Therapeutic efficacy of chloroquine and sulfadoxine/pyrimethamine against *Plasmodium falciparum* infection in Somalia

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Objective To assess the efficacy of chloroquine and sulfadoxine/pyrimethamine in the treatment of uncomplicated *Plasmodium falciparum* infections in Somalia.

Methods Patients with clinical malaria in Merca, an area of high transmission of the disease, were treated with the standard regimens of chloroquine (25 mg/kg) or sulfadoxine/pyrimethamine (25 mg sulfadoxine and 1.25 mg pyrimethamine per kg). Similar patients in Gabiley, an area of low transmission, received the standard regimen of chloroquine. The clinical and parasitological responses were monitored for 14 days.

Findings Chloroquine treatment resulted in clinical failure in 33% ($n = 60$) and 51% ($n = 49$) of the patients in Merca and Gabiley respectively. There were corresponding parasitological failures of 77% RII/RIII and 35% RII/RIII. Patients who experienced clinical failure had significantly higher initial parasitaemia than those in whom there was an adequate clinical response, both in Merca ($t = 2.2$; $P < 0.04$) and Gabiley ($t = 2.8$; $P < 0.01$). With the sulfadoxine/pyrimethamine treatment, 98% ($n = 50$) of the patients achieved an adequate clinical response despite a parasitological failure rate of 76% RII/RIII.

Conclusion Chloroquine should no longer be considered adequate for treating clinical falciparum malaria in vulnerable groups in the areas studied. Doubts about the therapeutic life of sulfadoxine/pyrimethamine in relation to malaria are raised by the high levels of resistance in the Merca area and underline the need to identify suitable alternatives.

Keywords Malaria, Falciparum/drug therapy; Chloroquine/therapeutic use; Sulfadoxine/therapeutic use; Pyrimethamine/therapeutic use; Antimalarials/therapeutic use; Drug resistance; Treatment outcome; Treatment failure; Somalia (*source MeSH, NLM*).

Mots clés Paludisme plasmodium falciparum/chimiothérapie; Chloroquine/usage thérapeutique; Sulfadoxine/usage thérapeutique; Pyriméthamine/usage thérapeutique; Antipaludique/usage thérapeutique; Résistance aux médicaments; Evaluation résultats traitement; Echec thérapeutique; Somalie (*source: MeSH, INSERM*).

Palabras clave Paludismo falciparum/quimioterapia; Cloroquina/uso terapéutico; Sulfadoxina/uso terapéutico; Pirimetamina/uso terapéutico; Antimaláricos/uso terapéutico; Resistencia a las drogas; Resultado del tratamiento; Insuficiencia del tratamiento; Somalia (*fuente: DeCS, BIREME*).

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Introduction

Chloroquine-resistant *Plasmodium falciparum* was first detected in Somalia in 1986, when resistance occurred in low frequency and degree in a semi-immune population (*1*). By 1989 the prevalence of chloroquine resistance had reached 30% and 70% among semi-immune and less immune populations, respectively (*2*, *3*). Resistance evidently developed more rapidly both in frequency and degree than in neighbouring Ethiopia, where it emerged at about the same time (*4*) and where the drug achieved a better response (*5*). In contrast, chloroquine resistance in Kenya reached high levels, forcing the abandonment of the drug as the first-line treatment for uncomplicated malaria (*6*).

The spread and intensification of resistance to antimalarials in Somalia has possibly been exacerbated by the conflict that has continued since 1991, causing the collapse of the health care infrastructure and the displacement of large numbers of people. The therapeutic usefulness of chloroquine therefore needs to be reassessed.

In all previous in-vivo studies the assessment of antimalarial drug responses was based solely on parasitological criteria. In areas of intense malaria transmission and high communal immunity, however, these criteria may be inadequate, and the clinical efficacy of commonly used antimalarials should be ascertained.

The purpose of this study is to assess the therapeutic efficacy of chloroquine and of sulfadoxine/pyrimethamine against uncomplicated falciparum infections in Somalia. The implications for malaria treatment are discussed.

