Efficacy of chloroquine and sulfadoxine/pyrimethamine mono- and combined therapy against falciparum malaria in Sudan

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نجاعة المداواة المفرَدة أو المشتركة بالكلوروكوين والسلفادوكسين/بيريميثامين ضد الملاريا المنجلية الخالية من المضاعفات في السودان

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الخلاصة: قام الباحثون بتقييم نجاعة المداواة المفرَدة بالكلوروكوين أو بالسلفادوكسين/بيريميثامين في عدة مواقع مخفرية في شمال السودان، وكذا نجاعة المداواة المشتركة بالعلاجَيْن معاً في منطقتَيْن من جنوب السودان. وقد شمل هذا التقييم المرضى بالملاريا المنجلية غير المترافقة بمضاعفات، والمعرضين لكثافة طفيلية وافية. وقد بلغت نسبة فشل الكلوروكين في المناطق الشمالية والمناطق الجنوبية 43.4٪ و80.2٪ على التوالي. وكانت معدلات فشل المعالجة في الأطفال أعلى بكثير من معدلاتها بين البالغين، في حين لم تشاهد فوارق يُعْتَدُّ بها بين الجنسين. أما نسبة الفشل الإجمالية للمعالجة المنفردة بالسلفادوكسين/بيريميثامين فبلغت 4.4٪، في حين بلغت نسبة فشل المداواة المشتركة بالدواءين معاً 14.5٪ و5.9٪ في المنطقتَيْن على الترتيب.

ABSTRACT We assessed the efficacy of chloroquine and sulfadoxine/pyrimethamine monotherapy in several sentinel sites in northern Sudan and the efficacy of combined therapy in 2 sites. Chloroquine efficacy in children under 5 years was also assessed in 2 sites in southern Sudan. Patients with indications of uncomplicated falciparum malaria and sufficient parasite density were enrolled. The chloroquine failure rates in the northern and southern sites were 43.4% and 80.2% respectively. Treatment failure was significantly higher in children than adults, while there was no significant sex difference. Sulfadoxine/pyrimethamine had an overall failure rate of 4.4%. Combination of the 2 drugs had a failure rate of 14.5% and 5.9% in the 2 sites.

Efficacité de la chloroquine et de la sulfadoxine/pyriméthamine en monothérapie et en association contre le paludisme à P. falciparum au Soudan

RÉSUMÉ Nous avons évalué l'efficacité de la chloroquine et de la sulfadoxine/pyriméthamine en monothérapie dans différents sites sentinelles dans le nord du Soudan et en association dans 2 sites. L'efficacité de la chloroquine chez l'enfant de moins de 5 ans a également été évaluée dans 2 sites situés dans le sud du Soudan. Ont été enrôlés dans cette étude des patients répondant à l'indication de paludisme à P. falciparum non compliqué et présentant une densité parasitaire suffisante. Les taux d'échec associés à la chloroquine dans les sites du nord et du sud étaient respectivement de 43,4 % et 80,2 %. L'échec thérapeutique s'est avéré significativement plus important chez l'enfant que chez l'adulte, mais il n'est apparu aucune différence significative liée au sexe. Avec la sulfadoxine/pyriméthamine, on a observé un taux d'échec global de 4,4 %. L'association des deux médicaments a obtenu respectivement un taux d'échec de 14,5 % et 5,9 % dans les 2 sites concernés.

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Introduction

Malaria is a global disease but most of the burden is in sub-Saharan Africa where falciparum malaria in particular affects young children and pregnant women [*1*]. Chloroquine has been the mainstay for malaria treatment for the past 40 years. However, its use has been severely limited by the emergence and spread of chloroquine resistance in most endemic regions, and few countries are unaffected [*2*]. Chloroquine resistance in Africa was first reported about 2 decades after it was first observed in south-east Asia, but within 10 years almost the whole area of distribution of *Plasmodium falciparum* was involved. This demonstrated the potential for the explosive spread of drug resistance where transmission was intense as in sub-Saharan, sub-Equatorial countries and east Africa. By 1985 chloroquine resistance affected 24 African countries including Sudan [*3*] and there is now no country in sub-Saharan Africa that has not reported chloroquine resistance. This suggests that the situation of multi-drug resistance that has been seen in South-east Asia may appear in Africa sooner rather than later. Hence Africa is potentially facing one of the greatest public health challenges [*3*].

