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Original Article

Efficacy and safety of dihydroartemisinin-piperaquine in Indonesian children infected with uncomplicated *Plasmodium falciparum* and *Plasmodium vivax*

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Abstract

Background Dihydroartemisinin-piperaquine (DPQ) has been used since 2006 in Papua, Indonesia and is planned as an alternative artemisinin-based combination therapy for wider use in Indonesia. Confirmation of the drug's efficacy and safety in children outside Papua is needed.

Objective To measure the day-42 clinical and parasitological efficacy of DPQ in children with uncomplicated falciparum and vivax malaria.

Methods This cross-sectional and observational study was held in Kalimantan and Sulawesi in 2010. Seventy and sixty children under 15 years of age with uncomplicated falciparum and vivax malaria were selected according to the 2003 WHO protocol for monitoring therapeutic efficacy of antimalarial treatments and was confirmed by microscopy and PCR. All subjects were treated with DPQ based on a dosage regimen of dihydroartemisinin 2-4 mg/kg BW/dose and piperaquine 16-32 mg/kg BW/dose, in single daily doses for 3 days and closely observed for 42 days. Data was analyzed using intention-to-treat (ITT) and per protocol (PP) populations.

Results The mean fever and asexual parasite clearance times were 1.0 day and 1.6 days, respectively, in children with uncomplicated falciparum malaria, and 1.1 days and 1.2 days, respectively, in children with uncomplicated vivax malaria. Clinical symptoms reduced over 50% by day 7. Hemoglobin recoveries showed improvement on days 14, 28 and 42, at 70.6%, 83.8% and 89.1%, respectively, in the falciparum malaria group, and 60.3%, 65,5% and 83.6%, respectively, in the vivax malaria group. Adequate clinical and parasitological response to DPQ on day 42 in the ITT and PP populations were reported as 98.6% (95% CI 92.3 to 99.7%) and 100% (95% CI 94.7 to 100%), respectively, in the falciparum group, and 91.7% (95% CI 81.9 to 96.4%) and 96.5% (95% CI 88.1 to 99.0%), respectively, the vivax group. Mild adverse events commonly noted were cough, abdominal pain, diarrhea, anorexia, and vomiting.

Conclusion DPQ was effective against falciparum and vivax malaria with adequate clinical and parasitological response of ≥ 95%, rapid fever and asexual parasite clearance, good hematological recovery and mild adverse events. **[Paediatr Indones. 2011;51:351-60]**.

Keywords: *dihydroartemisinin-piperaquine, P.falciparum, P.vivax, children, Indonesia.*

Artemisinin-based combination therapy (ACT) is recommended as a malarial control strategic intervention by the WHO.[1] Three ACTs have been introduced in Indonesia, namely artesunate-amodiaquine (AAQ), artemether-lumefantrine (ALT), and dihydroartemisin-piperaquine (DPQ). ACT is given only for treatment of malarial cases confirmed either by microscopy or rapid

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diagnostic test (RDT) to prevent the development of parasite resistance to artemisinin.

AAQ was chosen for the ACT program in 2004, based on an African study.[2] AAQ is a non-fixed dose, single, daily regimen for three days of administration. At first, AAQ was recommended to replace conventional antimalarial drugs (chloroquine and suphadoxine-pyrimethamine) only for treatment of uncomplicated *P. falciparum* malaria in areas where diagnostic confirmation was available. Subsequently, AAQ was gradually introduced to all endemic areas, and also for treatment of *P. vivax* malaria due to the spread of chloroquine resistance in *P. vivax*. The efficacy of AAQ varies (67- 96.5%)[3-5] and compliance has been unclear, due to the number of pills that should be taken and the triggering of mild to severe adverse events.

ALT was the first fixed-dose ACT and is administered twice daily over three days. This ACT was used for treatment of uncomplicated *P. falciparum* during an epidemic of malaria in Bukit Menoreh in 2002. ALT was reported to be very effective and safe for treatment of uncomplicated *P.falciparum*, with adequate clinical and parasitological response (ACPR) of > 95%. However, ALT was found to be ineffective for treatment of uncomplicated *P. vivax,* with an ACPR of 44%.[6] Considering the similar prevalence of *P. falciparum* and *P. vivax*, the lack of microscopists available, and the fact that ALT is not a single daily regimen, the malaria control program does not include ALT in the ACT program. However, ALT has been registered for private and clinician demand.

DPQ also comes as a fixed-dose, single, daily regimen for three days of administration. This drug has been used in Mimika, Papua since 2006, and was subsequently recommended for use in Papua in 2009, based on a 2004 Mimika study.[5-6] DPQ has been shown to be effective and safe, with good patient compliance for treatment of uncomplicated *P. falciparum* and *P. vivax* malaria in Papua, as well as in other countries. However, limited data on the use of DPQ in Asian children is available. To provide supporting evidence-based data for wide-scale use of DPQ, further evaluation of its efficacy and safety in children, as a vulnerable group outside of Papua, is needed.

The Global Fund Round 8 of Indonesia supported intensified malaria control in the islands of Kalimantan and Sulawesi. Program activities included monitoring ACT-resistance for 5 years (2010-2014). Therefore, we wished to evaluate DPQ efficacy and safety for treatment of uncomplicated falciparum and vivax malaria in children under 15 years of age in these locales.