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Methods

Study areas

The study was conducted between July and September 1997 in the Merca area of south Somalia and in the Gabiley area of the north-western region of the country. There is a mesoendemic pattern of malaria in the Merca area (*7*), which contains two large villages and three small ones, all located within a radius of 10 km. During 1997 this area experienced prolonged rains and flooding. In the Gabiley area, malaria transmission is low, seasonal peaks occurring after the rainy seasons in April and July. Low rainfall and drought often occur and the years with exceptionally heavy rains lead to malaria epidemics. This results in low or zero immunity in the population. As scarce rains and drought are common in the area, seasonal exacerbations leading to malaria epidemics occur.

Patients

Before enrolment a detailed history was obtained from adult patients or from the parents or guardians of child patients, and a physical examination was performed. Patients who were pregnant or who had severe malaria or other concomitant disease were excluded. Informed consent was obtained from the patients or their parents or guardians. The study was approved by the health authorities and village elders of the study areas. In the Gabiley area, the Ministry of Health and the Director of Planning approved the study, and the Head of Malaria Control was the team leader.

Patients were recruited in the villages of Wagade, Mushani and Malable in the Merca area and in a hospital outpatient department in the Gabiley area. The inclusion criteria were: symptoms compatible with clinical malaria with fever ($\geqslant$ 37.5 °C) or a history of fever within the previous 24–48 hours, monoinfection with *P. falciparum* and a parasite density of 1000 or more asexual parasites/μl, and no history of antimalarial intake for the previous two weeks. In the Merca area of high malaria transmission, 68 and 53 patients were recruited for chloroquine and sulfadoxine/pyrimethamine treatment respectively. Eight and three patients in the respective groups were excluded because they missed follow-up schedules. Five of the 54 patients from the Gabiley area of low malaria transmission were excluded for the same reason. Children accounted for one-third of the patients in the Gabiley area and for 90% of the chloroquine group in the Merca area (Table 1).

Treatment and follow-up

The efficacy of chloroquine was assessed at both sites and that of sulfadoxine/pyrimethamine was assessed only in the Merca area, by means of a modified WHO 14-day in-vivo protocol (*8*). The allocation of chloroquine or sulfadoxine/pyrimethamine to every patient in Wagade or Mushani was determined by tossing a coin, and individuals in Malable village were allocated one or other treatment (random allocation). Chloroquine (Pharmacia, Sweden) was administered at 10 mg per kg body weight on days 0 and 1, and at 5 mg per kg on day 2. Sulfadoxine/pyrimethamine (Hoffmann – La Roche, Switzerland) was given as a single dose at 25 mg sulfadoxine and 1.25 mg pyrimethamine per kg. All medications were given under supervision. The patients were monitored on days 0, 1, 2, 3, 7 and 14 for clinical responses, and on days 0, 3, 7 and 14 for parasitological responses. They were asked to report at any time if symptoms recurred. Thick blood smears were taken, stained with Giemsa's stain and read in accordance with the WHO protocol (*8*). The clinical responses were classified as follows: (i) *early clinical failure* if the symptoms persisted or deteriorated within the first three days in the presence of parasitaemia; (ii) *late clinical failure* if there was a recurrence of symptoms and fever with a measurable axillary temperature of 37.5 °C or above on the fourth day or later in the presence of parasitaemia; and (iii) *adequate clinical response* if the symptoms cleared within the first three days, irrespective of the presence of parasitaemia, and did not recur.

Table 1. **Baseline characteristics of patients in Gabiley and Merca areas**

Parameters	Gabiley area	Merca area	
	Chloroquine *n* = 49	Chloroquine *n* = 60	Sulfadoxine/ pyrimethamine *n* = 50
Children (number)	16	54	50
Mean age in years ± SD[a]	6.3 ± 4.0	4.8 ± 3.6	4.6 ± 3.0
Adults (number)	33	6	0
Mean age in years ± SD	28.33 ± 13.0	26 ± 9.1	NA[b]
Male (%)	57	45	60
Axillary temperature ⩾37.5 °C (%)	77.6	70.0	68.0
Parasitaemia			
Geometric mean parasite density	15 513 (7631–17 371)[c]	6507 (4332–9774)	3870 (2709–5528)

[a] SD = standard deviation.
[b] NA = not applicable.
[c] Figures in parentheses are 95% confidence intervals.

Parasitological failure was defined as the presence of asexual parasites on day 7 or day 14. The responses were classified as RIII or RII resistance if the parasite densities on day 3 were at least 25% or less than 25% respectively of the initial parasitaemia, i.e. on day 0, and remained positive on day 7, or as RI resistance if the parasitaemia cleared on day 7 but reappeared on day 14. The absence of parasitaemia on day 7 and day 14 was classified as the S response. Children who met the criteria for clinical failure were treated with an alternative drug and were not followed up again.

