Activities of artesunate and amodiaquine against intestinal helminth in children with *Plasmodium falciparum* malaria in endemic areas

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Malaria and helminthes infections are major causes of morbidity and mortality in children and are a public health problem in endemic areas of sub-Saharan Africa [1–3]. The prevalence of concomitant infection with intestinal helminthes of malaria is unknown, but the high prevalence of both infections exists in individuals living in Africa and elsewhere in the world where the infections are endemic [3, 4]. Several studies have reported that co-infection with helminthes affects the natural history and progression of malaria [4]; however, the contribution of antimalarial drug treatment on the co-infection is unknown.

Artesunate and amodiaquine are effective antimalarial drugs in the treatment of uncomplicated falciparum malaria. Recently, the use of an artemisinine-based combination option was adopted for the new policy on the management of malaria in Nigeria in 2004 [5]. One of the most frequently used of these combinations is artemether–amodiaquine, the individual drugs of which are readily available and readily used uncombined. Artemether has been reported to show activity against adult human schistosome parasites [6], but there is no clear-cut documentation of the effects of this drug, and amodiaquine, a potential artemisinine-based combination candidate, against intestinal helminthes.

The present study reports the antihelminthic activities of artesunate or amodiaquine nested in a trial designed to evaluate antimalarial drug efficacy in children suffering from acute uncomplicated falciparum malaria.

The study was carried out in Ibadan, Nigeria, from May 2005 to August 2006. A total of 109 children with acute uncomplicated *Plasmodium falciparum* malaria were enrolled onto the study. For enrolment in the study, each child had to meet the following criteria: (1) age<13 years; (2) fever or history of fever in the 24–48 h preceding presentation; (3) pure *P. falciparum* parasitaemia >2,000 asexual forms/μL; (4) no other concomitant illness or evidence of severe malaria; (5) no history of antimalarial use in the 2 weeks preceding presentation; (6) negative urine tests for antimalarial drugs (Dill-Glazko and lignin) [7]. Written informed consent was obtained from the parents/guardians of each child prior to enrolment. The study protocol was approved by the Ethics Committee of the Ministry of Health, Ibadan, Nigeria.

After obtaining detailed clinical and parasitological assessment at enrolment, the children were randomised to receive: (1) artesunate (AS) at 4 mg/kg daily for 7 days (day 0–6) or (2) a three-day regimen of amodiaquine (AQ) base at 10 m/kg daily (day 0–2). The drugs were given orally and supervised by the physician. Each child underwent clinical and parasitological examination daily on days 1–7 and on day 14. At each visit, finger-prick blood samples were collected and used as thick and thin blood smears for the
quantification of parasitaemia. Stool samples were also obtained within 24 h of enrolment and then on days 3, 7 and 14 for the determination of the presence, identification and quantification of the helminthes ova. The stool samples collected from the patients were concentrated by employing the formaldehyde-ether method [8] and examined microscopically within 24 h of collection to identify the presence of helminthes ova. The fever clearance time (FCT) was defined as the time taken for the body temperature to fall to below 37.5°C and remain below this value for >48 h. Malaria parasite clearance time (MPCT) was the time interval from the start of antimalarial treatment until the asexual parasite count fell below the detectable levels in a peripheral blood smear. Helminthes parasite excretion time (HPET) was the time interval from the start of antimalarial treatment until the helminthes ova fell below microscopically detectable levels and did not recur in the stool sample for the remaining time of the follow-up period.

Data were analysed using version 6 of the Epi Info software (Centers for Disease Control and Prevention, Atlanta, GA, USA). Kaplan-Meier plots are also presented to compare helminthes carriage rates following treatment in those who were helminthes carriers at presentation. Differences in survival time were assessed by the inspection of Kaplan-Meier curves and log-rank tests. All tests of significance were two-tailed. P-values ≤0.05 were taken to indicate significant differences.

