Double-blind study to assess the efficacy of chlorproguanil given alone or in combination with chloroquine for malaria chemoprophylaxis in an area with *Plasmodium falciparum* resistance to chloroquine, pyrimethamine and cycloguanil

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Abstract

In this study the efficacy of chlorproguanil (20 mg base weekly) was compared in schoolchildren with that of chloroquine (200 mg base weekly) and that of both drugs combined (20 mg base + 200 mg base weekly). The double blind trial was performed in the rice field area of the Ruzizi valley in Burundi, where *Plasmodium falciparum* is widely resistant to chloroquine, and where pyrimethamine resistance with cycloguanil cross-resistance had been demonstrated. After 17 weeks, when the trial was ended, 60% breakthroughs had been observed among the children taking chloroquine, 72% among those under chlorproguanil and 61% among those under chlorproguanil and chloroquine. In children weighing between 15 and 24 kg, the failure rate was signficantly higher in those treated with chlorproguanil than in the group treated with chloroquine. No difference in efficacy was observed in children weighing 25 to 39 kg. There was no significant increase of efficacy when chlorproguanil was given in association with chloroquine. The mean titre of fluorescent antibodies was the same in each treated group on week 5 and week 15. The comparison of these data with the infection rates in non-protected children suggests that malaria could not be prevented with any of the drug regimens utilized in the study.

Introduction

In malarious endemic zones where resistance of *Plasmodium falciparum* to chloroquine occurs, it is becoming more and more difficult to advise on an efficient drug regimen for malaria chemoprophylaxis.

The superior efficacy of amodiaquine over chloroquine (SCHMIDT *et al.*, 1977; WHO, 1973), also confirmed in chloroquine-resistant *P. falciparum* infections in the field (WATKINS *et al.*, 1984; SPENCER *et al.*, 1984), led to the recommendation of replacing chloroquine with amodiaquine for chemoprophylaxis in areas with chloroquine-resistant *P. falciparum* (WHO, 1985). The recent reports of agranulocytosis and liver damage induced by amodiaquine when given for prophylaxis (HATTON *et al.*, 1986; NEFTEL *et al.*, 1986) prompted another recommendation for the discontinuation of this drug as a chemosuppressant (WHO, 1986).

Severe, sometimes lethal cutaneous reactions have been observed with the use of the combination of sulphadoxine/pyrimethamine (Fansidar^{R}) (MILLER *et al.*, 1986), and the discontinuation of the utilization of the drug for chemoprophylaxis has been recommended (WHO, 1985; CDC, 1985).

A few cases of agranulocytosis have been reported when the combination of dapsone/pyrimethamine (Maloprim^{R}) was administered at weekly doses of 100 mg dapsone and 12·5 mg pyrimethamine (one tablet), as adult dosage (BENGTSSON, 1979; WOODRUFF *et al.*, 1980); this toxic effect is much more common when the weekly dose is doubled (BRUCE-CHWATT & HUTCHINSON, 1984).

The biguanides, proguanil (Paludrine^{R}) or chlorproguanil (Lapudrine^{R}), on the other hand, which have remarkably few side effects, have been recommended in recent years from different authoritative sources (Public Health Laboratory Service, 1983; OLSEN, 1983; ROMBO *et al.*, 1983).

The purpose of this study was to measure the prophylactic efficacy of chlorproguanil, given at weekly intervals either alone or in combination with chloroquine and compare it with that of chloroquine, in semi-immune children living in a hyperendemic area where *P. falciparum* resistance to chloroquine, pyrimethamine and cycloguanil has been demonstrated.

Material and Methods

Study area

This study was conducted in the village of Maramvya, located in the rice-field area of the Ruzizi valley, Burundi, where malaria is hyperendemic with a peak of transmission at the end of the rainy season (June). The main vector is *Anopheles arabiensis; An. gambiae* and *An. funestus* are also present but are only secondary vectors.

Detailed epidemiological data have been given in previous papers (COOSEMANS *et al.*, 1984; COOSEMANS, 1985). Resistance of *P. falciparum* to chloroquine is widespread as is its resistance to pyrimethamine and cycloguanil (COOSEMANS *et al.*, 1985; COOSEMANS & NGUYEN-DINH, 1985).

Subjects

300 schoolchildren between 6 and 14 years of age, living within a radius of 10 km around Maramvya, and weighing less than 40 kg were selected for the trial. The average weight was 23·3 kg (standard deviation: 4·72), the sex ratio male/female was 2·3. Full identification allowed easy tracing of missing children during the trial.

Drug regimen

One week before the start of the study (1 October 1985) all the subjects were given a single dose of sulphadoxine/pyrimethamine (Fansidar^{R}): 15-24 kg = 1 tablet; 25-34 kg = 1·5 tablets; 35-39 kg = 2 tablets.