Statistical analysis

Geometrical means of parasite densities were calculated for persons with detectable asexual forms of *P. falciparum*. Proportions were compared by means of the χ^2 test with Yates' correction or by means of Fisher's exact test. Student's *t*-test was applied to continuous data.

Results

Clinical response

The treatment outcomes are summarized in Table 2. In the Merca area, 67% of the chloroquine group showed an adequate clinical response and 33% experienced an initial clinical improvement, followed by the recurrence of fever between day 7 and day 14, indicating late clinical failure. The six adults all achieved adequate clinical response. In the Gabiley area, 35% of the patients experienced early clinical

Table 2. **Clinical and parasitological responses of *P. falciparum* to chloroquine and sulfadoxine/pyrimethamine in Gabiley and Merca areas**

Responses	Gabiley area		Merca area			
	Chloroquine		Chloroquine		Sulfadoxine/ pyrimethamine	
	No.	(%)	No.	(%)	No.	(%)
Clinical						
Early clinical failure	17	34.7	0	0	0	0
Late clinical failure	8	16.3	20	33.3	1	2.0
Adequate clinical response	15	30.6	40	66.7	49	98.0
ACR/LCF[a]	9	18.4	0	0	0	0
Total	**49**	**100**	**60**	**100**	**50**	**100**
Parasitological						
S/RI[b]	20	40.8	14	23.3	12	24.0
RII[c]	14	28.6	36	60.0	29	58.0
RIII[d]	3	6.1	10	16.6	9	18.0
UNC[e]	12	24.5	0	0	0	0
Total	**49**	**100**	**60**	**100**	**50**	**100**

[a] Adequate clinical response or late clinical failure.
[b] Cleared parasitaemia or recurrence of parasitamia during follow-up.
[c] Parasitaemia on day 3 reduced to <25% of initial level and positive on day 7.
[d] Parasitaemia on day 3 reduced to ⩾25% of initial level and positive on day 7.
[e] Unclassifiable because of clinical deterioration on day 1 ($n = 9$) and day 2 ($n = 3$); received alternative medication before day 3.

failure, 16% had late clinical failure, and 31% showed an adequate clinical response. In the remaining nine patients, parasitaemia was higher on day 7 than on day 3 but the patients were not yet febrile. These nine patients were given alternative medication since it was considered unsafe to wait for the occurrence of clinical symptoms. There was no difference in clinical response between children and adults in the Gabiley area. In the Merca area there was an adequate clinical response in all patients except one in the sulfadoxine/pyrimethamine group.

Parasitological response

In the chloroquine treatment, 77% of infections in the Merca area showed RII/RIII responses, 12% showed the RI response, and only one showed the S response. The remaining six patients gave positive results on day 7 with low parasitaemia (mean = 292 asexual parasites/µl; 95% confidence interval (CI): 153–559) but negative results on day 14 in what was classified as a late S response. Of the six adults, two showed S/RI responses and four showed the RII response. In Gabiley, 35% of the infections exhibited RII/RIII responses, and 18% and 22% showed RI and S responses respectively. The parasitological responses of the remaining 12 subjects were unclassifiable, these patients having received alternative medication before day 3 because of deterioration in their clinical condition. There was no difference in parasitological response between children and adults in the Gabiley area. In the Merca group there were too few adults for a meaningful analysis to be made. Among the sulfadoxine/pyrimethamine group in the Merca area, 76% of the infections exhibited RII/RIII responses and three showed late S responses. The S and RI responses were combined since true recrudescence could not be differentiated from reinfection, and recrudescence after day 14 (late RI) could not be detected by the follow-up at 14 days.

In the Merca area, 58% and 60% of the chloroquine-treated patients with RII and RIII parasitological responses respectively achieved adequate clinical responses. However, no such clinical responses were associated with the RII and RIII infections in the Gabiley area. Of the 40 patients with adequate clinical responses in the Merca area, 83% were still parasitaemic on day 14, whereas only 27% of the 15 patients with similar responses in the Gabiley area were parasitaemic ($P < 0.001$, Fisher's exact test). Patients who experienced clinical failures had significantly higher initial parasitaemia than those who achieved adequate clinical responses, both in Merca ($t = 2.2$; $P < 0.04$) and Gabiley ($t = 2.8$; $P < 0.01$).