In the Sudan a *P. falciparum*-resistant strain was first observed in the irrigated area of Gezira in 1979 and later reported in Sennar in 1983 [*4*] and Khartoum in 1983 [*5*], which was later confirmed by *in vitro* testing [*6*], and in Gedaref in 1985. Chloroquine resistance was reported from 5 sentinel sites in 2001 [*7*] and from 16 sentinel sites distributed in 10 states in the country in activities supervised by the National Malaria Control Programme during the period 1997–2001 [Monira K, Omer B. unpublished report, 2001]. In brief, numerous studies on chloroquine resistance have been conducted in Sudan in different areas, the results of which show varying degrees of chloroquine resistance mostly ranging from 30% to 80%. As a result of all previous experience in monitoring antimalarial drug efficacy, it is clear that there is an urgent need to establish a system for continuous monitoring of antimalarial drug resistance in order to provide adequate time to allow national authorities to formulate satisfactory treatment guidelines [*8*]. Chloroquine and sulfadoxine/pyrimethamine have been respectively the first- and second-line treatment drugs for uncomplicated *P. falciparum* malaria in Sudan according to the 1998 protocol. This study was conducted to assess the therapeutic efficacy of these lines of treatment for uncomplicated *P. falciparum* malaria in the country and to provide data needed to update treatment guidelines in the country.

Methods

Study area

The study was conducted during the transmission season, August to December of 2002/2003. Sudan is characterized by 2 main areas according to the type of transmission, low/moderate transmission in the relatively dry north, and intense transmission in the more humid South. Total population is about 30.3 million residing in an area of 2.5 million km^2.

The first phase of the study was carried out during 2002 to assess chloroquine efficacy in 5 sentinel sites in the northern regions of the country (Damazin, Medani, Kosti, Obeid and Khartoum). About 80% of the country's population lives in these areas and the transmission is seasonal or unstable following the rainy season. The acquired immunity of the communities living in these areas is considered to be low and leads to disease outbreaks (epidemic-prone area).

The second phase of the study was conducted in the same area to assess sulfadoxine/pyrimethamine efficacy in 4 sentinel sites [Medani, Obeid, Kassala and Damazin (2 arms sulfadoxine/pyrimethamine versus chloroquine and sulfadoxine/pyrimethamine) and also in Khartoum (2 arms chloroquine versus chloroquine and sulfadoxine/pyrimethamine)]. During the same time, chloroquine alone was tested in 2 sites in Juba and Malakal in southern Sudan where approximately 20% of the country's population lives. The communities residing in this area are considered to have high acquired immunity, no epidemics occur and the transmission is stable throughout the year due to the long rainy season.

All of the above-mentioned sites were selected according to World Health Organization (WHO) criteria of selection to fulfil the needed requirements in representing all malaria endemicity in the whole country. All of these selected sites are permanent sites for continuous monitoring of antimalarial drugs resistance, according to the national plan of action approved by the WHO [*9*].

Study population

Inclusion criteria for enrolment of patients in the South (Juba and Malakal) were: children between 6 and 59 months of age, presenting with fever, all signs compatible with uncomplicated malaria, *P. falciparum* monoinfection with parasite density between 2000 and 200 000 asexual parasites/μL. In the other sites in north and central Sudan (Medani, Damazin, Obeid, Kassala and Khartoum) the study targeted patients over 6 months (all ages) with fever or a history of fever in the last 24 hours after excluding other causes of fever, falciparum monoinfection with parasite density between 1000 and 100 000 asexual parasites/μL). Willingness to be followed up and informed consent from the patient or patient's guardian in the case of children were also considered. All patients who did not fulfil the inclusion criteria were excluded, including patients with signs and symptoms of severe malaria or danger signs (inability to drink or breastfeed, vomiting, recent history of convulsion, lethargy or unconsciousness and inability to sit and stand), those with febrile illness other than malaria and pregnant women. The study design was a simple prospective evaluation of clinical and parasitological response to directly observed treatment for uncomplicated malaria [*9*].

