Therapeutic efficacy of sulfadoxine–pyrimethamine, amodiaquine and the sulfadoxine–pyrimethamine–amodiaquine combination against uncomplicated *Plasmodium falciparum* malaria in young children in Cameroon

Leonardo K. Basco,[1] Albert Same-Ekobo,[2] Vincent Foumane Ngane,[3] Mathieu Ndounga,[4] Theresia Metoh,[5] Pascal Ringwald,[6] & Georges Soula[7]

Objective To evaluate the therapeutic efficacy of sulfadoxine–pyrimethamine, amodiaquine, and the sulfadoxine–pyrimethamine–amodiaquine combination for the treatment of uncomplicated *Plasmodium falciparum* malaria in young children in Cameroon.

Methods In a randomized study we evaluated the effectiveness and tolerance of (i) sulfadoxine–pyrimethamine (SP) (25 mg/kg body weight of sulfadoxine and 1.25 mg/kg of pyrimethamine in a single oral dose), (ii) amodiaquine (AQ) (30 mg/kg body weight in three divided daily doses), and (iii) the sulfadoxine–pyrimethamine–amodiaquine combination (SP+AQ) (same doses as in the other two treatment groups, given simultaneously on day 0) in young children in southern Cameroon. The parasitological and clinical responses were studied until day 28 in accordance with the modified 1996 WHO protocol for the evaluation of the therapeutic efficacy of antimalarial drugs.

Findings Of 191 enrolled patients, 6 and 8 were excluded or lost to follow-up before day 14 and between day 14 and day 28, respectively. For the AQ-treated patients, parasitological and clinical evaluation on day 14 showed late treatment failure in 2 of 61 (3.3%) and adequate clinical response with parasitological failure in one (1.6%). There was an adequate clinical response in all patients treated with SP or SP+AQ. Therapeutic failure rates on day 28 were 13.6%, 10.2% and 0% in the SP, AQ, and SP+AQ groups, respectively. Anaemia improved in all three regimens. AQ produced faster fever clearance but was associated with more transient minor side-effects than SP. SP+AQ reduced the risk of recrudescence between day 14 and day 28 but increased the incidence of minor side-effects.

Conclusion SP+AQ can be recommended as a temporary means of slowing the spread of multidrug resistance in Plasmodium falciparum in Africa while the introduction of other combinations, including artemisinin derivatives, is awaited.

Keywords Malaria, Falciparum/drug therapy; Sulfadoxine/therapeutic use/administration and dosage; Pyrimethamine/therapeutic use/administration and dosage; Amodiaquine/therapeutic use/administration and dosage; Drug combinations/pharmacology; Drug resistance; Treatment outcome; Cameroon (*source: MeSH, NLM*).

Mots clés Paludisme Plasmodium falciparum/chimiothérapie; Sulfadoxine/usage thérapeutique/administration et posologie; Pyriméthamine/usage thérapeutique/administration et posologie; Amodiaquine/usage thérapeutique/administration et posologie; Association médicamenteuse/pharmacologie; Résistance aux médicaments; Evaluation résultats traitement; Cameroun (*source: MeSH, INSERM*).

Palabras clave Paludismo falciparum/quimioterapia; Sulfadoxina/uso terapéutico/administración y dosificación; Pirimetamina/uso terapéutico/administración y dosificación; Amodiaquina/uso terapéutico/administración y dosificación; Combinación de medicamentos/farmacología; Resistencia a las drogas; Resultado del tratamiento; Camerún (*fuente: DeCS, BIREME*).

Bulletin of the World Health Organization 2002;80:538-545.

Voir page 543 le résumé en français. En la página 544 figura un resumen en español.

Introduction

The spread of chloroquine-resistant *Plasmodium falciparum* malaria in Africa poses a serious challenge to the management of malaria infections, which is based on rapid diagnosis and treatment with suitable drugs. Chloroquine is no longer effective in Cameroon except in the northern provinces, i.e. there is a clinical and/or parasitological failure rate exceeding 25% on day 14 (*1–3*). Similar observations on the declining clinical efficacy of chloroquine have been reported with

[1] Researcher, Unité de Recherche Paludologie Afro-tropicale, Institut de Recherche pour le Développement, Laboratoire de Recherche sur le Paludisme, Organisation de Coordination pour la Lutte contre les Endémies en Afrique Centrale (OCEAC), Yaoundé, Cameroon.

[2] Professor, Laboratoire de Parasitologie, Faculté de Médecine, Université de Yaoundé I; and Department of Community Health, Ministry of Public Health, Yaoundé, Cameroon.

[3] Senior Technician, Ministry of Public Health, Yaoundé, Cameroon; and Laboratoire de Santé Publique, OCEAC, Yaoundé, Cameroon.

[4] Researcher, Centre d'Études sur les Ressources Végétales, Délégation Générale à la Recherche Scientifique et Technique, Brazzaville, Congo; and Laboratoire de Recherche sur le Paludisme, OCEAC, Yaoundé, Cameroon.

[5] Doctoral Student, Laboratoire de Parasitologie, Université de Yaoundé I; and Laboratoire de Recherche sur le Paludisme, OCEAC, Yaoundé, Cameroon.

[6] Medical Officer, Communicable Diseases, Surveillance and Response, Anti-infective Drug Resistance Surveillance and Containment, World Health Organization, Geneva, Switzerland.

[7] Medical Officer, Service de Coopération, Ministère français des Affaires Etrangères; and Laboratoire de Santé Publique, OCEAC, B.P. 288, Yaoundé, Cameroon (email: oceac@camnet.cm). Correspondence should be addressed to this author.

Ref. No. **01-1334**

increasing frequency from other African countries, notably in Central and East Africa (*4–6*).