The outcome measures used in this study were compared with those of the WHO 14-day in vivo protocol for areas of intense transmission (*8*). Among the chloroquine-treated group in the Merca area, four and six patients from the late clinical failure and adequate clinical response groups respectively would have been classified as early treatment failures under the WHO criteria. Nine patients with adequate clinical responses to sulfadoxine/pyrimethamine would have been classified as early treatment failures. On day 3 the level of parasitaemia in all these patients was at least 25% of the initial value, a criterion for early treatment failure according to the WHO protocol.

Discussion

The standard regimen of chloroquine failed to produce adequate clinical responses in 33% and 51% of the patients in the Merca and Gabiley areas, respectively. In the Gabiley area over one-third of patients experienced early clinical failure, whereas there was no early clinical failure in the Merca area. In contrast, all the patients with clinical failure in the Merca area had experienced an initial clinical improvement, whether RI, RII or RIII infections were involved. This suggested that the clinical impact of chloroquine resistance was reduced by the relatively early development of immunity resulting from the intensive contact between humans and parasites which occurred in this area. The role of immunity in treatment outcome was underlined by the achievement of adequate clinical responses by some 60% of the chloroquine-treated patients with RII/RIII infections in the Merca area. This might also explain the phenomenon of the late S responders, in which some patients from the area were parasitaemic on day 7 but had become negative by day 14 without additional treatment, as reported by Barat et al. (*9*). Residual parasites, eventually cleared by the host's immune mechanism, might have been involved (*10*). The lack of age-related clinical and parasitological responses in the Gabiley area could be explained by the low exposure of the community to malaria. However, the opposite could be indicated by the clinical improvement achieved by all six adults in the Merca area, even though two-thirds of them showed RII responses. Besides immunity, the degree of initial parasitaemia seems to influence the clinical outcome of treatment.

The results demonstrated a dramatic increase in the frequency and degree of chloroquine resistance in the Merca area in comparison with a prevalence of 30% RII/RIII responses among asymptomatic subjects in 1989 (*2*). However, high levels of chloroquine resistance (70% RII/RIII)

among children and immigrants suffering from clinical malaria were reported from another part of the country in 1988 (*3*).

Although sulfadoxine/pyrimethamine produced an adequate clinical response in 98% of the patients, an ominously high degree of parasite resistance (76% RII/RIII) was observed. Similar clinical efficacy rates have been reported elsewhere in Africa but at much lower rates of parasitological failure (*9*, *11*, *12*). In the absence of a functioning treatment policy and regulatory systems, sulfadoxine/pyrimethamine was made easily accessible in Somalia, even for rural communities, through aid organizations and the private market. The high rate of parasitological failure in the Merca area is not, therefore, surprising, given the relatively long half-life of sulfadoxine/pyrimethamine, which is likely to exert undesirable pressure for a considerable time once its concentration drops below the critical threshold. Drug pressure associated with the widespread use of sulfa-based antibiotics, e.g. cotrimoxazole, for the treatment of bacterial infections might have added to the problem. Ronn et al. (*13*) observed high levels of sulfadoxine/pyrimethamine resistance in a Tanzanian community previously exposed to drug pressure from dapsone/pyrimethamine and sulfadoxine/pyrimethamine.

Our findings indicate that chloroquine should no longer be considered satisfactory for treating clinically manifest falciparum malaria in children, pregnant women and non-immune persons in the Merca and Gabiley areas. Malaria transmission is unstable in large parts of Somalia, resulting in little or no communal immunity. If suitable meteorological conditions were to occur, treatment failures could lead to devastating epidemics affecting all age groups (*3*). The obvious option for a first-line treatment in such circumstances would normally be that of sulfadoxine/pyrimethamine, which is already available and in use. However, the high level of RII/RIII sulfadoxine/pyrimethamine resistance reported here raises doubts about the therapeutic life span of the combination in the treatment of malaria. Continuous monitoring of its clinical efficacy in different parts of the country is therefore necessary. Chloroquine is being increasingly replaced by sulfadoxine/pyrimethamine in order to combat uncomplicated malaria in Africa but clinical failure following the use of this combination can be expected sooner or later. There is a clear need to look beyond sulfadoxine/pyrimethamine and to identify suitable alternatives. ■

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Conflicts of interest: none declared.

