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Efficacy of Amodiaquine in uncomplicated falciparum malaria in Nigeria in an area with high-level resistance to Chloroquine and Sulphadoxine/Pyrimethamine

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Abstract Falciparum Malaria is hyperendemic in southern Nigeria and chloroquine resistance is an increasing problem. Therefore, the parasitological and haematological response to treatment with amodiaquine was studied in children under 5 years during a 14-day follow-up. Of 105 children who accomplished the study (out of 114 who were enrolled), 95.3% were parasite-negative on thick blood film on day 7, which decreased to 89.5% on day 14. The haemoglobin levels increased on average by 1.3% on day 14 (±1.9) and more pronounced in children with anaemia < 10 g/dl on enrolment. The number of patients with adverse events (mainly pruritus and nausea) was few. This study shows that amodiaquine is effective, safe and affordable in an area with high resistance to chloroquine.

Introduction

Chloroquine (Cq) has been the mainstay for the treatment of *Plasmodium falciparum* (*P. f.*) infection in sub-Saharan Africa for decades because of its safety and affordability. The widespread use of this drug eventually led to increasing resistance; therefore, in some African countries other drugs, such as sulphadoxine/pyrimethamine (SP) have replaced Cq as first line treatment of Malaria (Shretta 2000). Meanwhile, there are a number of reports documenting an increasing resistance of *P. f.* to SP as well. The remaining alternatives in Africa are limited; most of them are more expensive or less safe than Cq. Amodiaquine, a 4-aminoquinoline developed in 1946, might be an effective and cost-efficient alternative to Cq and SP. Amodiaquine has a good safety profile (Olliario 1996), and is affordable. Despite a well-known cross-resistance with Cq it may be effective in areas with high-level resistance to Cq (Sowunmi and Salako 1992; Ringwald 1998; Brasseur 1999). Mèdecins sans Frontières (MSF) is running a malaria project in Southern Nigeria. A high resistance to both Cq and SP in this area is well-documented (Ezedinachi 1996; Falade 1997; Antia-Obong 1997). A study carried out by MSF in Bayelsa State in 2001 showed a combined early- and late-treatment failure rate as high as 38.7% for Cq and 43.6% for SP (Hardwick 2001, unpublished). Despite this high- level resistance to Cq and SP, these drugs are still officially recommended as first and second line treatment for falciparum malaria by the Ministry of Health in Bayelsa State.

We conducted a study on the efficacy of Amodiaquine in Bayelsa state to evaluate its usefulness as first line treatment for uncomplicated falciparum malaria in children under 5 years of age.

Materials and methods

The study was carried out in Southern Nigeria, at the beginning of the rainy season in June and July 2002. The area is covered by swamp forest. The mean annual rainfall ranges from 2,000 mm to 4,000 mm in the rainy season (March–November) with a relative humidity of up to 80%. The mean temperature is between 26°C and 30°C at that time of the year (Oyegun 1999). This climate provides ideal breeding-conditions for mosquitoes and therefore malaria is perennial and hyperendemic.

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The prevalence of malaria in school children in the rainy season is at least 60.3% (J. Graupner, not published).

Our aim was to include 120 children under 5 years of age in three different communities in Bayelsa state. The study has been approved by an ethics committee of the Ministry of Health/Bayelsa state. Before a new patient was enrolled, an informed consent was given by the caretaker and it was made sure that the information given was comprehensible. The inclusion criteria were according to WHO guidelines for the assessment of therapeutic efficacy of antimalarial drugs: (1) age 6–59 months, (2) mono-infection with *P. f.*, (3) parasitaemia 2.000–200.000/µl, (4) haemoglobin not below 5 g/dl, (5) absence of bacterial co-infection, (5) absence of "danger signs"—like inability to drink or breastfeed, convulsions, persistent vomiting or coma.

On enrolment each child was examined by a physician to exclude other common causes of fever such as bacterial co-infections like pneumonia, otitis media, skin abscesses or urinary tract infections. Study patients were given amodiaquine 10 mg/kg (total dose 30 mg/kg) for a period of 3 days observed on day 0, 1 and 2 by a study nurse; body temperature and a thick and a thin Giemsa-stained blood film were taken on day 0, 3, 7 and on day 14. In case of body temperature above 37.4°C during follow-up, each child had a medical examination to exclude co-infection.

The medication was crushed in a mortar and given with a spoon mixed with water by a study nurse. In case of vomiting within 30 min, we repeated the full dose of amodiaquine. If another incident of vomiting occurred the child was excluded from the study. No concomitant medication was given except paracetamol for the first 24 h if the body temperature was above than 38.5°C. On follow-up mothers/caretakers were asked for possible side effects with a questionnaire.

Parasitaemia was measured under field conditions by counting the number of asexual parasites against a number of leucocytes in the thick blood film, based on a putative mean count of 8,000 leukocytes per µl. Haemoglobin was estimated by Lovibond comparator on enrolment and day 14 (Woodliff 1966). Response to therapy was classified according to WHO criteria (WHO 1996).

