Paediatrica Indonesiana

VOLUME 52 January • 2012 NUMBER 1

Original Article

Artesunate-amodiaquine treatment for children with uncomplicated malaria in Kalimantan and Sulawesi: clinical complaints, tolerability and compliance

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Abstract

Background Artesunate–amodiaquine combination (AS+AQ) is one type of artemisinin-based combination therapy (ACT) and has been used in Indonesia since 2004 for uncomplicated malaria, both in adults and children. However, its use in the Indonesia Malaria Program has not yet been evaluated.

Objective To evaluate the clinical complaints and tolerability to AS+AQ treatment, as well as compliance in children with uncomplicated malaria.

Methods This was a cross-sectional study, conducted in sentinel puskesmas (primary health centers) in Kalimantan and Sulawesi. Subjects were 126 children aged under 15 years, with *P. falciparum, P. vivax*, or mixed *falciparum-vivax* malaria infections. All subjects were treated with a single dose of AS+AQ for three consecutive days and followed-up 3 times (D3, D7 and D28) to record clinical complaints and tolerability after drug administration. Parents/guardians underwent in-depth interviews on the knowledge, attitudes and practices of the ACT used as well as clinical complaints following AS+AQ treatment.

Results Of the 126 subjects evaluated, 30 were infected with *P. falciparum*, 59 with *P. vivax*, and 37 with both species. About 84% of the subjects reported clinical complaints after AS+AQ administration (D0-D2), most commonly lethargy, nausea and vomiting, similar to the clinical symptoms of malaria. All complaints were reported to be mild and tolerable. Only one subject was lost to follow-up.

Conclusion Clinical complaints experienced by malaria-infected children following AS+AQ treatment were relatively tolerable. Subjects' compliance to AS+AQ treatment was satisfactory. **[Paediatr Indones. 2012;52:10-5]**.

Keywords*: ACT, artesunate-amodiaquine, malaria, children, clinical complaint*

Malaria is endemic to Indonesia, particularly in the eastern part of the country. The 2010 National Basic Health Research (Riskesdas) showed the prevalence of malaria in children aged 1 – 14 years to be relatively high compared to the prevalence of all malaria cases nationally.[1] Since 2004, as recommended by WHO, the Malaria Program in Indonesia adopted the use of artemisinin-based combination therapy (ACT) as the first line antimalarial, instead of chloroquine due to increased chloroquine resistance. Since then, the recommended ACT used in Indonesia has been the non fixed-dose combination of artesunate–amodiaquine (AS+AQ) for uncomplicated *falciparum* malaria.[2] Clinical studies, mostly from Africa, have shown that the AS+AQ combination is safe and well tolerated in adults, as well as children.[3, 4, 5]

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Some studies also reported good efficacy with AS+AQ for uncomplicated *falciparum* malaria, with tolerable adverse events.[6-8] However, other studies reported varying efficacies of AS+AQ treatment. In Papua, drug efficacies were reported to be 78 – 96% for *Plasmodium falciparum* and 67% for *Plasmodium vivax*.[9] Furthermore, low coverage of effective ACT utilization (33.7%) in Indonesia was also reported.[1] Poor compliance to AS+AQ use due to untolerable adverse events may contribute to this low coverage. Another possibility is that a greater number of antimalarial drugs are administered as a consequence of the non fixed-dose drug combination. Currently, AS+AQ for the Malaria Program in Indonesia is available only as a non-fixed dose combination.

The objective of this study was to evaluate clinical complaints from and tolerability to AS + AQ treatment, as well as patient compliance in children under 15 years of age with uncomplicated malaria.

Methods

We conducted a cross-sectional study as a part of the pharmacovigilance study of "Monitoring drug resistance in subjects with *Plasmodium falciparum* and *Plasmodium vivax* malaria in Kalimantan and Sulawesi" in 2010.[10] Data was collected over 6 months (July to December 2010) from 8 sentinel primary health centers in Kalimantan (West and Central) and Sulawesi (North and Central). Subjects were under 15 years of age with uncomplicated *P. falciparum, P. vivax* or mixed malaria infection (all clinically and parasitologically confirmed), and met the inclusion criteria. Parents/guardians provided written informed consent.