Résumé

Efficacité thérapeutique de la chloroquine et de la sulfadoxine/pyriméthamine contre l'infection à *Plasmodium falciparum* en Somalie

Objectif Evaluer l'efficacité de la chloroquine et de la sulfadoxine/pyriméthamine dans le traitement des infections non compliquées à *Plasmodium falciparum* en Somalie.

Méthodes Les patients atteints de paludisme clinique dans la région de Merca, où la transmission de la maladie est intense, ont été traités selon le schéma standard par la chloroquine (25 mg/kg) ou la sulfadoxine/pyriméthamine (25 mg/kg de sulfadoxine et 1,25 mg/kg de pyriméthamine). Des patients de mêmes caractéristiques mais dans la région de Gabiley, où la transmission de la maladie est faible, ont reçu le traitement standard par la chloroquine. La réponse clinique et la réponse parasitologique ont été suivies pendant 14 jours.

Résultats Le traitement par la chloroquine s'est soldé par un échec clinique chez 33 % des patients (n = 60) dans la région de Merca et 51 % des patients (n = 49) dans la région de Gabiley. Les taux d'échec parasitologique correspondants (RII/RIII) étaient respectivement de 77 % et 35 %. Chez les patients ayant présenté un échec clinique, la parasitémie initiale était significativement plus élevée que chez ceux ayant montré une réponse clinique satifaisante, aussi bien dans la région de Merca (t = 2,2 ; p<0,04) que dans celle de Gabiley (t = 2,8 ; p<0,01). Avec la sulfadoxine/pyriméthamine, 98 % des patients (n = 50) ont présenté une réponse clinique satisfaisante malgré un taux d'échec parasitologique (RII/RIII) de 76 %.

Conclusion Dans les régions étudiées, la chloroquine ne doit plus être considérée comme traitement adéquat du paludisme clinique à falciparum dans les groupes vulnérables. Les hauts niveaux de résistance observés dans la région de Merca soulèvent des doutes quant à la durée de vie thérapeutique de la sulfadoxine/pyriméthamine pour le traitement du paludisme et soulignent la nécessité d'identifier des alternatives convenables.

Resumen

Eficacia terapéutica de la cloroquina y la sulfadoxina/pirimetamina contra la infección por *Plasmodium falciparum* en Somalia

Objetivo Evaluar la eficacia de la cloroquina y la sulfadoxina/pirimetamina en el tratamiento de las infecciones por *Plasmodium falciparum* sin complicaciones en Somalia.

Métodos Se trató a pacientes con paludismo clínico de Merca, un área de alta transmisión de la enfermedad, con las pautas estándar de cloroquina (25 mg/kg) o sulfadoxina/pirimetamina (25 mg/kg de sulfadoxina y 1,25 mg/kg de pirimetamina). Se administró también el régimen ordinario de cloroquina a pacientes comparables de Gabiley, una zona de transmisión baja. La respuesta clínica y parasitológica se controló por espacio de 14 días.

Resultados El tratamiento con cloroquina no tuvo efecto clínico en el 33% (n = 60) y el 51% (n = 49) de los pacientes de Merca y Gabiley, respectivamente. Los casos correspondientes sin efecto parasitológico (fracasos RII/RIII) representaron el 77% y el 35%. Los pacientes que no respondieron clínicamente presentaron una parasitemia inicial significativamente mayor que la de quienes sí lo

hicieron, tanto en Merca ($t = 2,2$; $P < 0,04$) como en Gabiley ($t = 2,8$; $P < 0,01$). Con el tratamiento de sulfadoxina/pirimetamina, el 98% ($n = 50$) de los pacientes respondieron favorablemente a nivel clínico, pese al 76% de fracasos RII/RIII observado a nivel parasitológico.

Conclusión La cloroquina ha dejado de constituir una opción adecuada para tratar el paludismo clínico por *falciparum* entre los grupos vulnerables de las áreas estudiadas. Los altos niveles de resistencia observados en el área de Merca plantean dudas respecto a la vida terapéutica de la sulfadoxina/pirimetamina como agente antipalúdico y subrayan la necesidad de identificar alternativas adecuadas.

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