Methods

Data was analyzed as a part of an in-vivo study of dihydroartemisinin-piperaquine in subjects with *P. falciparum* and *P. vivax* malaria in Kalimantan and Sulawesi, Indonesia. The study was approved by the Ethics Committee of the National Institute of Health Research and Development, Indonesian Ministry of Health.

This was a cross-sectional study and a prospective evaluation of the clinical and parasitological response to directly observed treatment for *P. falciparum* and *P. vivax* malaria using the 2003 WHO protocol.[7] The in-vivo study was carried out at 2 selected health centers as sentinel sites in each province, West and Central Kalimantan, and North and Central Sulawesi. However, there were no malaria cases in children in West Kalimantan, so we evaluated data only from 6 health centers in Central Kalimantan, and the North and Central Sulawesi provinces. Data was collected from July to December 2010.

Subjects were selected according to the modified WHO protocol for monitoring therapeutic efficacy of antimalarial drugs. Inclusion criteria were age 6 months-14 years, males or females, monoinfection with *P. falciparum* or *P. vivax,* asexual parasitemia by *P. falciparum* ≥ 1,000/ul or parasitemia by *P. vivax* ≥ 250/ul, axillary temperature ≥ 37.5°C or history of fever during the previous 48 hours, ability to swallow oral medication, ability and willingness to comply with the study protocol for the duration of the study and to comply with the study visit schedule, as well as informed consent from the parents or guardians.[7] Exclusion criteria were the presence of one or more general danger signs or any signs of severe and complicated malaria, pregnancy or lactation, presence of mixed infection, presence of severe malnutrition or severe disease, presence of febrile conditions due to diseases other than malaria (measles, acute lower tract respiratory infection, severe diarrhea with dehydration, etc.), or other known underlying chronic diseases (e.g. cardiac, renal, or hepatic diseases, HIV/

AIDS), and history of hypersensitivity reactions to any antimalarial drug. [7]

All study subjects were observed for a period of 42 days**.** Complete medical history, demographics, and contact address details were collected and standard physical examinations were performed at baseline (day 0, pre-dose). Follow-up with physical and microscopy examinations was performed on a fixed schedule at days 1, 2, 3, 7, 14, 21, 28, 35, 42, as well as any day the subject felt unwell.

Thick and thin blood films stained with Giemsa were examined on day visits or other days, if the subject returned and parasitological reassessment was required. Parasite density was calculated by counting the number of asexual parasites against the number of white blood cells (WBCs) in the thick blood film, using a hand tally counter. When the number of asexual parasites was less than 10 per 200 WBCs in follow-up smears, counting was done against at least 500 WBCs. Hemoglobin was measured by Sahli hemoglobinometer on days 0, 14, 28 and 42. Blood blot on Whartman filter paper on day 0 and/or day parasite reappearance were used for molecular analysis.

A fixed-dose DPQ regimen was given to subjects with uncomplicated *P. falciparum* malaria and *P. vivax* malaria at the sentinel Health Centers. One tablet of DPQ (Arterakine® from PharbacoCentral Pharmaceutical Joint Stock Company, Thanh Xuan-Soc Son, Hanoi, Vietnam, consisted of 40 mg dihydroartemisinin and 320 mg piperaquine. DPQ 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 daily dose on days 0, 1, and 2. The number of tablets given was rounded off to the nearest quarter of a tablet. Tablets were crushed and sugar was added. All DPQ doses were administered under supervision by a qualified trained doctor, nurse or midwife designated by the principal investigator. Study subjects were observed for acute adverse reactions or vomiting for 30 minutes–1 hour after drug administration. Any subject who vomited during this observation period was re-treated with the same dose of DPQ and observed for an additional 30 minutes-1 hour. If the study subject vomited again he/she was withdrawn from the study and offered rescue therapy parenterally (as per National Malaria Treatment Guidelines).[8] All adverse events were noted throughout the study.

Axillary temperature was measured by digital thermometer. Fever was defined if the axillary temperature was $\geq 37{,}5\ ^{0}C$.

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 multiplied by assuming a WBC density of 5000 WBCs/μl. Blood slides were considered negative when the examination of 1000 WBCs did not reveal any asexual parasites. The presence of gametocytes on initial or follow-up slides was noted, and this information was an addition to the in-vivo study evaluation. All slides were cross-checked by an expert microscopist at the National Institute of Health Research and Development, Indonesian Ministry of Health.

Study subjects were classified as therapeutic failures (early/ETF or late/LTF) or adequate responders (ACPR), based on the results of these assessments. The proportion of subjects experiencing a therapeutic failure during the follow-up period was used to estimate the efficacy of DPQ. Molecular analysis by polymerase chain reaction (PCR) was performed to confirm parasite species and to distinguish between a true recrudescence or relapse due to treatment failure and episodes of re-infection with falciparum malaria.[9]

Safety was assessed by collecting the nature and incidence of adverse events (AEs). AEs were assessed through direct questioning.