Current options for the treatment of acute uncomplicated chloroquine-resistant *P. falciparum* infections in Africa include the use of amodiaquine (AQ) and sulfadoxine–pyrimethamine (SP). The choice of these drugs is based not only on their clinical efficacy but also on their affordability to the great majority of African patients, good tolerance, safety for young children, and low toxicity risk. Their high but not total clinical efficacy when used separately has been demonstrated in recent clinical trials conducted in chloroquine-resistant zones of Africa (*7–10*). The side-effects are well known and documented. Toxic reactions occur with each of them but are rarely associated with the standard therapeutic doses, and the clinical benefit derived from SP and AQ outweighs the risk of toxicity. Orally administered quinine is an alternative option and is generally reserved for patients who have failed to respond to chloroquine, AQ, and/or SP. Other available antimalarial drugs, such as mefloquine, halofantrine, artemisinin derivatives, lumefantrine, and atovaquone, are highly effective against chloroquine-resistant *P. falciparum* but do not satisfy all the above criteria and are not, therefore, indicated at present for the treatment of most malarial infections in Africa.

Because of the high prevalence of chloroquine-resistant *P. falciparum* malaria, several East African countries have adopted SP for the first-line treatment of uncomplicated malaria (*11*). Although this drug remains highly effective, some studies conducted recently in East Africa have reported treatment failures (*12–14*). In Yaoundé, Cameroon, a failure rate of 12% was observed in children aged over 5 years and in adults treated with SP and followed up for at least 14 days (*7*). These observations are in agreement with previous experience in South-East Asia, where SP is no longer effective (*15*, *16*). The rapid development of resistance to SP when the drug is employed on the national or regional scale is attributable to the requirement of few point mutations in the parasite's dihydropteroate synthase gene (for sulfadoxine) and dihydrofolate reductase gene (for pyrimethamine) (*17*).

Most malaria experts believe that AQ is still useful and effective in areas of low-grade chloroquine resistance (*18*). Cameroon has officially adopted the use of AQ in its antimalarial drug policy. Recent therapeutic monitoring at various sentinel sites in the country indicates that AQ has high efficacy in the treatment of falciparum malaria in children under 5 years of age (*3*). In fact, there is some evidence that AQ is less effective in areas where chloroquine resistance has attained a high level, essentially in Asia, and this has led to concerns about potential cross-resistance between chloroquine and AQ (*19–23*). In Yaoundé studies indicate that there was no treatment failure with AQ in children aged over 5 years or in adults, but parasitological failure was evident in 9 of 67 (13.4%) children aged under 5 years on day 14 (*7*, *24*). These observations raise the question as to how long SP and AQ, used alone, can remain effective in Africa.

One of the possible therapeutic strategies for prolonging the clinical efficacy of an antimalarial drug and reducing the risk of selecting drug-resistant malaria parasites is to use drug combinations (*25–27*). This strategy has been adopted in multidrug-resistant areas in South-East Asia, where mefloquine–sulfadoxine–pyrimethamine, which is no longer used, quinine–tetracycline, and mefloquine–artemisinin derivatives have been employed for first-line treatment. A similar strategy involving the use of drugs suitable for Africa is probably necessary in the face of the increasing prevalence of chloroquine resistance and the threat of resistance to SP. The aim of the present study was to assess the efficacy and tolerance of AQ and SP, alone and in combination, for the treatment of uncomplicated *P. falciparum* malaria in children aged under 10 years.

Methods

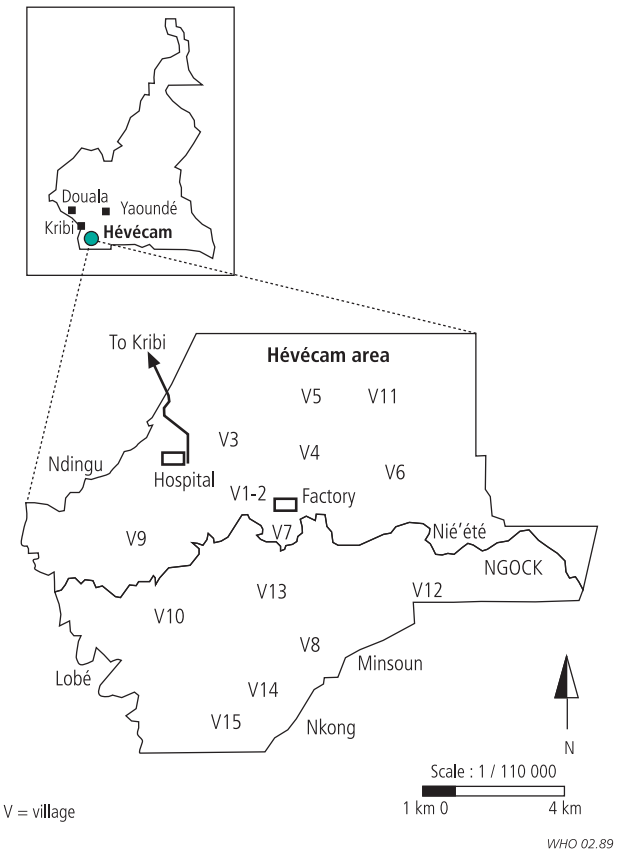
Study site

The clinical study was conducted from January to March 2001 in the rural district of Akom II in south-west Cameroon, about 350 km from Yaoundé (Fig. 1). The study site is located in the tropical rain forest area near the border with Equatorial Guinea. The population of Akom II is estimated to be 23 000, of whom about a quarter are employed in the rubber industry. The people are of various geographical and tribal origins, and there is a large presence of migrant workers originating from the north-west provinces or the far north of Cameroon. The district contains 15 villages, 14 of which had one dispensary each and the other, with the largest population, had two. When necessary, the dispensaries refer patients to a local secondary care hospital with 140 beds. Malaria transmission is intense and continuous throughout the year in the area. The health records indicate that malaria accounts for 40% of consultations, 60% of hospitalized patients, and 36% of mortality among hospitalized children.