The enrolment characteristics of the children (aged 6.5±2.7 years [mean±standard deviation], range 3–14) between the two treatment groups were similar. All of the children responded promptly to treatment, and none developed severe malaria. Helminthes were detected in the stool of 109 children from both groups (in 102 children before treatment and in seven children after the initiation of treatment). The overall median (range) FCT was 1.0 (1–2 days) and was not significantly different between the two treatment groups. None of the studied children had significant adverse effects as monitored by clinical symptoms (data not shown), but three children treated with amodiaquine reported pruritus, which interfered with sleep. The overall mean MPCT±SD was 2.8±1.7 days and was significantly shorter in the artesunate (1.3±0.5 days) group than in the amodiaquine group (2.8±1.8 days, P=0.0001). Conversely, the helminthes parasite excretion time (HPET) was significantly shorter with amodiaquine treatment compared to artesunate treatment (5.4±3.7 vs. 8.5±4.9, P=0.003). A significantly higher proportion of the children treated with artesunate, compared to those treated with amodiaquine, were helminthes carriers on days 3 (40/61 vs. 21/48, P=0.03) and 14 (21/61 vs. 7/48, P=0.03). However, the geometric mean helminthes ova count (mg stool) was similar on days 0, 3 and 7, but significantly lower on day 14 following treatment with the artesunate compared with amodiaquine (P=0.01).

All 109 children completed 28 days of follow-up for the evaluation of the response of P. falciparum to the antimalarial drugs treatment. Of these, one child in the artesunate group had subsequent reappearance of P. falciparum within 14 days, confirmed as recrudescence by genotyping.

The helminthes parasites found in the stool samples were Ascaris lumbricoides which was the most prevalent (32%), hookworm (6.4%), Trichuris trichiura (6.1%), Enterobius vermicularis (0.8%), Diphyllobothrium latum (0.3%) and Strongyloides stercoralis (0.3%). Multiple infections of the helminthes occurred in 10 children (9.2%).

In the 109 children who were helminthes carriers, a total of 934, 293, 367 and 291 helminthes ova were counted on days 0, 1, 7 and 14, respectively. The probability of the continuing release of infective helminthes in the stool for transmission advantage is related to helminthes density and the duration of carriage by the host. Figure 1 shows a Kaplan-Meier plot (survival curve) of the cumulative probability of the remaining helminthes ova carrier following treatment with artesunate and amodiaquine in children who were helminthes carriers at presentation. This probability was higher with artesunate than with amodiaquine. Thus, compared with amodiaquine, children treated with artesunate alone had a significantly higher propensity to remain helminthes carriers (log rank statistic=4.67, P=0.03).

The efforts to reduce childhood morbidity and mortality resulting from infectious diseases can be optimised when the activities of a single agent or combination of agents against one infective organism becomes effective therapeutically to eradicate or eliminate other co-morbid infective organisms. In the present study, our result showed that, though the co-

Fig. 1 Kaplan-Meier plot (survival curve) of the cumulative probability of remaining helminthes carriers in children who were helminthes carriers at enrolment and following treatment with artesunate (solid line) and amodiaquine (broken line) (log rank statistic=4.67, P=0.03)
infection of intestinal helminthes with *P. falciparum* malaria may occur very readily in children with acute uncomplicated malaria infection [3], artesunate and amodiaquine not only clear asexual *P. falciparum* parasitaemia singly or when combined [9], but, individually, they have relative antihelminthic activity.

It is of interest that, despite the faster clearance of *P. falciparum* parasitaemia in artesunate-treated children, helminthes clearance time was shorter in amodiaquine-treated children. The reason(s) for this observation is not clear from the present study and may possibly be explained by the mechanism by which these two drugs act on the intestinal helminthes, one more cidal than the other; or due to individual drug pharmacokinetic profiles with differences in concentrations, moment residence time and half-lives of each drug providing more potent activity in respect of AQ than AS; or the drugs elicit differences in the trigger of host immune response that increases the ability to clear the helminthes parasites. The artesunate-treated children showed more propensities to remain helminthes carriers over the follow-up period (Fig. 1). The cumulative probability from the Kaplan-Meier survival analysis, amongst other antihelmintic parameters considered, seem to show higher clinical significance. While artesunate, within the 14-day follow-up period, significantly reduced the available mass of the infective intestinal helminthes in artesunate-treated children, amodiaquine grossly reduced the carriage rate by seven-fold in the few carriers in the amodiaquine-treated children. This observation suggests that the activity of artesunate may be static on helminthes and may be responsible for the higher proportion of helminthes carriers following treatment by day 14 in the artesunate treatment group.

Despite the interesting findings in our study, the short duration of the follow-up of helminthes excretion in the children, the absence of placebo and the combination of the two treatment arms limits the interpretation of our findings. More studies are needed to further clarify the contributions of these factors.

Overall, it would appear that the relative antihelminthic activities of artesunate and amodiaquine, despite the clearance of *P. falciparum* parasite demonstrated in the present study, contribute to the potential usefulness of these drugs singly or as combination antimalarials in children with acute malaria in endemic areas, particularly in Africa.

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**References**