Data are presented descriptively in percentage with a 95% confidence interval (95% CI), or by arithmetic or geometric mean with range, using the SPSS 15 software program. Chi-square test was used to analyze significant differences of anemia proportion, and Wilcoxon matched-pairs test was used for differences in hemoglobin values. The proportion of therapeutic efficacy was assessed by survival analysis, in which the cumulative treatment success was calculated by Kaplan-Meier method. All enrolled subjects (including those who were withdrawn from the study or who were lost to follow-up) were included in the analysis until the last day before dropping out, using an intention-to-treat (ITT) approach to this population. In the per protocol (PP) population, subjects withdrawn from the study or lost to follow-up were not included in the analysis.

Results

There were 130 children with uncomplicated malaria due to infection with *P. falciparum* or *P.vivax* participating in our study. The number of males (52.3%) and females (47.7%) was similar, and most subjects were indigenous people (96.1%). Subjects' ages ranged from 8 months to 14 years and body weight ranged from 7.5 - 50 kg. Of the 130 subjects infected with *P. falciparum* or *P.vivax*, 4.6% were infants, 30.8% were children under five years, and 64.6% were children from 5-14 years old. Falciparum malaria was commonly found in children aged 5-14 years (75.7%), and about half (48.3%) of vivax malaria was found in children under five years. Though all subjects had a history of fever in the previous 48 hours, there were only 48.5% with fever (≥ 37.5°C) at baseline, with axillary temperatures ranging between 34.9-40.2 ^{0}C. Most subjects (91/127 or 76.4%) were anemic (Hb < 11 g/dl), with 46.9% of all subjects having mild anemia (Hb 9.0-10.9 g/dl) and the remaining 27.7% having moderate anemia (Hb 7.5-8.9 g/dl). Surprisingly, one clinical falciparum subject had only 20 asexual parasites per uL on day 0, though, on screening he had a density of about 1,000 per uL. The range of asexual parasite density was wide in subjects infected with *P. falciparum* (20-105,873 per uL), as well as in subjects infected with *P. vivax* (268-49,513 per uL). About a quarter of *P. falciparum* subjects and almost all *P. vivax* subjects displayed gametocyte carriage, with *P. falciparum* mean gametocytemia of 11/uL and *P. vivax* mean gametocytemia of 29/uL (**Table 1**).

Clinical symptoms in subjects under five years were reported by parents or guardians. In general, subjects felt unwell (67.3-91.4%), with headaches, sweating, and lethargy on enrollment. Other symptoms are listed in **Table 2**. Common signs were pallor (34.3%) and splenomegaly (27.1%) in uncomplicated falciparum malaria subjects, while

Table 1. Baseline characteristics of subjects infected with *P. falciparum* and *P. vivax* on enrollment

Characteristics	*P. falciparum* (n=70)	*P. vivax* (n=60)
Sex		
male: female, %	52.9 : 47.1	51.7 : 48.3
Indigenous subjects, %	98.6	93.3
Mean age, years (range)	7.5 (10 mos-14 yrs)	5.2 (8 mos-14 yrs)
Age groups		
< 1 year, %	1.4	8.3
1—4 years, %	22.9	40.0
≥ 5 years, %	75.7	51.7
Mean weight (range), kg	22.9 (8.9 to 50)	16.2 (7.5 to 41)
Mean axillary temperature (range), ^{0}C	37.5 (35.2 to 40.2)	37.1 (34.9 to 39.8)
Fever ≥37.5°C, %	57.1	38.3
Mean hemoglobin (range), g/dl	9.8 (7.8 to 13.2)	9.7 (7.5 to 12.6)
Anemia <11g/dl, %	75.0*	78.0**
Geometric mean asexual parasite density (range), per uL	5,245 (20 to 105,873)	3,530 (268 to 49,513)
Geometric mean gametocyte density (range), per uL	11 (3 to 93)	29 (3 to 133)
Gametocyte carriage, %	24.3	90.0

*n=68, **n=59

Table 2. Clinical signs and symptoms of subjects infected with *P. falciparum* or *P. vivax* on enrollment

Signs and symptoms	*P. falciparum* (n=70)	*P. vivax* (n=60)
Symptoms, %		
Unwell	91.4	85.0
Headache	82.0	67.3
Sweating	78.6	75.0
Myalgia	75.4	55.3
Lethargy	73.9	75.4
Anorexia	65.7	46.7
Insomnia	54.3	23.3
Dizziness	51.7	30.4
Nausea	51.5	39.6
Rigor	41.4	58.3
Cough	40.0	40.0
Vomiting	35.7	28.3
Abdominal pain	31.8	28.8
Palpitation	16.7	2.2
Diarrhea	4.4	6.7
Other	17.1	6.7
Signs, %		
Pallor	34.3	21.7
Common cold	14.3	23.3
Hepatomegaly	5.7	6.7
Splenomegaly	27.1	18.3

Table 3. Outcomes of *P. falciparum* and *P. vivax* subjects treated with DPQ at day 42 observation

Outcome	*P. falciparum* (n=70)	*P. vivax* (n=60)
Withdrawn consent, n {%(95% CI)}	0	1{1.7(0.3 to 8.9)}
Protocol violation, n {%(95% CI)}	0	1 (1.7(0.3 to 8.9)}
Lost to follow-up, n {%(95% CI)}	1 (1.4(0.3 to 7.7))	1{1.7(0.3 to 8.9)}
LTF, n {%(95% CI)}	0	2{3.5(1.0 to 11.9)}
LCF		1{1.7(0.3 to 9.3)}
LPF		1{1.7(0.3 to 9.3)}
ACPR, n {% (95% CI)}		
ITT	69{98.6(92.3 to 99.7)}	55{91.7(81.9 to 96.4)}
PP	69{100(94.7 to 100)}*	55{96.5(88.1 to 99.0)}**

*n=69, **n=57

common cold signs (23.3%) and pallor (21.7%) were common in uncomplicated vivax malaria subjects (**Table 2**).