Patients

Children aged under 10 years who presented with symptoms of acute malaria infection, a positive blood smear with a parasite

Fig. 1. **Maps of Cameroon and Akom II area showing location of study site**



density of at least 2000 asexual parasites/μl of blood, monoinfection with *P. falciparum*, a rectal temperature of at least 38.0 °C, and a haematocrit exceeding 15% were enrolled in the study after the free and informed consent of their parents or guardians was obtained. The following children were excluded: those who had signs and symptoms of severe and complicated malaria, as defined by WHO (*28*); those with severe malnutrition defined as body weight below –3 standard deviations of the WHO standard; and those with clinically evident concomitant infectious disease, a history of allergic reaction to sulfonamides, or for whom there was a potential problem with follow-up, e.g. if a trip outside the village was planned. The study was approved by the Ministry of Public Health.

Initial laboratory examination

The study children underwent a complete physical examination, including collecting samples of capillary blood by fingerpricking to prepare blood smears and determine haematocrit. Giemsa-stained thick blood smears were examined under the microscope, and asexual parasites were counted against 200 leukocytes. The parasite density was expressed as the number of asexual parasites per μl of blood by assuming a mean normal leukocyte count of 8000/μl of blood. Heparinized capillary blood was centrifuged for five minutes in order to evaluate the extent of anaemia.

Treatment regimens

The children were randomly assigned in blocks to receive (i) a single oral dose of SP (25 mg per kg body weight of sulfadoxine + 1.25 mg per kg body weight of pyrimethamine), (ii) oral AQ (total dose of 30 mg base per kg body weight in three equally divided daily doses) either as liquid suspension (2 mg per ml) or 200-mg tablets, or (iii) a combination of SP and AQ administered at the same dose as in (i) and (ii), respectively, with SP and the first dose of AQ being given simultaneously on day 0. All doses were administered under supervision and each patient's mouth was examined to ensure that the drugs had been swallowed. After drug ingestion the patients were observed for at least 30 min. Children who vomited during the observation period received the same repeat doses. The personnel who administered the doses were different from those who followed the patients up and examined the blood smears.

Children who exhibited early or late treatment failure with SP and/or AQ and those showing an adequate clinical response and parasitological failure on day 14 or day 28 were treated with oral quinine (25 mg base per kg body weight per day in three divided doses for five days), in accordance with the Cameroonian national guidelines on antimalarial treatment. In addition to antimalarial drugs, oral paracetamol was administered (50 mg/kg body weight per day in three divided doses) for fever exceeding 38.5 °C. In the event of concomitant bacterial infection that was absent on day 0 but present during the follow-up period, amoxycillin was administered at 50 mg per kg body weight per day for seven days.

Monitoring parasitological and clinical responses

Therapeutic efficacy was monitored using the modified 1996 WHO protocol (*29*). In the standard WHO protocol, patients' parasitological and clinical responses are observed on days 3, 7 and 14, and on any other day in the event of clinical aggravation. In our study the clinical response was monitored twice daily on an outpatient basis until day 2, once daily from day 3 to day 7, and on day 14 and day 28. Asexual parasites were counted against 1000 leukocytes. The parasitological response was monitored on days 2, 3, 7, 14 and 28. All patients were followed up by means of home visits.

Therapeutic efficacy was evaluated in relation to three criteria: (i) the fever clearance time, defined as the time taken to attain a rectal temperature below 38.0 °C; (ii) the proportion of negative thick smears on days 7, 14 and 28; and (iii) the number of early and late treatment failures. The clinical and parasitological responses were classified as early treatment failure, late treatment failure or adequate clinical response, in accordance with the WHO definitions (*29*). Early treatment failure is defined by one of the following criteria: positive smear and signs and symptoms of severe malaria on days 1, 2 or 3; positive smear (parasite density greater than that on day 0) and fever on day 2; positive smear and fever on day 3; or positive smear on day 3 (parasite density at least 25% of pretreatment density). Late treatment failure is defined by one of the following criteria: positive smear and signs and symptoms of severe malaria between days 4 and 14; or positive smear and fever between days 4 and 14. Adequate clinical response refers to one of two conditions in patients for whom the 14-day follow-up has been completed: negative smear on day 14, with or without fever; or positive or negative smear and apyrexia during follow-up, without previous fulfilment of the criteria for early treatment failure or late treatment failure.

Statistical analysis

On the basis of a previous study that we carried out in Yaoundé, we calculated that the minimum number of subjects per treatment group should be 50 in order to detect a reduction in the fever clearance time of at least 12 hours in the SP+AQ group, with a standard deviation of 18 and alpha and beta values set at 0.05 (unilateral test) (*7*). However, we increased this sample size by 10% in order to take account of individuals lost to follow-up. Enrolled patients who self medicated with another antimalarial drug and patients who were lost to follow-up were excluded from the analysis.

Qualitative variables were compared using either the χ^2 or Fisher's exact tests, and quantitative variables were compared by analysis of variance or the Kruskaul–Wallis test. The 95% confidence intervals of proportions were calculated using the exact binomial test and the level of significance (*P*) was fixed at 0.05 for all statistical tests. The data were analysed by means of EpiInfo (version 6.04d).