Treatment and follow-up of patients

All patients were screened and blood samples examined microscopically using Giemsa stain thick and thin blood smears. The parasite count was determined per 200 white blood cells (at × 40 magnification) and expressed as parasites/μL. Patients who met all of the inclusion criteria were enrolled in the study.

Treatment was calculated according to body weight and given by the medical team directly. Good quality drugs supplied by WHO were used at the standard, recommended dose.

The patients were followed up closely during scheduled days and during any other day if the patient felt unwell. Duration of follow-up depended on transmission with a longer duration of follow-up in low transmission areas and shorter duration in high transmission areas. Thus in the north, the patients were followed for 28 days and in the south they were followed for 14 days.

Classification of treatment outcome

All patients' data were entered on a case report form. This included all clinical and parasitological information and observations of the medical personnel.

Response to treatment was classified by standard methods using WHO protocol [*9*]. The patients were classified as: early

treatment failure, late clinical failure, late parasitological failure, and adequate clinical and parasitological response. Further classifications were: loss to follow-up and withdrawal. Loss to follow-up described patients who were enrolled and participated at the start but who could not be traced during the follow-up period, despite all efforts of the medical team. Withdrawal described patients who ended their participation voluntarily, or who developed any concomitant febrile illness during the study which would interfere with the classification of their outcome. Full description of these 2 categories and their reason for ending the study is available in the case report form.

Further analysis was performed by *Epi-Info*, version 6. The chi-squared test was calculated for comparison by sex and age group. $P \leq 0.05$ was considered significant.

Ethical considerations

In the present study the tests were conducted under the direct supervision of qualified medical personnel and at all times during the study the safety and welfare of each individual patient was the priority over their continuation in the study.

Results

In the first phase of study assessing chloroquine efficacy in 2002 in Medani, Damazin, Obeid, Kosti and Khartoum, 9102 patients were examined, 967 of whom were positive for *P. falciparum* malaria (slide positivity rate = 10.6%) (Table 1). The majority were excluded due to low parasite count of less than 1000 parasites/μL. Patients who did not want to participate in the study from the start were also excluded and others were excluded for clinical reasons. Thus only 155 patients met all the inclusion criteria and were enrolled in the study. There were 3 patients who were lost to follow-up or withdrew (1.9%) so in the end 152 patients were classified for treatment outcome. Patients enrolled ranged in age from 1.0 to 70 years.

The total treatment failure rate of chloroquine in the above-mentioned sites (except Khartoum which failed to record any cases at the time of the study) was 43.4% ranging from 38.9% in Medani to 53.3% in Kosti. Treatment failure was found to be highly significant in children ($P = 0.02$) compared to adults while there was no significant sex difference ($P = 0.84$).

In the second phase, a total of 4207 patients with fever or history of fever were screened (Table 2). Of these, 1085 were positive for *P. falciparum* monoinfection (slide positivity rate = 25.8%). Of the slide-positive patients, 526 were enrolled in different sentinel sites, and were treated with either chloroquine or sulfadoxine/pyrimethamine alone or in combination (chloroquine + sulfadoxine/pyrimethamine). Thus chloroquine was tested in Juba and Malakal where 308 children were examined and 239 were found positive for *P. falciparum* (slide positivity rate = 77.6%). Of these, 113 met all of the inclusion criteria and were enrolled in the study but 7 (6.2%) were lost to follow-up or withdrew. Total chloroquine failure rate in Juba and Malakal was very high indicating the highest level of resistance (80.2%), 80.0% in Juba, 80.4% in Malakal.