In falciparum and vivax malaria subjects treated with DPQ, clinical symptoms decreased gradually at each follow-up observation. More than 56% of subjects were asymptomatic by day 7.

While there were only 57.1% and 38.3% febrile (>37.5^{0}C) subjects with *P. falciparum* and *P. vivax* malaria, respectively, on day 0 (pre-treatment), almost all subjects were afebrile by day 1 (**Figure 1**). Fever detected in the post-treatment period was mainly caused by upper respiratory illnesses. The mean fever clearance times (FCTs) were 1.0 (1-2 days) and 1.1 (1-3 days) in subjects with uncomplicated falciparum and vivax malaria, respectively.

Of all treated subjects who completed the study and were cured (ACPR cases), the mean asexual parasite clearance times were 1.6 (range: 1-7days) in the falciparum group and 1.2 (range: 1-2 days) in the vivax group. Almost all subjects had cleared asexual parasitemia by day 2 (**Figure 2**). Only one *P. falciparum*-infected subject had asexual parasitemia on day 3 with a low density (10/uL).

There were 24.3% falciparum malaria subjects with gametocytemia on day 0 (pre- treatment). However, gametocytemia was detected up to day 28 after DPQ treatment without primaquine in this group. Conversely, of the 90.0% of vivax malaria subjects with gametocytemia on day 0, gametocytemia was only detected up to day 2.

After treatment with DPQ, mean hemoglobin (Hb) levels of the falciparum and vivax malaria groups significantly improved on days 14, 28 and 42 compared to the mean Hb levels at day 0 ($P \leq 0.001$) (**Figure 3**). In addition, more than 60% of malaria subjects showed evidence of hemoglobin recovery (hemoglobin levels greater than at day 0) on days 14, 28 and 42 (**Figure 4**). The proportions of anemia in falciparum subjects on days 14 (39/70 or 55.7%), 28 (38/70 or 54.3%) and 42 (35/66 or 53.0%) were significantly ($P < 0.001$) reduced compared to the proportion of anemia on day 0 (51/68 or 75.0%). Similarly, the proportions of anemia in vivax subjects on days 14 (39/59 or 66.1%),

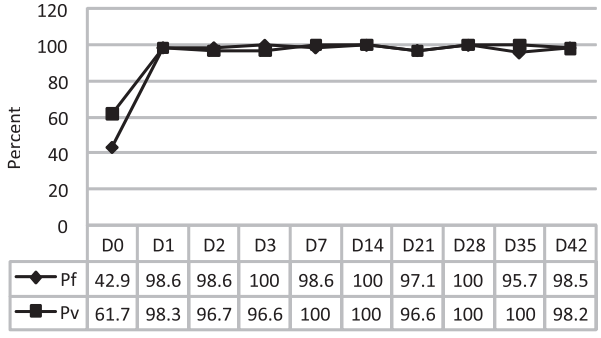

Figure 1. Percentage of DPQ-treated subjects infected with P.falciparum or P.vivax malaria with fever clearance on observation days 0-42

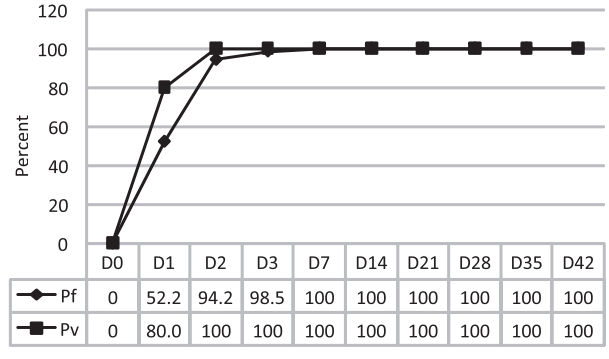

Figure 2. Percentage of DPQ-treated subjects infected with P. falciparum or P. vivax malaria with asexual parasite clearance on observation days 0-42

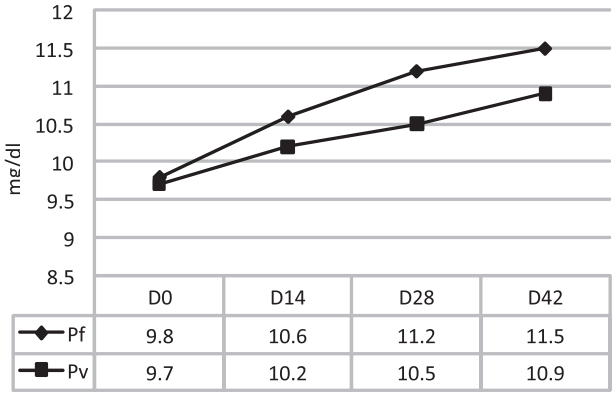

Figure 3. Mean Hb levels in P. falciparum and P. vivax subjects treated with DPQ on observation days 0, 14, 28, and 42