All subjects were treated with a single dose of artesunate (50mg/tablet) combined with amodiaquine (200 mg/tablet) for three consecutive days (Days 0, 1 and 2). Artesunate dosage was 4mg/kg body weight/day and amodiaquine dosage was 10mg/kg body weight/day. All subjects were followed-up three times through visits to the health centers on days 3, 7 and 28 where clinical complaints after drug administration were evaluated and recorded. Parents/guardians were also asked to observe all clinical complaints experienced by their children after taking AS+AQ, and to record this information daily on a case record form designed for this purpose. We also interviewed parents/guardians to obtain their knowledge, attitude, and practice of ACT use, and subjects' compliance to ACT treatment.

Results

From July to December 2010, 126 children with malaria aged 8 months to 14 years (mean 6.02 years, mode 3 years) were recruited into our study. Among these, 30 subjects (23.8%) had *Plasmodium falciparum* infection, 59 subjects (46.8%) had *Plasmodium vivax* infection and 37 subjects (29.4%) had *falciparum-vivax* mixed infection (**Table 1**).

Almost all subjects (99.2%) completed the treatment course. One subject with a *falciparum-vivax* mixed infection was lost to follow-up. At least

Table 1. Characteristics of subjects with *P. faciparum, P. vivax* and *falciparum-vivax* mixed infections

Characteristics	P. falciparum (n=30)	P. vivax (n=59)	Mixed (n=37)	Total (n=126)
Gender: M: F, %	63.3 : 36.7	55.9 : 44.1	54.1 : 45.9	57.1 : 42.9
Mode age, years (range)	5 (1–14)	3 (0.75–13)	7 (0.67–13)	3 (0.67–14)
< 5 years old, %	30.0	57.6	32.4	43.7
5 – 14 years old, %	70.0	42.4	67.6	56.3
Mode body weight, kg (range)	10.0 (9.0 – 48.0)	10.0 (8.0 – 50.0)	20.0 (7.0 – 43.0)	10.0 (7.0 – 50.0)
Treatment completed (%)	100.0	100.0	97.3	99.2
Dropped out, %	0	0	2.7	0.8
Clinical complaints,* %	83.3	83.1	86.5	84.1
Mode number of clinical complaints	2	3	3	3

*Denotes percentage of patients with at least 1 reported clinical complaint on D0–D2 following AS+AQ administration

one clinical complaint was experienced at D0 – D2 by 84.1% of subjects after taking AS + AQ, while the majority of subjects reported three clinical complaints. All clinical complaints following AS+AQ administration reported by parents/guardians to the health centers were recorded on case record forms at specific times during the follow-up period. **Figure 1** shows the various clinical complaints experienced by children after taking AS+AQ.

Some effects experienced during the three-day treatment were similar to the clinical symptoms of malaria, e.g., lethargy, nausea, vomiting and tremors. There was a variety of clinical complaints at D0, the most common being lethargy reported by 33.5% of subjects. The percentage of subjects with clinical complaints tended to decrease at D1 and D2, with the exception of abdominal pain (15.1% on D0 increasing to 18.3% on D1, then decreasing to 13.5% on D2 (**Figure 1**). Other