Sulfadoxine/pyrimethamine was tested in Damazin, Obeid, Medani and Kassala. A total of 1917 patients were screened, 564 of them were positive for *P. falciparum* malaria (slide positivity rate = 29.4%). Of these patients, 204 met all of the inclusion criteria and were enrolled but 4 (2.0%) were lost to follow-up or withdrew. Sulfadoxine/pyrimethamine total failure rate was 4.4% ranging from 2% in central Sudan (Medani) to 7.7% at the border with Eritrea and Ethio-

pia (Kassala). Patients enrolled ranged in age from 0.75 years to 80 years.

Of 1837 patients in Khartoum, 184 were positive for *P. falciparum* malaria (slide positivity rate 10.0%). Only 139 met the inclusion criteria and were enrolled in the study; 70 were assigned to receive chloroquine alone and 69 to receive chloroquine + sulfadoxine/pyrimethamine. Failure rates with the 2 treatments were 51.4% and 14.5% respectively. In Damazin there were 316 patients of whom 228 were positive for *P. falciparum* malaria (slide positivity rate 72.2%). Of these, 120 met the inclusion criteria and were enrolled; 50 were assigned to receive sulfadoxine/pyrimethamine alone and 70 to receive chloroquine + sulfadoxine/pyrimethamine. Failure rates with the 2 treatments were 4.0% and 5.9% respectively. The total failure rate for chloroquine + sulfadoxine/pyrimethamine for both Khartoum and Damazin was 10.2%

Comparisons between age categories and sex versus treatment outcome with chloroquine are summarized in Tables 3 and 4. Treatment failure was significantly higher in children than adults, 68.2% and 31.8% respectively ($P < 0.0001$) but there was no significance difference between males and females ($P = 0.9$).

Discussion

Chloroquine, the cheapest and the most readily available antimalarial drug, is still used as the first line of treatment for uncomplicated malaria in almost all African countries, including Sudan, despite varying levels of resistance [*10,11*]. This is probably because of the poor economic situation in most African countries because the newer drugs are expensive, and also because of the justifiable fear of the development of resistance to the new drugs in the future. To take further action in updating drug policy, all

Table 1 Therapeutic response to chloroquine by study area

Study area	Total no. of cases	No. +ve for P. falciparum	No. enrolled	Lost to follow-up or withdrew		ACPR		ETF		LCF		LPF		Total failure	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Medani	6653	198	55	1	1.8	33	61.1	10	18.5	7	13.0	4	7.4	21	38.9
Damazin	90	55	33	1	3.0	18	56.3	10	31.3	0	0.0	4	12.5	14	43.8
Obeid	705	646	51	0	0.0	28	54.9	13	25.5	4	7.8	6	11.8	23	45.1
Kosti	554	64	16	1	6.3	7	46.7	4	26.7	3	20.0	1	6.7	8	53.3
Khartoum	1100	4	–	–	–	–	–	–	–	–	–	–	–	–	–
Total	9102	967	155	3	1.9	86	56.6	37	24.3	14	9.2	15	9.9	66	43.4

ACPR = adequate clinical parasitological response.
ETF = early treatment failure.
LCF = late clinical failure.
LPF = late parasitological failure.

Table 2 Therapeutic response of chloroquine (CQ), sulfadoxine/pyrimethamine (SP) and CQ+SP by study area