Results

In June and July 2002, we screened 972 children under the age of five; 532 (55%) were positive for malaria; 114 children met the inclusion criteria, 105 of the children accomplished the study. Of the 114 enrolled patients, 9 were lost to follow up: One patient was sent to a traditional healer on the enrolment day, the others were lost to follow-up because the caretaker could not been found (two before the end of treatment, six between day 4 and 14). Nobody withdrew because of side effects. Interrogation of other patients and villagers confirmed that none of them died (Table 1).

Table 1 Basic characteristics on enrolment

Number of children enrolled ($n = 114$)	
Agudama	35
Kaiama	45
Sagbama	34
Gender/Male	51 (44.7%)
Mean age (month)	30 (6–58)
No. with fever > 37.4°C	47 (41.2%)
Hb mean in g/dl	9.6 (5–13)
Mean parasite count	22.299/ul

Parasitological and clinical response

Of 105 children who finished the study, 81 (77.1%) became parasite free on day 3 and 100 (95.3%) remained so on day 7 (adequate clinical and parasitological response [ACPR]). Two children met the WHO criteria of early treatment failure—one child had a parasitaemia on day 3 of > 25% compared to parasitaemia at enrolment; the other child was still febrile and not parasite free on day 3 (early treatment failure [ETF]), one was classified as late clinical failure because of persistent fever and parasitaemia on day 7 (late clinical failure [LCF]) and out of those who have been negative on day 7, eight had a recrudescence on day 14 and were therefore considered as late parasitological failure [LPF]. In all eight cases, the mothers reported that the children had no fever during the previous days. The remaining 94 (89.5%) children had an adequate clinical and parasitological response (Table 2).

Haematological response

The mean haemoglobin was 9.6 g/dl (± 1.7). Fourteen days after initiation of treatment an average increase of 1.3 g/dl of haemoglobin was observed (± 1.9). In the subgroup of patients with haemoglobin below 10.0 g/dl on enrolment, the improvement was even more pronounced, in average 1.8 g/dl (Table 3).

Discussion

Because of the increasing frequency of Cq-resistance in Africa, affordable alternatives are urgently needed. Hardwick demonstrated a clinical failure rate to Cq of 38.7% in this rural delta region of southern Nigeria.

Table 2 Study results

Final outcome	
Adequate clinical and parasitological response	94 (89.5%)
Early treatment failure	2 (1.9%)
Late clinical failure	1 (1.0%)
Late parasitological failure	8 (7.6%)

Table 3 Findings on parasite clearance and haematological response

Parasite clearance (%)	
On day 3	77.1%
	95.3%
On day 14	89.5%
Increase of haemoglobin levels on day 14	
Mean	1.3 g/dl
Hb on day 0 > 10 g/dl	0.5 g/dl
Hb on day 0 < 10 g/dl	1.8 g/dl

Amodiaquine proved to be effective and safe as first line treatment of falciparum malaria in small children in rural Nigeria. 94 out of 105 children (89.5%) had an adequate clinical and parasitological response, only eight (7.6%) had a recrudescence on day 14. There were only three (2.9%) who failed to respond at all. Although amodiaquine shares a similar mode of action with Cq and cross-resistance is possible, amodiaquine is still effective in vitro (Pradines 1998; Guiyedi 2001) and in vivo (Oliario 1996; van Dillen 1999; Brasseur 1999; Sowunmi 2001) in areas with a high level of Cq resistance. This might be partly explained by the fact that the concentration of amodiaquine in infected erythrocytes is higher than that of Cq (Hawley 1996). Although amodiaquine is available in Bayelsa state it is hardly used as first line treatment, since it is not recommended in Nigeria as first line treatment of falciparum malaria.

Amodiaquine is well-tolerated and no child had to be withdrawn from the study because of adverse effects. In our series, adverse effects occurred in only 4.5% of patients, which is a low figure compared to previous studies on other 4-aminoquiolines—pruritus in 27% (Sowunmi and Salako 1992), side effects in 10.7% (Oliario 1996), pruritus in 17%, vomiting in 6% (Brasseur 1999), pruritus in 10% (Sowunmi 2001). This may be due to the age of our study patients (mean 30 months) and/or their inability to express these symptoms. The haemoglobin levels increased rapidly after therapy with amodiaquine. This can be considered as another indicator for effective treatment (Ekvall 1998).

For follow-up, WHO recommends a 14- or 28-day protocol, the latter requires PCR-technique. The assessment of the therapeutic efficacy of Cq and amodiaquine was not done in parallel because the assessment on amodiaquine was an extension due to the satisfactory figures obtained with a chloroquine and sulphadoxine/pyrimethamine resistance study. However, the assessment on amodiaquine was conducted by the same team in the area, using an identical protocol and therefore we consider the results comparable.

Conclusion

Amodiaquine is an effective and alternative drug for treating falciparum malaria in a region with high resistance to Cq and SP. Unfortunately, most alternatives are too expensive (mefloquine), less safe (halofantrine) or not yet recommended for general use (lumefantrine). This study confirms that Amodiaquine may be an alternative, effective and cost-efficient drug for treating uncomplicated falciparum malaria. Before its general use is recommended in Nigeria or elsewhere additional studies in other areas are warranted and monitoring for the development of resistance of plasmodia against this drug should be maintained.

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