 5 PHCs without inpatient facilities.

Results: Of a total 182 recruited subjects, 168 malaria cases could be analyzed. There were 71 cases in the ANT group and 97 cases in the DHP group. The characteristics of subjects receiving ANT and DHP at baseline were similar except the proportion of axillary temperature ≥37.5^{0}C, and proportion of anaemic subjects (Hb <11 g/dl) in the ANT group were higher than DHP group (61.8% vs 23.8%, and 83.1% vs 48.5%). Subjects in ANT group also had a lower proportion of asexual parasitemia on day-3 than DHP group (1.4% vs 10.3%). The therapeutic efficacy of ANT and DHP, were 95.1% [95% confidence interval (CI) = 88.8-99.1] and 91.9% (95% CI = 84.3-96.0) by day 42. Both drugs had mild adverse events.

Conclusion: The use of ANT is safe and has similar efficacy to DHP for treatment of adults and children patient with uncomplicated malaria at Primary Health Care. ***(Health Science Indones 2014;2:101-5)***

Key words: malaria, artemisinin-naphthoquine, dihydroartemisinin-piperaquine, primary health care.

Using Artemisinin-based Combination Therapy (ACT) is one of four efforts to accelerate the elimination of malaria in Indonesia.[1] Currently the ACT preparation that is free for widespread use in Indonesia is dihydroartemisinin-piperaquine (DHP). Dihydroartemisinin-piperaquine is a fixed dose of combination 40 mg dihydroartemisinin and 320 mg piperaquine phosphat, once daily for three days. This drug is a combination of an active metabolite form of artemisinin and piperaquine. Artemisinin quickly eliminates parasites in early day of onset while piperaquine with its long half-life between 19 and 28 days eliminates the residual parasites. Recently drug (ACT) monitoring conducted by National Institute of Health Research and Development (NIHRD), Indonesia shows DHP is safe and effective with the cure rates of higher than 95% for the treatment of uncomplicated malaria.[2-4] Our previous study with ANT conducted in adult (majority male) patients showed ANT to be very effective (>95%), safe and tolerable for treatment of uncomplicated malaria.[5]

The primary objective of this trial was to compare the safety and efficacy of ANT with DHP, moreover there are other objectives as follow: to compare the proportion of fever clearance and asexual parasite clearance on day-3 follow up of ANT with DHP for the treatment of uncomplicated malaria in adults and children at Primary Health Care.

METHODS

Study design

This is a quasi-experimental trial, two parallel groups and multi-canters held from August to November 2012, at 10 PHCs in 5 provinces of Indonesia. The highest malaria endemic district was selected from each province, and from each district two PHCs, one with and one without in patient facility were chosen as the trial locations. Considering the safety of a new study drug and the first drug trial conducted at the PHC level, 5 PHCs with inpatient facilities were assigned as study (ANT) group locations, and another 5 PHCs without inpatient facilities were assigned as comparators.

Study subjects and procedures

Subjects with uncomplicated malaria were enrolled from outpatient clinics at PHCs as well as from referred symptomatic malaria subjects from active case finding (mass blood survey) in the district. The inclusion criteria are as follows: having positive any-malaria by microscopy, age more than six months with minimum body weight 7 kgs, and able to orally consume medicine. The exclusion criteria are subjects with severe or complicated malaria, suffering from severe diseases, under nourished, having severe anemia (Hb<8 g/dl), having fever caused by other causes instead of malaria, having ACT allergic history, or pregnant or breast feeding women.

The study was conducted based on the 2009 World Health Organization (WHO) guidance.[6] Subjects are followed-up on day 3, 7, 14, 21, 28, 35, 42 and at any time the subject feels ill. Considering ANT is administered only on day 0, and to adjust to the conditions and difficulties of subjects using health services in the remote areas, we modified the schedule of follow-up of the subjects to day 3, 14, 28 and 42 (every two weeks).

A standard case Record Form (CRF) was completed to record demographic information (age, sex and body weight) details of symptoms (including symptoms duration). Clinical findings were documented and the axillary temperature were measured with a digital thermometer. Thick and thin smears were examined at day-0, 3, 14, 28, and 42, and to evaluate healing improvement hemoglobin was measured on day-0, 14, 28, and 42. Blood spot for PCR examination was collected on day 0 and on day of failure, to distinguish between recrudescent and new infection of *P.falciparum* infection. Subjects were allowed to go home after the doctor explained the results of the microscopic examination on each visit.