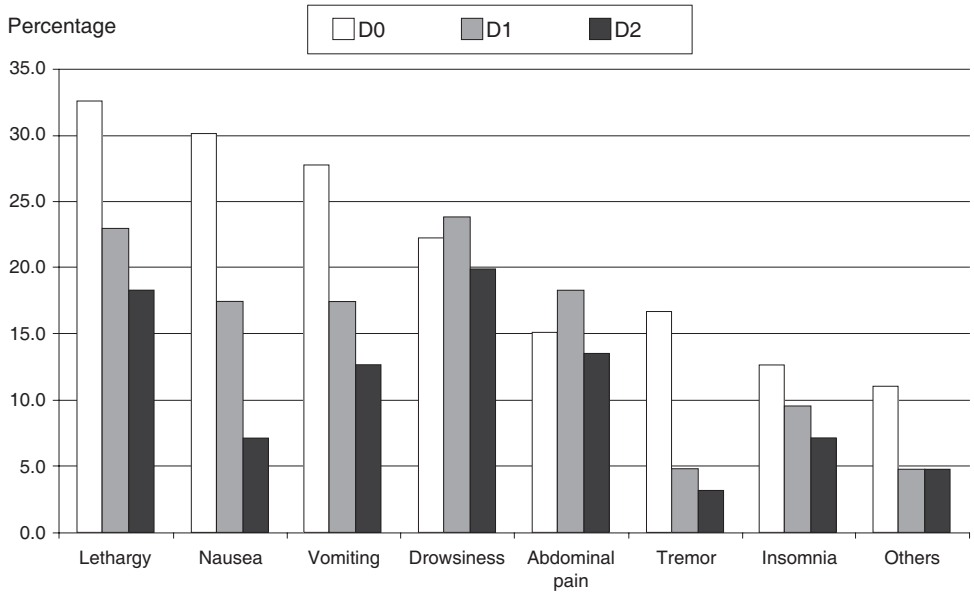

Figure 1. Percentage of children with clinical complaints during AS+AQ treatment

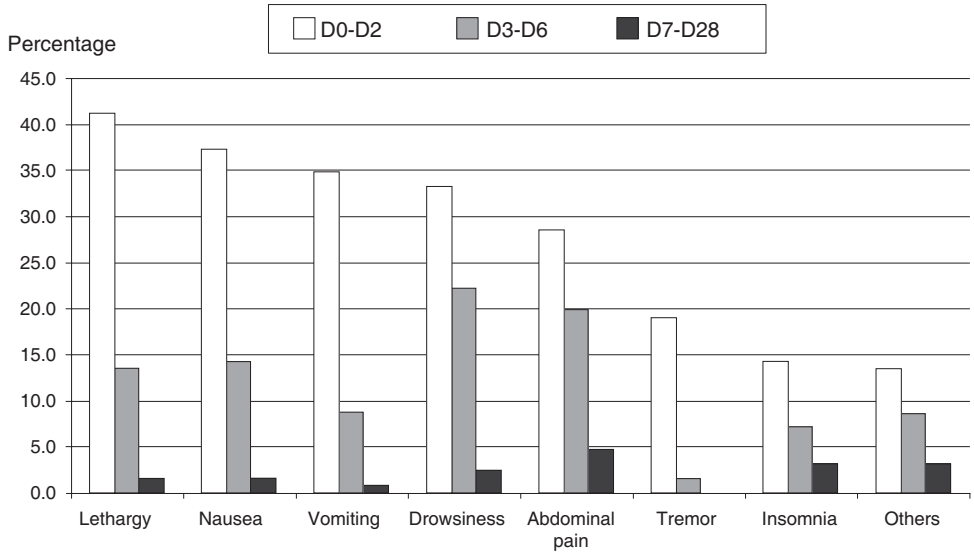

Figure 2. Percentage of subjects undergoing AS + AQ treatment with clinical complaints at health center visits on D0-D28