The weekly prophylaxis lasted 17 weeks (8 October 1985 - 28 January 1986) and was given according to the following scheme: (i) 100 children received 20 mg base chlorproguanil (Lapudrine^{R}) (one tablet) + 2 placebo tablets; (ii) 100 children received 200 mg base chloroquine (2 tablets) + one placebo tablet; (iii) 100 children received 200 mg base chloroquine (2 tablets) + 20 mg chlorproguanil (one tablet).

The drugs for each patient's weekly dose were wrapped in stapled envelopes mentioning only the trial number of the child. Each envelope contained two large pills and one small pill.

Meetings were organized before and during the trial to inform all people involved (school direction, teachers, parents).

Drugs were administered each Tuesday by one of the authors (M.B.). Missing children at each round, on average less than 10%, were treated at home at the latest the day after the day of treatment. During the Christmas holidays, parties were organized at school. Compliance was exceedingly good, with 100% coverage at each round of drug distribution.

Surveys

Thick blood films were taken at fortnightly intervals. Using a magnification of 10 × 100, 200 fields were examined for parasites. Children found positive were treated with sulphadoxine/pyrimethamine and discarded from the sample.

Palpation of the spleen was performed in the standing position, using Hackett's classification. A serological study was done on blood samples (25 µl on filter paper) taken on weeks 5 and 15. The indirect fluorescent antibody (IFA) test was performed using *P. falciparum* antigen from culture. Screening was carried out at the dilution of 1/40. Positive samples were further diluted.

Straight lines were calculated from the cumulative prevalences (weeks 3 to 17) by the method of least squares. To compare the different treatments a test of parallelism was done. If the hypothesis of equality of the slopes was accepted, an analysis of covariance was made to verify the hypothesis of equality of intercepts.

Results

On week 0, 70% of the children were positive for *P. falciparum* and 21% for *P. malariae*. Of the *P. malariae* infections, 84% were associated with *P. falciparum*. One case of *P. ovale* was observed. Parasitaemia was higher than 2000 trophozoites/mm^3 in 13% of the *P. falciparum* infections. The propor-

Table 1—Comparison of three antimalarial prophylactic treatment regimens using chloroproguanil (CPG), chloroquine (CQ) or both combined in schoolchildren

Treatment[a]	Weight[b]	Cumulative Frequency of Positives (%) weeks 1	3	5	7	9	11	13	15	17
CQ[1]	15-24 kg (n=69)	0	0	3	10	20	32	45	57	62
	25-39 kg (n=31)	0	0	3	7	16	29	42	55	58
	total (n=100)	0	0	3	9	19	31	44	55	60
CPG[2]	15-24 kg (n=71)	0	1	7	18	27*	49*	53*	67*	79*
	25-39 kg (n=29)	0	0	0	4	24	35	41	45	55
	Total (n=100)	0	1	5	14	26*	44*	50*	61*	72*
CQ+CPG[3]	15-24 kg (n=67)	2	3	10	18	27	41*	47*	53*	62*
	25-39 kg (n=33)	0	0	6	15	27	30	36	42	58
	Total (n=100)	1	2	9	17	27	37*	43*	50*	61*

*subjects n-1

[1]200 mg chloroquine weekly
[2]20 mg chlorproguanil weekly
[3]200 mg chloroquine and 20 mg chlorproguanil weekly.

[a]children were treated on week 0 with Fansidar (R)
[b]15-24 kg: mean weight = 20·5 kg and standard deviation = 2·4
25-39 kg: mean weight = 28·5 kg and standard deviation = 3·2
total: mean weight = 23·0 kg and standard deviation = 4·6

tion of positive fields for asexual forms in the whole sample (parasite density index) was 0·25. The proportion of fields positive in persons found positive (positive parasite density index) was 0·36.

Splenic enlargement was recorded in 56% of the subjects with an average enlarged spleen index of 1·61.

After breaking the key code (random attribution) at the end of the trial, it appeared that the three groups of children were comparable: there was no significant difference for weight (analysis of covariance, p = 0·25), for sex (chi-square test, p = 0·17), for splenomegaly (chi-square test, p = 0·83) or for initial prevalence (chi-square test, p = 0·78).

The treatment with sulphadoxine/pyrimethamine on week 0 was successful. Only one child remained positive on week 1. Two children were taken to hospital during the trial for pulmonary diseases; thick films of both were negative.

The results of the different prophylactic regimens are summarized in Table 1 for all three groups of children and for two weight ranges (15 to 24 kg and 25 to 39 kg).