Results

Of the 191 study children who were enrolled in the study, 64 were allocated to the SP group, 62 to the AQ group, and 65 to the SP+AQ group. Clinical and parasitological monitoring was complete until day 14 for 185 children (97%) and until day 28 for 177 children (93%). Two patients were excluded because of concurrent infections, i.e. purulent otitis media on day 1 and measles on day 4, and four were lost to follow-up before day 14; two of these six patients were from the SP group, 1 was from the AQ group, and three were from the SP+AQ group. Two additional patients were excluded because of self medication with quinine on days 17 and 28, and six additional patients were lost to follow-up between day 14 and day 28; three of these additional patients were from the SP

group, two were from the AQ group, and three were from the SP+AQ group. The 10 patients lost to follow-up left their village for several weeks, mostly to return to their home provinces in north-western or northern parts of the country.

The characteristics of patients enrolled and followed up until day 14 are summarized by treatment group in Table 1. There was no statistically significant difference ($P > 0.05$) in any of the parameters. A total of 36 children (13 in the AQ group, 12 in the SP group, and 11 in the SP+AQ group) were aged 60–119 months. Although the WHO protocol specifies that the target population for the test of therapeutic efficacy comprises children under 5 years of age in an area of intense transmission, these 36 children were included because the study population largely consisted of a migrant population originating from areas of low transmission. A total of 26 children (14%) had hyperthermia (> 40 °C) before treatment. The WHO protocol sets a lower limit (38 °C) and an upper limit (40 °C) for body temperature in the inclusion criteria but these 26 patients (9, 9, and 8 in the SP, AQ and SP+AQ groups, respectively) were enrolled in our study because there were no danger signs. These hyperthermic patients were immediately given a rectal suppository of paracetamol. The WHO protocol also sets a lower limit of 2000 asexual parasites per µl and an upper limit of 100 000 asexual parasites per µl for inclusion; however, six patients with an initial parasitaemia exceeding 100 000 asexual parasites per µl were included in the study as there were no danger signs.

The clinical and parasitological responses of the study patients are presented in Table 2. The fever clearance time was significantly faster in the AQ and AQ+SP groups than in the SP group ($P < 0.05$). The therapeutic efficacy of the three regimens was equivalent when the clinical and parasitological responses were evaluated on day 14 ($P > 0.05$). Only two of 61 AQ-treated patients experienced late treatment failure and one patient showed an adequate clinical response with a positive smear, while all patients treated with either SP or SP+AQ showed an adequate clinical response with a negative smear on day 14. However, if clinical and parasitological evaluation was extended until day 28, late treatment failure between day 14 and day 28 and an adequate clinical response with a positive smear on day 28 were observed in the SP and AQ groups, but not in the SP+AQ group. In the latter group, all 59 patients remained apyretic and aparasitaemic until day 28. The SP+AQ combination was thus significantly more effective than either SP or AQ administered alone in obtaining an adequate clinical response with a negative smear on day 28 ($P < 0.05$).

All three treatment regimens resulted in the correction of pretreatment anaemia within two to four weeks (Fig. 2). Haematocrit had generally increased by 5–6% on day 14 and by 7–8% on day 28, with no significant difference between treatment regimens ($P > 0.05$). The predominant complaint was fatigue in patients treated with AQ, with or without SP (Table 3). Fatigue was not only more frequent but also more prolonged in these two treatment groups than in the SP alone group ($P < 0.05$). Patients who were treated with AQ, with or without SP, complained more frequently of headache and vomiting ($P < 0.05$). There was an increased frequency of pruritus in the AQ-treated groups but it was not significantly different from that in the SP group ($P = 0.069$). Three patients presented with a cutaneous reaction: dermatitis in the hip area on day 1 in an AQ-treated patient, diffuse urticaria on day 5 in an AQ-treated patient, and purulent vesicles in the thoracic region in an SP-treated patient.

Table 1. **Pretreatment clinical and laboratory characteristics of patients assigned to different treatment regimens**[a]

Parameter	SP group ($n = 62$)	AQ group ($n = 61$)	SP+AQ group ($n = 62$)
Age (months)			
Mean ± standard deviation (SD)	36.0 ± 20.5	35.2 ± 20.3	38.9 ± 25.0
Range	5–89	4–75	3–119
⩾5 years of age (%)	19.4	21.3	17.7
Sex ratio (M/F)	0.94	1.10	1.07
Duration of fever (days)			
Mean ± SD	2.48 ± 2.4	2.36 ± 1.9	2.53 ± 1.9
Range	0–14	0–7	0–7
⩾3 days (%)	37.1	37.7	38.7
Self-medication with antimalarial drug (%)	17.7	29.5	24.2
Body temperature (°C)			
Mean ± SD	38.8 ± 0.8	38.7 ± 0.8	38.9 ± 0.7
Range	38.0–40.5	38.0–40.6	38.0–40.6
38.0–39.9 °C (%)	85.5	85.2	87.1
⩾40 °C (%)	14.5	14.8	12.9
Parasite density (per µl blood)			
Range	2730–152 000	2670–213 000	3000–267 000
Geometric mean	12 820	16 220	16 820
⩾100 000/µl (%)	1.6	4.9	3.2
Haematocrit (%)			
Median	28	29	28
Range	17–36	15–39	17–38
15–25% (%)	16.1	18.0	25.8

[a] For all parameters there were no statistically significant differences ($P > 0.05$) between treatment groups. SP = sulfadoxine–pyrimethamine; AQ = amodiaquine; SP+AQ = sulfadoxine–pyrimethamine–amodiaquine combination.