Study area	Total no. of cases	No. +ve for P. falciparum	No. enrolled	Drug given	Lost to follow up or withdrew		ACPR		ETF		LCF		LPF		Total failure	
					No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Juba	143	109	53	CQ	3	5.7	10	20.0	21	42.0	8	16.0	11	22.0	40	80.0
Malakal	165	130	60	CQ	4	6.7	11	19.6	25	44.6	9	16.1	11	19.6	45	80.4
Obeid	253	123	50	SP	2	4.0	46	95.8	1	2.1	0	0.0	1	2.1	2	4.2
Medani	1161	126	52	SP	2	3.8	49	98.0	1	2.0	0	0.0	0	0.0	1	2.0
Kassala	332	185	52	SP	0	0.0	48	92.3	0	0.0	2	3.8	2	3.8	4	7.7
Damazin	316	228	50	SP	0	0.0	48	96.0	0	0.0	0	0.0	2	4.0	2	4.0
Damazin			70	CQ+SP	2	2.9	64	94.1	2	2.9	1	1.5	1	1.5	4	5.9
Khartoum	1837	184	70	CQ	0	0.0	34	48.6	21	30.0	13	18.6	2	2.9	36	51.4
Khartoum			69	CQ+SP	0	0.0	59	85.5	7	10.1	3	4.3	0	0.0	10	14.5
Total	4207	1085	526	–	13	2.5	369	71.9	78	15.2	36	7.0	30	5.8	144	28.1

ACPR = adequate clinical parasitological response.
ETF = early treatment failure.
LCF = late clinical failure.
LPF = late parasitological failure.

Table 3 Treatment outcome of chloroquine by age category

Age category	Adequate clinical response		Treatment failure	
	No.	%	No.	%
Children	27	31.4	45	68.2
Adult (> 15 years)	59	68.6	21	31.8
Total	86	100.0	66	100.0

$\chi^2 = 20.9$, $P < 0.0001$.

malaria control programmes must weigh the cost–effectiveness of using cheap but often ineffective drugs compared to expensive but effective ones.

Our study showed that the chloroquine failure rate was 42.6% in northern and central Sudan and even higher in the southern part of the country where the total failure rate was 80.2%. These findings are consistent with results obtained earlier in Sudan, in a study conducted in Western Equatorial province [*12*] and also with a molecular study carried out in Bahr Elgazal in which they expected high levels of chloroquine resistance and predicted efficient treatment with sulfadoxine/pyrimethamine [*13*], as well as in a study carried out in 2001 [*14*]. Furthermore, a study in Kenya and Malawi indicated that chloroquine was no longer adequate for treatment of uncomplicated falciparum malaria [*2*], in some parts of Asia, such as Laos, the chloroquine failure rate has been reported to be 44.6% [*15*] and in Punjab, results showed a failure rate of 40% among Afghan refugees [*16*].

There are many factors that accelerate drug resistance, such as overuse when the drug is used alone extensively, poor compliance with drug treatment (missed use or irrational use) as a result of ignorance, or irrational prescribing due to poor training of physicians. Other factors include the intensity of transmission, population immunity and population movements [*2*].

In the present study, it is of interest that treatment failure was significantly higher in children than adults and chloroquine treatment failure was 68.2% and 31.8% respectively. This concurs with findings previously obtained in Sudan [*7*]. This is probably due to acquired immunity in adults while children have low acquired immunity in comparison. Age has been found to be a crucial factor in developing acquired immunity and also plays a vital role in severity of the disease. The degree of exposure of a population to the parasite in endemic areas seems to correlate broadly with age distribution in accordance with clinical symptoms and development of the immunity. This is a very strain-specific process that requires sufficient time for the host to develop that immunity [*17*]. We found no sex variation and the male/female distribution in treatment failure was almost the same.

It is currently believed that the increased rate of resistance exceeds the rate at which new antimalarial drugs are being developed. Changing the first-line drug too early will adversely affect all drugs, yet delay to change could be also catastrophic [*2*]. The question is at what level of chloroquine resistance should a malaria control programme change the first-line drug to a more effective one? It is currently thought to be 25% or less [*3*]. In addition to the results

Table 4 Treatment outcome of chloroquine by sex

Sex	Adequate clinical response		Treatment failure	
	No.	%	No.	%
Female	45	52.3	35	53.0
Male	41	47.7	31	47.0
Total	86	100.0	66	100.0

$\chi^2 = 0.01$, $P = 0.9$.

of efficacy studies, the perception of patients and clinicians about the drug must be considered in changing the drug policy in a country [*2*]. In the present study, on testing chloroquine efficacy during 2002, many patients withdrew from the start because they believed that chloroquine was an ineffective drug, the majority were excluded due to low parasitaemia and others for clinical reasons. In addition, the site at Khartoum failed to collect data because no malaria patients were identified (at the time of the study) because of the activities of a free malaria initiative in the state sponsored by WHO. All of these factors were considered contributory factors to reducing the sample size of the enrolled patients concerning chloroquine in central Sudan.