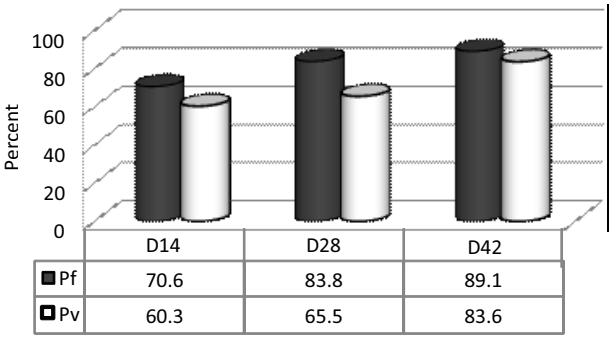

Figure 4. Percentage DPQ-treated subjects infected with P.falciparum or P.vivax with hemoglobin level recovery on observation days 14, 28, and 42

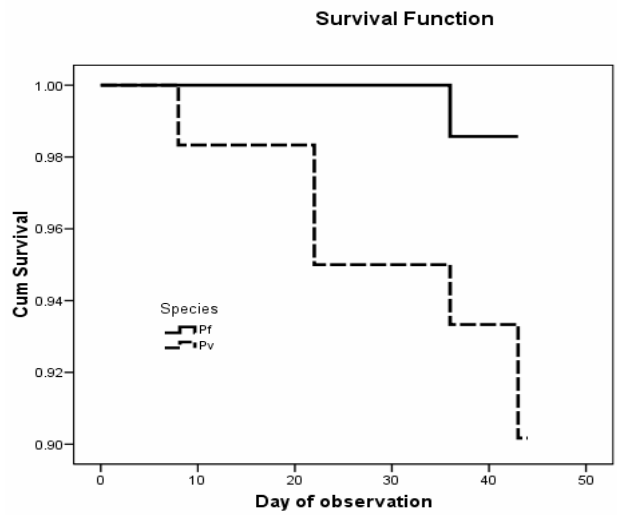

Figure 5. ACPRs in P. falciparum and P. vivax-infected subjects treated with DPQ by ITT analysis

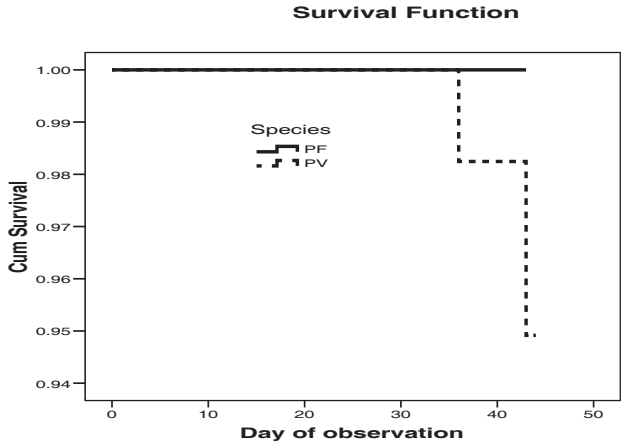

Figure 6. ACPRs in P. falciparum and P. vivax-infected subjects treated with DPQ by PP analysis

28 (36/56 or 64.3%) and 42 (34/56 or 60.7%) were significantly ($P < 0.001$) reduced compared to that on day 0 (46/59 or 78.0%).

Of the 70 treated falciparum malaria subjects, there were no withdrawn consents or protocol violation cases. However, one subject was lost to follow-up on day 35. The 69 falciparum subjects completed the study, and no early treatment failure (ETF) or late treatment failure (LTF) cases were found. Hence, the ACPRs of DPQ in the uncomplicated falciparum group were 98.6% (ITT subjects) and 100% (PP subjects) (**Table 3, Figure 5, 6**).

Of the 60 DPQ-treated vivax malaria subjects, one subject under five years of age withdrew on day 7 due to typhoid infection. Also, one protocol violation case in a one year-old boy was noted. He was diagnosed with vivax malaria on enrollment, but *P.falciparum* infection was detected by PCR on day 21. A third case was lost to follow-up on day 21. Therefore, only 57 treated vivax malaria subjects could be evaluated per protocol. During the study observation, there were no ETFs, but there were two LTFs, one Late Clinical Failure (LCF) case on day 35 and one Late Parasitological Failure (LPF) on day 42. The ACPRs of DPQ in the uncomplicated vivax malaria group were 91.7% (ITT analysis) and 96.5% (PP analysis) (**Table 3, Figure 5, 6**).

Clinical adverse events (AEs) during the study period which did not exist prior to DPQ treatment were recorded. The most common AEs were cough (25.4%) and abdominal pain (10.8%).