Discussion

Experience in Asia suggests that resistance to SP and AQ is probably inevitable also in Africa as an increasing number of countries resort to these drugs for the first-line treatment of chloroquine-resistant *P. falciparum* malaria. Before resistance to chloroquine, AQ and SP increases in Africa, the use of the SP+AQ combination may be rational and viable while the introduction of other therapeutic options is awaited. The drugs in this combination complement one another. The relatively slow action of SP in clearing fever may be compensated by the rapid action of AQ, which has an anti-inflammatory effect. The modes of action and target sites of the drugs are different, and, although the resistance gene for AQ has not been identified, the mechanism of resistance also differs. Since multidrug resistance to antimalarials is still rarely encountered in Africa, it seems that there is a very low probability of being infected with an isolate that is simultaneously resistant to sulfadoxine, pyrimethamine and amodiaquine at the present time. This implies that the drugs in the combination therapy would mutually protect each other from isolates that are resistant to one of the components.

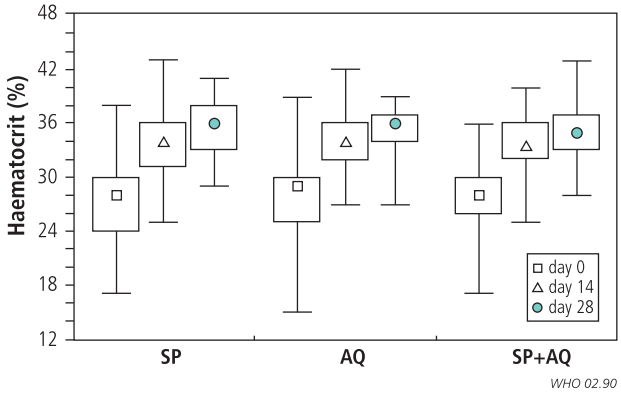
The results of the present study suggest the clinical benefit of combining SP and AQ for the treatment of acute uncomplicated falciparum malaria in young children residing in an area of intense transmission. This triple combination was

Table 2. **Clinical and parasitological response to sulfadoxine–pyrimethamine (SP) and amodiaquine (AQ), alone or in combination**

Parameter	SP group	AQ group	SP+AQ combination
Fever clearance time			
No. of patients with apyrexia on day 4	58	57	57
Mean (± standard deviation) (hours)	41.2 ± 20.0[a]	27.6 ± 12.2	28.4 ± 12.7
Range (hours)	14.7–94.0	13.7–72.5	13.7–70.2
Negative smears (%)			
Day 2	50.0	16.7[b]	38.7
Day 3	77.4	85.9	88.7
Day 7	100	98.4	100
Day 14	100	95.1	100
Day 28	89.7[a]	92.7[b]	100
Efficacy, day 14 (%)[c]			
No. of patients	62	61	62
ACR with negative smear	100 (94.2–100.0)[d]	95.1 (86.3–99.0)	100 (94.2–100.0)
ACR with positive smear	0	1.6 (0.04–8.8)	0
LTF	0	3.3 (0.4–11.3)	0
ETF	0	0	0
Efficacy, day 28 (%)			
No. of patients	59	59	59
ACR with negative smear	84.7 (73.0–92.8)[a]	86.4 (75.0–94.0)[b]	100 (93.9–100)
ACR with positive smear	1.7 (0–9.1)	3.4 (0.4–11.7)	0 (0–6.1)
LTF (day 14 to day 28)	13.6 (6.0–25.0)	10.2 (3.8–20.8)	0 (0–6.1)

[a] $P < 0.05$ when compared between SP and SP+AQ groups.
[b] $P < 0.05$ when compared between AQ and SP+AQ groups.
[c] ACR = adequate clinical response; LTF = late treatment failure; ETF = early treatment failure.
[d] Figures in parentheses are 95% confidence intervals.

Fig. 2. **Median haematocrit values and 25–75th percentiles by treatment group.** SP = sulfadoxine–pyrimethamine; AQ = amodiaquine; SP + AQ = sulfadoxine–pyrimethamine + amodiaquine combination. Bars represent range around median. There were no statistically significant differences ($P > 0.05$) between treatment groups.



more effective than each of the components administered alone and was well tolerated. Recent clinical studies conducted at several sites in southern Cameroon consistently showed that the prevalence of chloroquine-resistant *P. falciparum* had largely exceeded the 25% level (*3*). It is therefore of considerable value that, within the epidemiological setting of southern Cameroon, the SP+AQ combination remains totally effective in curing malaria-infected young children followed up until day 28.

Among previous studies on the SP+AQ combination, two were conducted in Mozambique (*30*, *31*). Their results cannot be compared directly with the present study because there was no comparison with SP and AQ administered singly and the enrolled subjects were asymptomatic. Furthermore, SP was administered with the last dose of AQ on day 2 in these studies. In a study conducted in the 1980s on Hainan Island, China (*32*), SP and AQ in a total dose of 25 mg/kg body weight were administered on day 0, as in our study, and a significantly shorter fever clearance time in the SP+AQ group was reported. However, the parasite clearance time did not differ significantly between treatment groups. On the basis of the meta-analysis of five evaluable studies on SP+AQ or chloroquine, it has been suggested that the fever clearance time is shorter with the combination therapy than with SP alone, that higher parasitological cure on day 28 is obtained with combination therapy, and that there is no evidence of serious side-effects when drug combinations are used (*33*).