In many endemic regions, the failure of chloroquine against *P. falciparum* has led to its replacement by sulfadoxine/pyrimethamine, which is the second line drug recommended by the malaria control programmes in most antimalarial drugs policies in the vast majority of African countries.

The replacement of chloroquine by sulfadoxine/pyrimethamine has led to the rapid selection of resistance to this drug in many areas of the world, including tropical Africa, due to its relatively long half-life compared with chloroquine [*18*]. In a study in Tanzania, poor therapeutic response was obtained when sulfadoxine/pyrimethamine was tested in children as a result of various contributory factors, the most important of which was the drug pressure from a prophylactic intervention [*19*].

Our study clearly showed that while chloroquine is failing as a first line drug in treating uncomplicated falciparum malaria infections in both low transmission areas in north Sudan and in intense transmission areas in south Sudan, sulfadoxine/pyrimethamine was still effective, with resistance ranging from 2% (Medani, central Sudan) to 7.6% (Kassala near the border) which may be explained by the fact that Kassala borders of Eritrea and Ethiopia. Our findings are consistent with other findings obtained before in Somalia which showed that chloroquine is no longer adequate for treating *P. falciparum* infections [*20*]. Similarly a study in Pakistan showed that resistance to sulfadoxine/pyrimethamine occurred at much lower rates ranging from 4% to 25% as compared to chloroquine at 18% to 62% [*21*]. A study conducted in adult patients in Cameroon infected by *P. falciparum* and treated with sulfadoxine/pyrimethamine demonstrated that, *in vivo*, one or two dihydrofolate reductase mutations (moderate pyrimethamine resistance) and wild-type dihydropteroate synthase did not affect clinical curing by sulfadoxine/pyrimethamine, most probably due to the synergistic action of the drug [*22*].

In all tests with sulfadoxine/pyrimethamine alone we observed that the drug was accompanied by an increase in gametocytes carriage (the infectious stage) in the great majority, if not all, of patients, which is similar to other studies [*23,24*]. This is a disadvantage as is the rapid development of resistance if sulfadoxine/pyrimethamine is used alone. Therefore sulfadoxine/pyrimethamine is recommended by WHO to be used in combination therapy, especially with artemisinin derivatives because these derivatives have many unique properties, such as the reduction of gametocyte carriage, rapid resolution of the parasites biomass and delay of resistance of the partner drug [*25*]. This approach of combination treatment has been adopted for cancer chemotherapy and, more recently, for treatment of AIDS. To treat tuberculosis or AIDS with a single drug is no longer regarded as ethical and the same practice should be applied to the treatment of malaria [*26*].

Regarding the combined use of chloroquine and sulfadoxine/pyrimethamine, resistance was relatively high which suggests that combination therapy is not useful with chloroquine because it is already an ineffective drug and cannot protect any partner drug, even the new antimalarial drugs such as artemisinin derivatives. Chloroquine is therefore not recommended to be used in any sort of combination [*25*].

Conclusion

Our study confirms that chloroquine should no longer be used as a first line drug to treat uncomplicated falciparum malaria due to the high level of resistance. In fact, a new antimalarial drug policy was introduced in 2004 in which artemisinin-based combination therapy was recommended by the National Technical Advisory Committee. The policy adopted sulfadoxine/pyrimethamine plus artesunate as first-line treatment and artemether/lumefantrine as a second-line for treatment of uncomplicated falciparum malaria. However, periodic monitoring of antimalarial drug treatment is needed to assess the effectiveness of drugs and the possible development of resistance.

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