Other AEs reported were vomiting, palpitation, anorexia, sweating, headache, nausea, diarrhea, rigor, lethargy, general unwellness, insomnia, myalgia, and dizziness (**Figure 7**). All AEs were mild and disappeared with or without symptomatic treatment.

Therefore, the safety and efficacy of DPQ in Asian children is important to determine, as most studies were reported from Africa. In African children, DPQ was shown to be effective (ACPR confirmed by PCR >94%) with rapid fever and parasite clearance, good hemoglobin recovery, and resulting in lowered

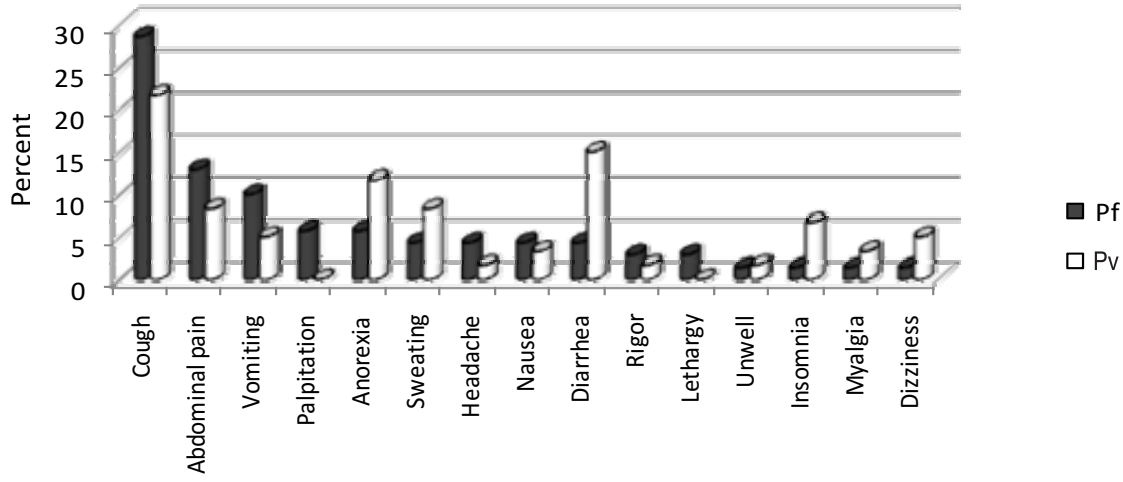

Figure 7. Percentage of adverse events in *P. falciparum* and *P. vivax*-infected subjects treated with DPQ throughout the 42 day observation period

Discussion

Artemisinin-based combination therapies have recently been widely adopted for the treatment of uncomplicated malaria worldwide. Selecting the ideal partner drug to combine with artemisinins in ACT regimens remains a challenge. Dihydroartemisinin-piperaquine, a newer artemisinin-based combination therapy, has shown excellent efficacy. Studies from Africa and Asia, including Indonesia, reported that DPQ is considered highly promising for wide use in Indonesia.[5-6,10-19] In addition, DPQ has been used increasingly in Southeast Asia and is part of the national treatment recommendations in China and Vietnam.

Artemisinin derivatives are safe and well-tolerated by children. The choice of ACT is determined largely by the safety and tolerability of partner drug.[20] Moreover, dosing is often difficult where pediatric formulations are unavailable. risk of recurrent parasitemia due to new infections or having better post-treatment prophylactic effects.[11,12,14,15,21,22] In contrast, most efficacy and safety of DPQ studies in Asia have been reported for all age groups, children up to adults.[5-6,10,13,16-19] One efficacy and safety DPQ study in Cambodian children showed a very effective cure rate of > 95% and mild adverse events.[23]

In Indonesia, DPQ use has increased gradually in Papua (starting in Mimika District in 2006) based on a series of antimalarial drugs studies.[5-6,24] DPQ is a well-known, efficacious antimalarial drug among Papuans and is known as "the blue pill," the color of a previous study drug (Duo-Cotecxin®). This is the first study reporting the efficacy and safety of DPQ use in non-Papuan Indonesian children. The strengths of this study are that it was performed in endemic areas outside of Papua, subjects were children aged <15 years, speciation was confirmed and corrected by PCR, and the follow-up period was prolonged (42 days).

We observed that DPQ was highly efficacious, with ACPRs of 98.6% and 100% in the ITT and PP subjects, respectively, for uncomplicated falciparum malaria. In uncomplicated vivax malaria, the ACPRs were 91.7% and 96.5% in the ITT and PP subjects, respectively. PCR correcting was not done since there were no *P. falciparum* treatment failure cases. The two *P. vivax* treatment failures occurred by days 35 and 42. On day 35, there was one LCF case in a baby girl aged 8 months, weighing 9.1 kg and treated with a half tablet of DPQ per day or a total dosage of 20 mg of dihydroartemisinin and 160 mg of piperaquine per day. The other case on day 42 was a LPF in a child aged 6 years, weighing 16 kg and treated with one tablet of DPQ per day. No post- treatment vomiting and diarrhea were reported in either of these subjects. Because piperaquine has a half-life of 2–3 weeks[25] and recurrent parasitemia occurs on days 35 and 42, the two treatment failures were likely first relapse cases. Unlikely genotyping for *P. falciparum* use to distinguish recrudescence and new infection or re-infection in treatment cases has been established, but genotype of *P. Vivax* use to distinguish relapse and resistance in treatment failure cases has not been established. Moreover, true relapses by reactivated hypnozoites may be a cause of recurrent parasitaemia.[9] The addition of a 14-day primaquine course for radical treatment in children aged above one year may improve the efficacy of DPQ in vivax malaria. Overall, the cure rates of DPQ meet with the WHO acceptance threshold (≥ 95%) for choosing ACT use for effective treatment.[20] The limitation of this study is that it was not designed specifically to evaluate the safety and efficacy of DPQ in children. We maximized use of the existing ACT monitoring data from Kalimantan and Sulawesi. However, the sample size was not large enough.