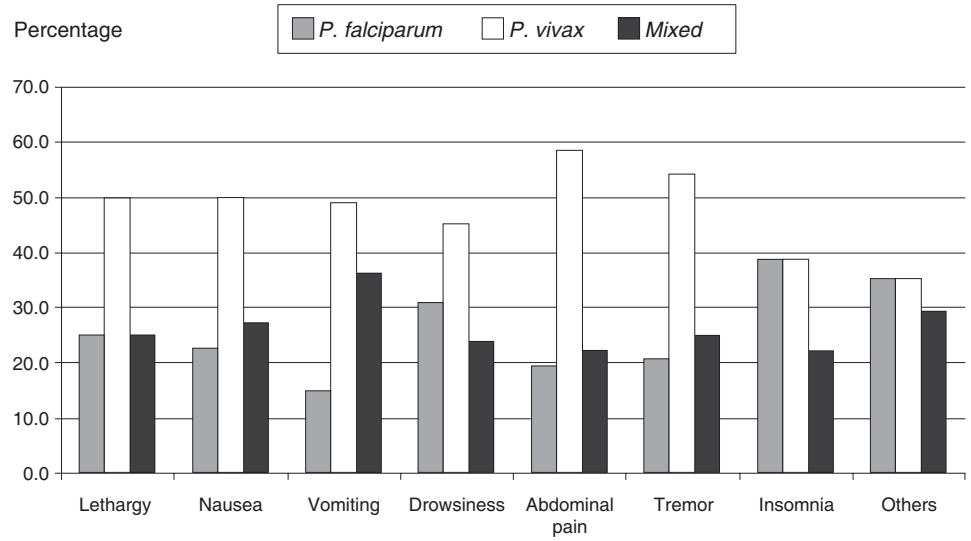

Figure 3. Percentage of clinical complaints reported on D0-D2 after AS+AQ treatment in subjects with *Plasmodium falciparum, Plasmodium vivax* and mixed *falciparum - vivax* infections

Table 2. Artesunate-amodiaquine dosage per kg body weight per day

Dosage Per kg BW/day	Artesunate	Amodiaquine
Mean, mg (range)	82.34 (37.5-200.0)	274.6 (100.0-700.0)
Appropriately dosed, %	94.4	96.0
Insufficient dosage, %	2.4	0.8
Over dosage, %	3.2	3.2

clinical complaints reported at D0 were pruritus (2.4%), skin rash (1.6%), bloating (1.6%), loss of appetite (1.6%), epistaxis (1.6%), diarrhea (0.8%), constipation (0.8%) and cracked lips (0.8%). Clinical complaints other than those due to malaria infection may have been caused by AS+AQ, but these complaints tended to diminish at D1 and D2.

On health center visits on D3-D6, the percentage of subjects with clinical complaints was markedly reduced by ≥ 50%, with even a 90% reduction for tremors (**Figure 2**). However, several complaints such as drowsiness, abdominal pain and others were reduced by less than 50%. On visits at D7-D28, the percentage of subjects with various clinical complaints was again further reduced but remained to be reported by < 5% of subjects.

The percentage of *P. vivax*-infected subjects with clinical complaints of lethargy, nausea, vomiting, drowsiness, abdominal pain and tremors on D0-D2 was greater (at 45.2 – 58.3% of subjects) compared to those from the other malarial infection types. Other complaints, such as insomnia, were experienced by similar percentages of subjects for both *P. falciparum* and *P. vivax* infections (**Figure 3**).

Information obtained from in-depth interviews of parents/guardians indicated that all clinical complaints during AS+AQ treatment were relatively mild and could be tolerated. Parents also confirmed that AS+AQ combination was effectively healing their children. This perception would help improve their compliance with the treatment. Clinical complaints due to AS+AQ medications were managed by taking symptomatic medications prescribed by the health center, or were treated traditionally, by giving sweetened tea to the children.

For practical purposes in the field, the AS +AQ dosage given to children was based on the dosage table adopted from the Malaria Guidelines.[2] On calculation, the mean dosages of artesunate and amodiaquine were 82.34 mg daily (about one and a half tablets per day) and 274.60 mg daily (about 1¼ tablet per day), respectively (**Table 2**).

It was calculated that most subjects received appropriate dosages of AS+AQ. However, 3.2% of subjects received less than the recommended dosage of ACT, while 6.4% received slightly greater than the recommended dosage.

Discussion

According to the 2010 National Basic Health Research (Riskesdas), a national survey performed by the National Institute of Health Research Development (NIHRD), the prevalence of malaria in children aged 1 – 14 years was 9.7 – 10.7%, and 8.2% in children under one year of age. The study indicated that the percentage of malaria cases in children was similar to the national prevalence for people of all ages (10.6%).[1]

In areas where *P. falciparum* and *P. vivax* are prevalent, infants and young children are at greater risk of acquiring *P. vivax* infection than *P. falciparum* infection.[11] We observed similar results, with more children infected with *vivax* malaria (46.8%) than with *falciparum* (23.8%) or *falciparum-vivax* combination (29.4%). There were no gender-based differences in infection types.