Where there is a government-controlled system of drug supply, the cost of a complete curative dose of SP for an average adult weighing 60 kg is roughly equivalent to that of chloroquine, while AQ costs twice as much as chloroquine or SP. The SP+AQ combination would thus cost three times as much as chloroquine or SP alone. In a country where AQ is already used for the first-line treatment, such as Cameroon, the addition of SP for the SP+AQ combination therapy would increase drug costs by approximately 60%. By comparison, a five-day treatment with quinine tablets costs more than nine times as much as chloroquine therapy. In the private sector, the cost of 3 SP tablets and 20 chloroquine tablets is roughly the same (1.8 euro, ca US$ 1.6); also 12 AQ tablets cost 1.3 times more than 20 chloroquine tablets, taking into account that, in pharmacies, brand-named drugs are sold prepackaged and not by the exact number of tablets required by prescription. The approximate cost of the SP+AQ combination therapy in the private sector is about 2.3 times that of chloroquine but

Table 3. **Reported side-effects after sulfadoxine–pyrimethamine (SP) and amodiaquine (AQ) treatment, alone or in combination**

	No. in SP group ($n = 62$)	No. in AQ group ($n = 61$)	No. in SP+AQ combination group ($n = 62$)
Symptoms			
Fatigue	47 (75.8)[a, b]	54 (88.5)	59 (95.2)
Pruritus	3 (4.8)	8 (13.1)	9 (14.5)
Headache	0[b]	1 (1.6)	4 (6.5)
Dizziness	0	5 (8.2)	1 (1.6)
Vomiting	5 (8.1)[b]	10 (16.4)	14 (22.6)
Diarrhoea	4 (6.5)	4 (6.6)	9 (14.5)
Cutaneous eruption	1 (1.6)	2 (3.3)	0
Time for level of activity to increase (hours)			
Mean ± standard deviation	14.7 ± 23.5	33.4 ± 40.7[b]	26.7 ± 33.9
Range	0–120	0–168	0–120

[a] Figures in parentheses are percentages.
[b] Statistically significant difference ($P < 0.05$) between AQ and SP+AQ groups.

remains largely below the cost of quinine, halofantrine, artesunate, and co-artemether (3.2–4.5 times more expensive than chloroquine). Mefloquine is not registered for use in Cameroon. Cost-effectiveness analysis thus seems largely to favour the nationwide use of the SP+AQ combination in Africa.

If the SP+AQ combination is to be recommended for generalized use in Africa, it should be introduced immediately before a high rate of resistance to either component develops. In southern Cameroon the failure rate for the SP and AQ treatments, administered singly, is still low enough for the SP+ AQ combination to be recommended. In other countries a preliminary study is required in order to ascertain the level of therapeutic efficacy of each of these drugs administered separately to two different treatment groups, followed by a closely monitored clinical study on the SP+AQ combination. Clearly, there are insufficient recent clinical data on SP and AQ, alone or in combination, in many areas of Africa. The evaluation of their efficacy in different epidemiological settings should be a matter of priority. Nevertheless, the SP+AQ combination seems to be a safe, highly effective, relatively cheap, and viable therapeutic option that may be of immediate value and may ensure a more prolonged lifespan of these drugs in Africa. ■

Acknowledgements

We thank the patients and their parents or guardians for participating in the study and the managers of the Hévécam rubber company for facilitating our work. The study was supported by the Department of Cooperation, French Ministry of Foreign Affairs (Fonds d'Aide et de Coopération, mobilisateur paludisme) and Programme VIHPAL (coordinators: L. Basco and G. Soula), Action 2000, French Ministry of Research. Mathieu Ndounga and Theresia Metoh received a support grant from Programme VIHPAL.

Conflicts of interest: none declared.

Résumé

Efficacité thérapeutique de la sulfadoxine-pyriméthamine, de l'amodiaquine et de la sulfadoxine-pyriméthamine-amodiaquine contre l'accès palustre simple à *Plasmodium falciparum* chez le jeune enfant au Cameroun

Objectif Evaluer l'efficacité thérapeutique de la sulfadoxine-pyriméthamine, de l'amodiaquine et de la sulfadoxine-pyriméthamine-amodiaquine pour le traitement de l'accès palustre simple à *Plasmodium falciparum* chez le jeune enfant au Cameroun.

Méthodes Dans une étude randomisée, nous avons évalué l'efficacité et la tolérance de i) l'association sulfadoxine-pyriméthamine (SP) (25 mg/kg de poids corporel de sulfadoxine et 1,25 mg/kg de poids corporel de pyriméthamine en une dose orale unique), ii) l'amodiaquine (AQ) (30 mg/kg de poids corporel en trois prises quotidiennes) et iii) l'association sulfadoxine-pyriméthamine-amodiaquine (SP+AQ) (mêmes doses que dans les deux autres groupes de traitement, administrées simultanément au jour 0) chez le jeune enfant dans le sud du Cameroun. On a étudié les réponses parasitologiques et cliniques jusqu'au 28e jour, conformément au protocole OMS d'évaluation de l'efficacité thérapeutique des antipaludiques, modifié en 1996.

Résultats Sur les 191 malades recrutés pour l'étude, 6 ont été exclus ou perdus de vue avant le 14e jour et 8 entre le 14e jour et le 28e jour. Concernant les malades traités par l'AQ, l'évaluation parasitologique et clinique effectuée au 14e jour a montré un échec thérapeutique tardif chez 2 malades sur 61 (3,3 %) et une bonne réponse clinique accompagnée d'un échec parasitologique chez un autre (1,6 %). On a observé une bonne réponse clinique chez tous les malades traités par la SP ou la SP+AQ. Le taux d'échec thérapeutique au 28e jour était respectivement de 13,6 %, 10,2 % et 0 % dans les groupes SP, AQ et SP+AQ. L'anémie a reculé avec les trois schémas thérapeutiques. L'AQ a permis d'éliminer plus rapidement la fièvre, mais a été associée à des effets secondaires mineurs transitoires plus nombreux que la SP. La SP+AQ a diminué le risque de recrudescence entre le 14e et le 28e jour, mais augmenté l'incidence des effets secondaires mineurs.