Microscopic examination was done by a trained microscopist in each PHC, and later was validated by NIHRD microscopists in Jakarta. Hemoglobin examination was performed using the Sahli method by laboratory staff of PHC. Blood spot sample for PCR examination was collected by trained laboratory staff in PHC, while the examination was conducted in the NIHRD laboratory.

Study drugs

Eligible subjects in the study group were given ANT (Arco®, no. batch 12DB) based on artemisinin dosage of 14 - 30 mg/kg body weight and naphthoquine 5.5 - 12 mg/kg body weight, single dose under 1 hour supervision. In the comparator group, eligible subjects received DHP (Darplex®, no. batch 11HB) based on dihydroartemisinin dosage of 2 - 4 mg/kg body weight and piperaquine 16 - 32 mg/kg body weight, single dose daily for

three days. The administration of first dose of DHP was supervised, and the second and third doses were given in a package and administered at home after 24 hours and at 48 hours. If subject vomited within 60 minutes after taking the drugs, the full dose of ANT or DHP was reintroduced. Subjects who vomited for the second time were excluded from the study. These subjects were counted as protocol violations and were treated with parenteral treatment according to standard malaria treatment protocol at PHC. Following the treatment policy for radical treatment, primaquine was given together with the ACT without G-6PD test. The dosage of primaquine for subjects infected with *P.falciparum* was 0.75 mg of base/kg of body weight, single dose; and 0.5 mg of base/kg of body weight for 14 days for *P.vivax* infection or mixed *P.falciparum-P.vivax* infection. The administration of primaquine was done by the subjects in their home.

Subjects with recurrent asexual parasitemia on follow-up, between day 7 and day 42, were retreated with alternative antimalarial drugs according to standard malaria control treatment guideline.

Outcome evaluation

The primary efficacy endpoints in our study were proportion of treatment success on day 14 , 28 and 42 . Our secondary efficacy endpoints were the proportion of fever clearance and asexual parasitemia clearance on day 0 and day 3.[6] Therapeutic response was determined using clinical and parasitological criteria. Estimates of efficacy were derived from all patients who did not violate any of the inclusion or exclusion criteria. Per Protocol (PP) evaluation was performed to all subjects on ANT and on DHP who completed the study according to protocol. We did not check that all subjects on DHP took all their doses at their home. Whereas modified intention to treat (mITT) analysis was performed on the PP population and on subjects who were lost to follow-up or who withdrew consent.

The safety were reported as the proportion of adverse events during 42 days of follow up. Adverse events refers to events that appeared after the intervention during follow-up, regardless its relation with the treatment.

Statistical analysis

Central researchers visited study sites to monitor the completeness of data monthly. Completed and cleaned CRFs were brought to NIHRD for data entry using Epi Data software version 3.1 and analyzed with SPSS software version 17. The student's t-test was used for comparison of the two groups. Difference in proportions were examined using Fisher's exact test.

Ethics

This trial was approved in writing by the Ethics Committee of National Institute of Health Research and Development, Ministry of Health, and the Bureau of Food and Drug Control, Republic of Indonesia.

RESULTS

A total of 182 subjects with uncomplicated malaria were recruited in this trial at 10 PHCs during September-November 2012. We could not recruited as many subjects as the planned sample size because the incidence of malaria has decreased since the planning stage. Thirteen subjects were excluded due to microscopic errors and one false positives). Of the 168 remaining cases, there were 71 subjects in the ANT group (40 subjects had *P.falciparum infection*, 24 subjects with *P.vivax* and 7 subjects with mixed infection of *P.falciparum* and *P.vivax*) and 97 subjects in the DHP group (63 subjects with *P.falciparum*, 29 subjects with *P.vivax* and five subjects with mixed infection of *P.falciparum* and *P.vivax*) (Figure 1).

Of the 71 recruited subjects in ANT group, 10 cases did not complete the study. Six subjects withdrew their consent (1 *P.falciparum* withdrawn on day 3, 2 *P.vivax* withdrawn on days 0 and 3 mixed infection of *P.falciparum* and *P.vivax* withdrawn on days 0 and 3) and 4 subjects were lost to follow up (2 *P.falciparum* on day 28, and 2 *P.vivax* on days 3 and 28). There were also 10 cases in the DHP group that did not complete the trial. One subject withdrew consent (*P.falciparum* withdrawn on day 0), 2 took other antimalarial drugs (1 *P.falciparum* on day 6 and 1 *P.vivax* on day 28), and 7 were lost to follow up (3 *P.falciparum* on days 0 and 3, and 3 *P.vivax* on days 0 and 28, 1 mixed infection of *P.falciparum* and *P.vivax* on day 0).