Artemisinin-based combination therapy (ACT) recommended by the Indonesian Malaria Program is a non-fixed combination of AS+AQ which is the drug of choice for uncomplicated malaria.[2] Although it has been used in Indonesia since 2004, the 2010 Survey showed that ACT use as an effective treatment for malaria in children (≤ 14 years) was low, only 4.2 – 32.6%.[1] This data was supported by evidence in our study, in that even now treatment with AS+AQ has just begun in Kalimantan and Sulawesi.[10] The lack of AS+AQ use as a routine therapy for malaria in those two study locations may be due to sporadic drug availability in the community health centers. In addition, information obtained from in-depth interviews with community health center personnel indicated that health providers did not use AS+AQ for malaria treatment because they were uncertain of its safety.[12]

Several studies in other countries reported that the AS+AQ combination was safe for children, with episodes of adverse events in 35 – 59% of subjects.[13,14] Compare to those studies, we found in a study prior to this one that a greater percentage (84%) of children experienced clinical complaints during AS+AQ treatment. However, this percentage was relatively lower than that of adult malaria subjects in the same study.[12] Despite the clinical complaints, most subjects (99.2%) completed the treatment and only one subject dropped out from the study due to loss to follow-up.[12]

Complaints frequently reported during the 3-day AS+AQ treatment, mostly on D0, were lethargy (32.5%), nausea (30.2%), vomiting (27.8%), drowsiness (22.2%) and abdominal pain (15.1%). In general, clinical complaints reported were similar to malaria clinical symptoms. In addition, clinical complaints such as pruritus and skin rashes occurred in 2.4% of subjects. The percentage of subjects with clinical complaints decreased on D2 and D3 of treatment, and continued decreasing at subsequent days of follow-up (D4 – D28).

Almost all clinical complaints from AS+AQ treatment were reportedly higher in children infected with *P. vivax*, compared to complaints in subjects with *P. falciparum* or *falciparum-vivax* mixed infection. Symptoms seemed to be more prominent in *vivax* malaria in children compared to *falciparum* malaria, although symptoms rarely resulted in complications or fatalities.[15,16] Most complaints following AS+AQ administration were similar to the symptoms of malaria and could not be considered as drug adverse events, since we did not record clinical symptoms before treatment. Such is a limitation of our study. Moreover, we did not use laboratory studies to look for other drug adverse effects.

Most subjects (95%) received appropriate dosage of AS+AQ, while the remainder received under dosage (2.4%) or slightly over the recommended dosage of artesunate (3.2%). The mean number of ACT tablets taken by children, based on body weight, was 1½ tablets/day of artesunate and 1¼ tablets/day of amodiaquine. These amounts were assumed to be tolerable, based on qualitative data obtained from in-depth interviews with parents/guardians who reported subjects to have had good compliance to the medication, despite experiencing clinical complaints. Clinical complaints were managed by symptomatic medications provided by health center personnel prior to treatment, or by traditional means of giving sweetened tea to the children.

Children with uncomplicated malaria experienced clinical complaints following AS+AQ administration which were able to be tolerated. Clinical complaints occurring at D0 tended to decrease at subsequent days of treatment. Subjects' compliance to treatment was satisfactory, with most subjects (99.2%) completing the treatment course.

Acknowledgments

We are grateful to the Chiefs of staff and staff members the following Puskesmas (primary health centers): Toho and Anjongan (District of Pontianak, West Kalimantan); Kasongan and Tumbang Samba (District of Katingan, Central Kalimantan); Banpres and Baluase (District of Sigi, Central Sulawesi); and Touluaan and Tambelang (District of Southeast Minahasa, North Sulawesi) for cooperation and collaboration in this study. We are also grateful to the Chiefs of the District Health Offices of the study sites, district supervisors and province coordinators for all support and technical assistance. We also thank the Global Fund for financial support of this study.

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