Conclusion L'association SP+AQ peut être recommandée pour ralentir temporairement la propagation de la multirésistance chez *Plasmodium falciparum* en Afrique, en attendant l'introduction d'autres associations, notamment des dérivés de l'artésinine.

Resumen

Eficacia terapéutica de la sulfadoxina-pirimetamina, la amodiaquina y la combinación sulfadoxina-pirimetamina-amodiaquina contra los casos no complicados de paludismo por *Plasmodium falciparum* en niños pequeños en el Camerún

Objetivo Evaluar la eficacia terapéutica de la sulfadoxina-pirimetamina, la amodiaquina y la combinación sulfadoxina-pirimetamina-amodiaquina como tratamiento de los casos no complicados de paludismo por *Plasmodium falciparum* en niños pequeños en el Camerún.

Métodos Realizamos un estudio aleatorizado para evaluar la eficacia de los siguientes tratamientos y la tolerancia a los mismos: (*i*) sulfadoxina-pirimetamina (SP) (25 mg/kg peso corporal de sulfadoxina y 1,25 mg/kg de pirimetamina en una sola dosis oral), (*ii*) amodiaquina (AQ) (30 mg/kg peso corporal en tres dosis diarias), y (*iii*) la combinación sulfadoxina-pirimetamina-amodiaquina (SP+AQ) (las mismas dosis que en los otros dos grupos, administradas simultáneamente el día 0) en niños de corta edad del sur del Camerún. Se analizaron las respuestas parasitológicas y clínicas hasta el día 28 de acuerdo con el protocolo modificado de la OMS de 1996 para la evaluación de la eficacia terapéutica de los medicamentos antipalúdicos.

Resultados De los 191 pacientes que participaron en el estudio, 6 y 8 fueron excluidos o se perdieron durante el seguimiento antes del día 14 y entre los días 14 y 28, respectivamente. Entre los pacientes tratados con AQ, la evaluación parasitológica y clínica realizada el día 14 reveló que el tratamiento había fracasado en 2 de 61 (3,3%) pacientes, y que en un paciente (1,6%) la respuesta clínica había sido suficiente pero persistían los cambios parasitológicos. En los pacientes tratados con SP o SP+AQ se observó en todos los casos una respuesta clínica adecuada. Las tasas de fracaso terapéutico al día 28 fueron del 13,6%, 10,2% y 0% en los grupos tratados con SP, AQ y SP+AQ, respectivamente. La anemia mejoró en respuesta a los tres regímenes. La AQ eliminó más rápidamente la fiebre, pero se acompañó de más efectos secundarios transitorios leves que la SP. La combinación SP+AQ redujo el riesgo de recrudecimiento entre los días 14 y 28, pero se asoció a una mayor incidencia de efectos secundarios leves.

Conclusión La combinación SP+AQ puede recomendarse como una opción transitoria para frenar la propagación de la polifarmacorresistencia de *Plasmodium falciparum* en África a la espera de introducir otras combinaciones, entre ellas de derivados de la artemisinina.