Significance difference between two groups were found in terms of age, baseline fever, history of fever and their anemic state. The patients in ANT group were slightly older, more feverish, had less history of fever and more anemic. Although the difference was not significant, the ANT group had younger patients, higher mean weight, narrower range of parasitemia and more gametocytes carrier (See table 1).

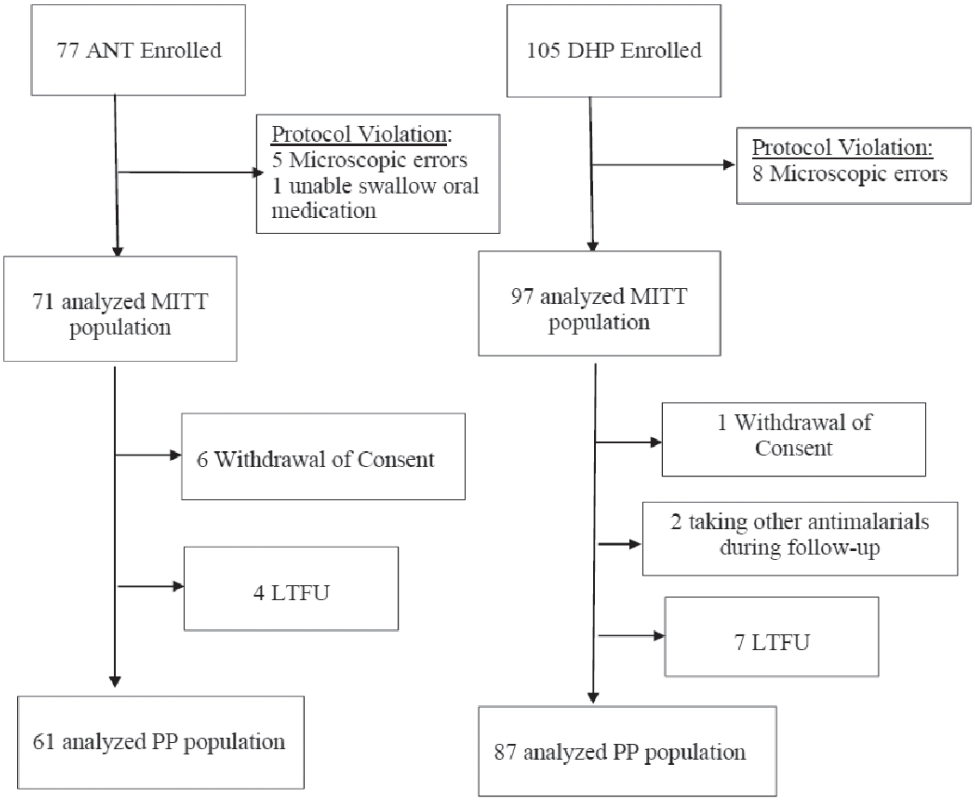

Figure1. Flow diagram of subject recruitment in Artemisinin Naphthoquine (ANT) and Dihydroartemisinin Piperaquine (DHP) groups

Table 1. Several characteristics of the subjects at baseline (day 0) and on day 3 of follow-up in Artemisinin Naphthoquine and Dihydroartemisinin Piperaquine groups

Characteristics	Type of treatment		p
	Artemisinin Naphthoquine	Dihydroartemisinin Piperaquine	
Age (years), median (range)	14.0 (1 – 57.0)	13.0 (1 – 73.0)	0.04
Type of parasites, n (%)			
P. falciparum	40 (56.3%)	63 (64.9%)	0.94
P. vivax	24 (33.8%)	29 (29.9%)	0.14
Mixed *P. falciparum- P. vivax*	7 (9.9%)	5 (5.2%)	0.75
Male subjects, n (%)	39 (54.9%)	52 (53.6%)	0.90
Weight, mean (range) kg	38 (8 - 75)	29 (7 - 84)	0.41
Anemia, n (%)	59 (83.1%)	48 (48.5%)	0.00
History of fever,n (%)	47 (66.2%)	85 (81.0%)	0.00
Fever ($\geq 37{,}5^0$C), n (%)			
Day 0	47 (61.8%)	25 (23.8%)	0.00
Day 3	1 (1.4%)	2 (2.1%)	0.79
Asexual parasitemia			
Baseline interquartile range (Q1-Q3), parasitaemia per uL	364.1–5870.7	197.6–9237.9	
Day 0, n (%)	71 (100%)	97 (100%)	1.00
Day 3, n (%)	1 (1.4%)	10 (10.3%)	0.05
Gametocytaemia carrier, n (%)	20 (26.3%)	21 (20.0%)	0.43

At day 3 of follow up, ANT group showed a better improvement than the DHP group. It had a lower proportion of patient with fever and asexual parasitemia (1.4% vs.2.1 % for fever and 1.4% vs. 10.3 % for asexual parasitemia).