We observed that DPQ use also resulted in rapid fever and asexual parasite clearances. However, common colds and recurrent asexual parasitemia may cause subsequent fever. Only one treated subject with falciparum malaria had longer low density asexual parasitemia until day 7, but it was cleared by day 42. Suspected resistance to artemisinin is defined by increased asexual parasite clearance time, as evidenced by 10% of cases with parasites detectable on day 3 after treatment with an ACT.[26] Only one falciparum malaria case had a longer asexual parasite clearance time. But ACT had only recently been introduced to Kalimantan and Sulawesi, and the emergence and spread of parasites resistant to artemisinin should therefore be prevented to sustain malaria control and elimination.

Artemisinin derivatives are potent and rapidly acting blood schizontocides of all malaria species and have a gametocytocidal effect in the early stages of *P. falciparum* gametocyte development.[27] Artemisinin derivatives reduce the density of gametocytes, but had not been known to eliminate gametocyte carriage of *Plasmodium falciparum*.[28-29] In our study, DPQ proved to be a good blood schizontocide and gametocytocide, since gametocyte carriage was no longer detected by day 3 in vivax malaria subjects. Unlike *P. vivax*, gametocyte carriage of *P. falciparum* was detected to day 28, similar to that of other studies,[21,23] however, the proportion reduced gradually on subsequent observation days. Therefore, addition of a single dose of primaquine to DPQ for radical treatment and faster gametocyte clearance could have a major effect on malaria transmission from treated patients.

Hemoglobin recovery is an additional parameter for measuring therapeutic response. About three-fourths of the subjects had anemia on enrollment (day 0), but that number was significantly reduced after treatment with DPQ. Hemoglobin recovery was observed in the form of increased mean hemoglobin levels, with subjects having greater mean hemoglobin levels on days 14, 28 and 42 than on day 0. Although malaria infection is not the only cause of anemia, our results were similar to that of other studies in which DPQ helped in the hemoglobin recovery of both falciparum and vivax subjects.[5,6, 10,12,15-17]

In our study, DPQ was well-tolerated for treatment of uncomplicated falciparum and vivax malaria in children. No subjects withdrew from the study due to adverse events. Similarly, other DPQ trials reported that most adverse events were consistent with the symptoms of malaria.[5,6,10,15,17,23] Mild gastrointestinal complaints were the most commonly reported adverse events.

Considering the advantages of DPQ and based on the principles of evidence-based medicine, DPQ is a potential ACT for the multiple first-line therapy policy of the Indonesian Malaria Control Program.

In conclusion, DPQ was effective for treatment of uncomplicated *P.falciparum* and *P.vivax* in children with ACPRs of 100% and 96.5%, respectively, rapid fever and asexual parasite clearance, and good hematological recovery. Cough and abdominal pain were common adverse events, but they were mild and disappeared with or without symptomatic treatment. DPQ is a promising ACT for multiple first-line therapy (MFT) policies in Indonesia.

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References

1. World Health Organization. World Malaria Report 2010. WHO Global Malaria Programme. Geneva: WHO; 2010.
2. Adjuik M, Agnamey P, Babiker A, Borrmann S, Brasseur P, Cisse Met, et al. Amodiaquine-artesunate versus amodiaquine for uncomplicated *Plasmodium falciparum* malaria in African children: a randomised, multicentre trial. Lancet. 2002;359:1365-72.
3. Tjitra E and Maladi. Artesunate plus amodiaquine vs artemisinin plus piperaquine for treatment falciparum and vivax malaria: preliminary findings. Artemisinin compounds clinical trial information exchange workshop; 2005 July 8, Bangkok, Thailand.
4. Setyaningrum E, Sutanto I, Fauzia M, Subandryo HD, Santoso B, Rosidi, et al. Efficacy of artesunate-amodiaquine in uncomplicated falciparum malaria cases, Lampung Province, Sumatra, Indonesia. In: Improving insight of antimicrobials and anti-parasitics towards better management of infectious diseases. Proceedings from the 6th Jakarta Antimicrobial Update 2005 in conjunction with the 1st International Parasitic Disease Update; 2005 April 16-17; Jakarta, Indonesia. Division of Tropical and Infectious Diseases, Department of Medicine, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital 2005, Jakarta.
5. Hasugian AR, Purba HLE, Kenangalem E, Wuwung RM, Ebsworth EP, Maristela R, et al. Dihydroartemisinin-piperaquine versus artesunate-amodiaquine: superior efficacy and post-treatment prophylaxis against multidrug-resistant *Plasmodium falciparum* and *Plasmodium vivax* malaria. Clin Infect Dis. 2007;44:1067-74.
6. 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.
7. World Health Organization. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. In: WHO/HTM/RBM/ 2003.50. Geneva: WHO; 2003.p.9-36
8. Ministry of Health. Malaria case management guideline. Directorate General of Disease Control and Environmental Health. Jakarta, 2009.p.12-20
9. World Health Organization. Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations; Informal consultation organized by the Medicines for Malaria Venture and cosponsored by the World Health Organization, 2007 May 29–31; Amsterdam, Netherlands. Geneva: World Health Organization.p.13-41
10. 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.
11. 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.
12. Kamya MR, Yeka A, Bukirwa H, Lugemwa M, Rwakimari JB, Staedke SG, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of malaria: a randomized trial. PLoS Clin Trials. 2007;2:20.
13. 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.
14. Zongo I, Dorsey G, Rouamba N, Dokomajilar C, Sere Y, Rosenthal J, et al. Randomized comparison of amodiaquine

plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Burkina Faso. Clin Infect Dis. 2007;45:1453–61.

15. Yeka A, Dorsey G, Kamya MR, Talisuna A, Lugemwa M, Rwakimari JB, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treating uncomplicated malaria: a randomized trial to guide policy in Uganda. PLoS ONE. 2008;3:2390.
16. Smithuis F, Kyaw MK, Phe O, Win T, Aung PP, Oo APP, et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. Lancet Infect Dis. 2010;10:673–81.
17. Mayxay M, Keomany S, Khanthavong M, Souvannasing P, Stepniewska K, Khomthilath T, et al. A phase III, non-inferiority trial to assess the efficacy and safety of dihydroartemisinin-piperaquine in comparison with artesunate-mefloquine in patients with uncomplicated *Plasmodium falciparum* malaria in Southern Laos. Am J Trop Med Hyg. 2010;83:1221-9.
18. Awab GR, Pukrittayakamee S, Imwong M, Dondorp AM, Woodrow CJ, Lee SJ, et al. Dihydroartemisinin-piperaquine versus chloroquine to treat vivax malaria in Afghanistan: an open randomized, non-inferiority, trial. Malar J. 2010;9:105.
19. Valecha N, Phyo AP, Mayxay M, Newton PN, Krudsood S, Keomany S, et al. An open-label, randomised study of dihydroartemisinin-piperaquine versus artesunate-mefloquine for falciparum malaria in Asia. PLoS ONE. 2010;5:e11880.
20. World Health Organization. Guidelines for the treatment of malaria. 2nd ed. Geneva: World Health Organization; 2010. p. 14-22
21. Arinaitwe E, Sandison TG, Wanzira H, Kakuru A, Homsy J, Kalamya J, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for falciparum malaria: a longitudinal, randomized trial in young Ugandan children. Clin Infect Dis. 2009;49:1629–37.
22. Nambozi M, Geertruyden JPV, 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.
23. Denis MB, Davis TME, Hewitt S, Incardona S, Nimol K, Fandeur T, et al. Efficacy and safety of dihydroartemisinin-piperaquine (artekin) in Cambodian children and adults with uncomplicated *falciparum* malaria. Clin Infect Dis. 2002;35:1469–76.
24. Ratcliff A, Siswantoro H, Kenangalem E, Wuwung RM, 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. Trans R Soc Trop Med Hyg. 2007;101:351-9.
25. Hung TY, Davis TM, Ilett KF, Karunajeewa H, Hewitt S, Denis MB, et al. Population pharmacokinetics of piperaquine in adults and children with uncomplicated falciparum or vivax malaria. Br J Clin Pharmacol. 2004;57:253–62.
26. World Health Organization. Global plan for artemisinin resistance containment (GPARC). Geneva: World Health Organization; 2011. p. 16
27. Kumar N. and Zheng H. Stage-specific gametocytocidal effect in vitro of the antimalaria drug qinghaosu on *Plasmodium falciparum*. Parasitol Res. 1990;76:214-8.
28 Targett G, Drakeley C, Jawara M, von Seidlein L, Coleman R, Deen J, et al. Artesunate reduces but does not prevent post-treatment transmission of *Plasmodium falciparum* to *Anopheles gambiae*. J Infect Dis. 2001;183:1254-9.
29. Price RN, Nosten F, Luxemburger C, ter Kuile FO, Paiphun L, Chongsuphajaisiddhi T, et al. Effects of artemisinin derivatives on malaria transmissibility. Lancet. 1996;347:1654-8.
30. Watkins WM, Mosobo M. Treatment of *Plasmodium falciparum* malaria with pyrimethamine-sulfadoxine: selective pressure for resistance is a function of long elimination half-life. Trans R Soc Trop Med Hyg. 1993;87:75–8.
31. White NJ. How antimalarial drug resistance affects post-treatment prophylaxis. Malar J. 2008;7:9.
32. Stepniewska K, White NJ. Pharmacokinetic determinants of the window of selection for antimalarial drug resistance. Antimicrob Agents Chemother. 2008;52:1589–96.