References

1. Ringwald P, Bickii J, Basco L. Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet* 1996;347:24-8.
2. Ringwald P, Same Ekobo A, Keudjian A, Kedy Mangamba D, Basco LK. [Chemoresistance of *Plasmodium falciparum* in urban areas of Yaoundé, Cameroon. Part 1: Surveillance of in vitro and in vivo resistance of *Plasmodium falciparum* to chloroquine from 1994 to 1999 in Yaoundé, Cameroon]. *Tropical Medicine and International Health* 2000;5:612-9 (in French).
3. Soula G, Ndounga M, Foumane V, Ollivier G, Youmba JC, Basco L, et al. [Evaluation of the resistance of *Plasmodium falciparum* to chloroquine in Cameroon and alternative therapies]. *Bulletin de Liaison et de Documentation de l'OCEAC* 2000;33:13-22 (in French).
4. Falade CO, Salako LA, Sowunmi A, Oduola AM, Larcier P. Comparative efficacy of halofantrine, chloroquine and sulfadoxine-pyrimethamine for treatment of acute uncomplicated falciparum malaria in Nigerian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997;91:58-62.
5. Bloland PB, Ettling M. Making malaria-treatment policy in the face of drug resistance. *Annals of Tropical Medicine and Parasitology* 1999;93:5-23.
6. Premji Z, Makwaya C, Minjas J. Current clinical efficacy of chloroquine for the treatment of *Plasmodium falciparum* infections in urban Dar es Salaam, United Republic of Tanzania. *Bulletin of the World Health Organization* 1999;77:740-4.
7. Ringwald P, Keudjian A, Same Ekobo A, Basco LK. [Chemoresistance of *Plasmodium falciparum* in the urban areas of Yaounde, Cameroon. Part 2: Evaluation of the efficacy of amodiaquine and sulfadoxine-pyrimethamine combination in the treatment of uncomplicated *Plasmodium falciparum* malaria in Yaoundé, Cameroon]. *Tropical Medicine and International Health* 2000;5:620-7 (in French).
8. Nevill CG, Verhoeff FH, Munafu CG, ten Hove WR, van der Kaay HJ, Were JB. A comparison of amodiaquine and chloroquine in the treatment therapy of falciparum malaria in Kenya. *East African Medical Journal* 1994;71:167-70.
9. Müller O, van Hensbroek MB, Jaffar S, Drakely C, Okorie C, Joof D, et al. A randomized trial of chloroquine, amodiaquine and pyrimethamine-sulphadoxine in Gambian children with uncomplicated malaria. *Tropical Medicine and International Health* 1996;1:124-32.
10. Nwanyanwu OC, Ziba C, Kazembe P, Chitsulo L, Wirima JJ, Kumwenda N, et al. Efficacy of sulphadoxine/pyrimethamine for *Plasmodium falciparum* malaria in Malawian children under five years of age. *Tropical Medicine and International Health* 1996;1:231-5.
11. Bloland PB, Lackritz EM, Kazembe PN, Were JB, Steketee R, Campbell CC. Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa. *Journal of Infectious Diseases* 1993;167:932-7.
12. Trigg JK, Mbwana H, Chambo O, Hills E, Watkins W, Curtis CF. Resistance to pyrimethamine/sulfadoxine in *Plasmodium falciparum* in 12 villages in north east Tanzania and a test of chlorproguanil/dapsone. *Acta Tropica* 1997;63:185-9.
13. Warsame M, Kilimali VA, Wernsdorfer WH, Lebbad M, Rutta AS, Ericsson O. Resistance to chloroquine and sulfadoxine-pyrimethamine in *Plasmodium falciparum* in Muheza district, Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;93:312-3.
14. Nwanyanwu OC, Ziba C, MacHesso A, Kazembe P. Efficacy of sulfadoxine-pyrimethamine for acute uncomplicated malaria due to *Plasmodium falciparum* in Malawian children under five years old. *Tropical Medicine and International Health* 2000;5:355-8.
15. Wernsdorfer WH, Payne D. The dynamics of drug resistance in *Plasmodium falciparum*. *Pharmacology and Therapeutics* 1991;50:95-121.
16. Smithuis FM, Monti F, Grundl M, Oo AZ, Kyaw TT, Phe O, et al. *Plasmodium falciparum*: sensitivity *in vivo* to chloroquine, pyrimethamine/sulfadoxine and mefloquine in western Myanmar. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997;91:468-72.
17. Cowman AF. The mechanisms of drug action and resistance in malaria. In: Hayes JD, Wolf CR, editors. *Molecular genetics of drug resistance*. Amsterdam: Harwood Academic Publishers; 1997. p. 221-46.
18. Olliaro PL, Nevill C, LeBras J, Ringwald P, Mussano P, Garner P, et al. Systematic review of amodiaquine treatment in uncomplicated malaria *Lancet* 1996;348:1196-201.
19. Hall AP, Segal HE, Pearlman EJ, Phintuyothin P, Kosakal S. Amodiaquine-resistant falciparum in Thailand. *American Journal of Tropical Medicine and Hygiene* 1975,24:575-80.
20. Khaliq AA , Fox E, Sarwar M, Strickland GT. Amodiaquine fails to cure chloroquine-resistant *Plasmodium falciparum* in the Punjab. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1987;81:157-9.
21. Sapak P, Garner P, Baea M, Narara A, Heywood P, Alpers M. Ineffectiveness of amodiaquine against *Plasmodium falciparum* malaria in symptomatic young children living in an endemic malarious area of Papua New Guinea. *Journal of Tropical Pediatrics* 1991;37:185-90.

22. Misra SP, Nandi J, Lal S. Chloroquine versus amodiaquine in the treatment of *Plasmodium falciparum* malaria in northeast India. *Indian Journal of Medical Research* 1995;102:119-23.
23. van Dillen J, Custers M, Wensink A, Wouters B, van Voorthuizen T, Voorn W, et al. A comparison of amodiaquine and sulfadoxine-pyrimethamine as first-line treatment of falciparum malaria in Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;93:185-8.
24. Ollivier G, Ndounga M, Obatte J, Soula G, Ringwald L, Foumane V et al. [*Evaluation of the therapeutic efficacy of amodiaquine among infants aged 6 months to 5 years for the treatment of uncomplicated* Plasmodium falciparum *malaria in the Nlongkak (Yaoundé) integrated health centre*]. Yaoundé: OCEAC; 1999 (unpublished technical document 1065 OCEAC/LSP/1999).
25. Peters W. The prevention of antimalarial drug resistance. *Pharmacology and Therapeutics* 1990;47:499-508.
26. White NJ, Olliaro PL. Strategies for the prevention of antimalarial drug resistance: Rationale for combination chemotherapy for malaria. *Parasitology Today* 1996;12:399-401.
27. Kremsner PG, Luty AJF, Graninger W. Combination chemotherapy for *Plasmodium falciparum* malaria. *Parasitology Today* 1997;13:167-8.
28. World Health Organization. Severe falciparum malaria [*Severe and complicated malaria*, third edition]. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000;94 Suppl. 1:1-90.
29. *Assessment of therapeutic efficacy for uncomplicated falciparum malaria in areas with intense transmission*. Geneva: World Health Organization; 1996. Unpublished document WHO/MAL/96.1077; available from: http://whqlibdoc.who.int/hq/1996/WHO_MAL_96.1077.pdf
30. Schapira A, Schwalbach JFL. Evaluation of four therapeutic regimens for falciparum malaria in Mozambique. *Bulletin of the World Health Organization* 1988;66:219-26.
31. Dinis DV, Schapira A. Comparative study of the efficacy and side-effects of two therapeutic regimens against chloroquine-resistant falciparum malaria in Maputo, Mozambique. *Bulletin de la Société de Pathologie Exotique* 1990;83:521-8.
32. Huang Q, Ouyang WC, Zhou JX, Wu Z, Zhang KY, Huang JK, et al. Effectiveness of amodiaquine, sulfadoxine-pyrimethamine, and combinations of these drugs for treating chloroquine-resistant falciparum malaria in Hainan Island, China. *Bulletin of the World Health Organization* 1988;66:353-8.
33. McIntosh HM, Greenwood BM. Chloroquine or amodiaquine combined with sulfadoxine-pyrimethamine as a treatment for uncomplicated malaria: a systematic review. *Annals of Tropical Medicine and Parasitology* 1998;93:265-70.