In table 2, we showed that either in mITT or PP population, the ANT and DHP showed similar rate of efficacy in day 14, 28 and 42. The rate of uncorrected and corrected efficacy were reached more than 80 % in both groups as soon as day 14. A total of 10 subjects had recurrent parasitemia during follow-up (two subjects in the ANT group and eight subjects in the DHP group). The two recurrences in the ANT group were both attributable to *P. falciparum*; and the eight recurrences in the DHP group were attributable to: six *P. falciparum*, one *P. vivax* and one mixed infection *P. falciparum* and *P. vivax*.

Table 2. Polymerase chain reaction uncorrected and corrected efficacy of Artemisinin Naphthoquine (ANT) vs Dihydroartemisinin Piperaquine (DHP) during follow-up period in any-malaria

Drug	Analysis	Efficacy (Polymerase chain reaction)			
		Uncorrected	p	Corrected	p
Day 14					
ANT	mITT	90.1% (64/71)	0.10	90.1% (64/71)	0.11
DHP		92.8% (90/97)		92.8% (90/97)	
ANT	PP	100% (61/61)	1.00	100% (61/61)	1.00
DHP		100% (87/87)		100% (87/87)	
Day 28					
ANT	mITT	84.5% (60/71)	0.12	84.5 % (60/71)	0.013
DHP		87.6% (85/97)		87.6% (85/97)	
ANT	PP	98.4% (60/61)	0.09	98.4% (60/61)	0.09
DHP		97.7% (85/87)		97.7% (85/87)	
Day 42					
ANT	mITT	78.9% (56/71)	0.94	81.7% (58/71)	0.92
DHP		82.5 % (80/97)		82.5 % (80/97)	
ANT	PP	91.8 (56/61)	0.28	95.1% (58/61)	0.39
DHP		91.9% (80/87)		91.9%(80/87)	

In general, subjects in ANT group experienced less adverse events compared to subjects in DHP group. In ANT group, the most common adverse events were anorexia (5.6%), while in DHP group, it was coughing (15.5%). Abdominal pain and diarrhea occurred more often in DHP group compared to ANT group (7.2% vs. 1.4%).

DISCUSSION

In this study, ANT combination is well tolerated for the treatment of patients with uncomplicated malaria in PHC facilities. Although we failed to complete the patients recruitment, our study find similar cure rates at day 42 after treatment with ANT (96%) and DHP (92 %) with previous studies. Additionally, in terms of safety, we found that ANT has a similar safety profile as DHP. [2-4, 7-10]

In 2003, researchers in China developed a new generation of ACT, which is 'single dose' artemisinin-naphtoquine (ANT). This is a combination of a fixed-dose, containing 125 mg of artemisinin and 50 mg of naphthoquine base (78.3 mg of naphthoquine phosphate). Artemisinin has a rapid onset of schizontocidal action, while the naphthoquine phosphate in the combination has a long half life (11.5 days).[11]

In our study, the efficacy rate of ANT had reached above 80 % for both treatment groups as soon as day 14 and had stay constant until day 42. Although DHP seems to perform better in mITT analysis while ANT showed higher percentage of efficacy in PP analysis, their differences were not significant. Thus, we believe both treatments performed similarly. This efficacy profile was consistent with our previous multicentre study in adult patients with uncomplicated malaria.[5]

In terms of safety, eventhough we used a higher dose of artemisinin (15 -30 mg/kg) compared to WHO recommendation (4 – 6 mg/kg), patients with ANT had no serious adverse events during 42 days of follow-up. Their safety profile is similar with their comparison group. It could happened that although

the dose was high, it was less than the study dosage used in pre-clinical studies.[12]

This single dose of ANT may benefit the public health by increasing patients compliance. Increase patients compliance will resulted in decreasing rate of anti-malarial resistance.[13] A study in Kenya showed that a shorter duration of arthemeter-lumefantrine with fewer tablets were likely to improve compliance of patients to AL.[14]

There are some limitations, our design is not a randomized control trial, number of samples is less than the planed sample size, and some problems with sample: 7.1% of samples are negative malaria by expert NIHRD microscopist and 12.4% were in-complete follow up (withdrawal of consent and lost to follow up). Consequently, the findings may not apply to other populations, and further randomized studies are needed to support this findings.

We conclude that the use of a single dose of ANT is safe and as efficacious as DHP for use at the remote Primary Health Care facilities for treatment of adults and children with uncomplicated malaria.

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