P. falciparum emerged a little faster in the chlorproguanil group than in the chloroquine group (Fig. 1); this difference was statistically significant (analysis of covariance, $p<0·025$). Comparison of the three treatments showed that the evolution was different in the chloroquine + chlorproguanil group from that in the two other groups; the parallelism between the three straight lines was not accepted (test of parallelism, $p<0·025$). It seems that the chloroquine in the combination group (chloroquine + chlorproguanil) was less active during the first weeks than when given alone.

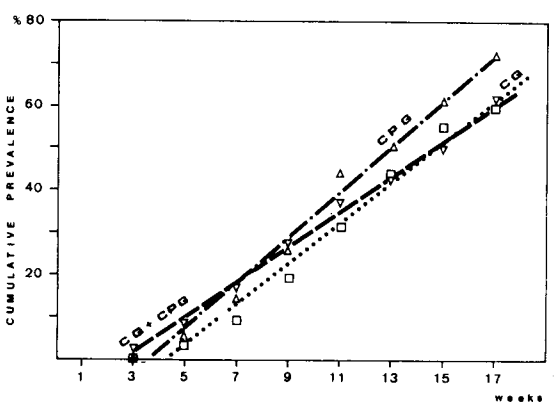

Fig. 1. Infection rates of *Plasmodium falciparum* in schoolchildren receiving weekly 200 mg chloroquine (CQ), 20 mg chlorproguanil (CPG), or 200 mg chloroquine and 20 mg chlorproguanil (CQ+CPG).
Children were treated at week 0 with Fansidar®. The mean weight of the children was 23·0 kg (standard deviation=4·6)
n = 100 for each treated group.
n-1 subjects in CPG and CQ+CPG groups from weeks 9 and 11 respectively.

CQ : Y = 4·74 X-19·8 R^2:0·98
CPG : Y = 5·38 X-19·6 R^2:0·99
CQ+CPG: Y = 4·20 X-11·3 R^2:1·00

(R^2: coefficient of determination)

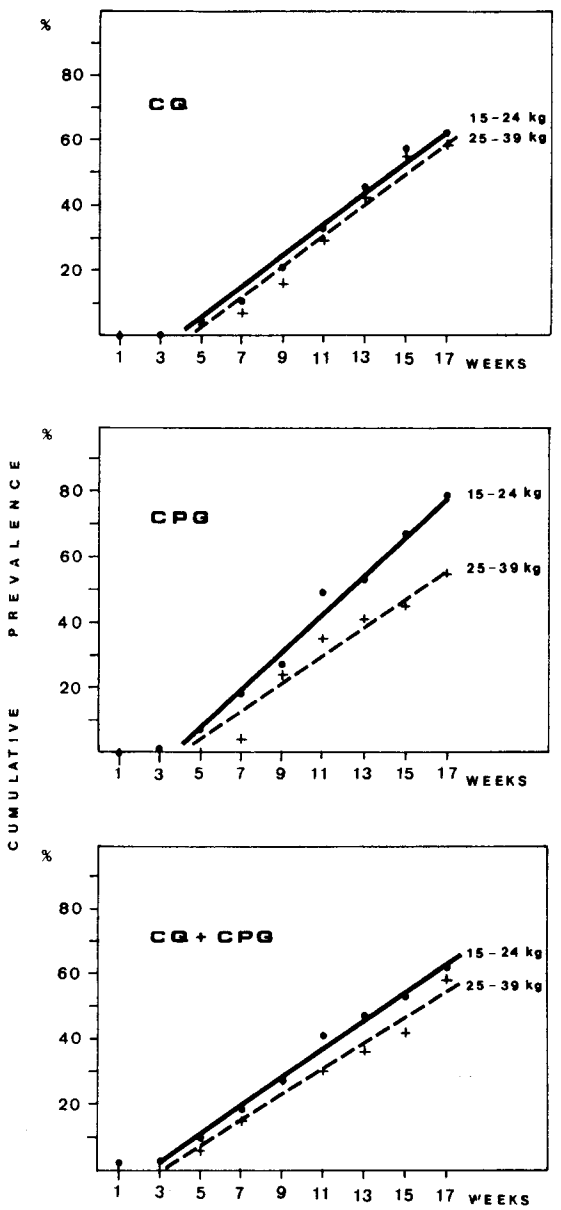

Fig. 2. Comparison of infection rates of *Plasmodium falciparum* between schoolchildren of two weight ranges (15-24 kg and 25-39 kg) under prophylaxis with chloroquine (CQ), chlorproguanil (CPG), or both drugs combined (CQ+CPG).
15-24 kg: mean weight 20·5 kg (standard deviation=2·4)
69% of the children
25-39 kg: mean weight 28·5 kg (standard deviation=3·2)
31% of the children

15-24 kg
CQ : Y=4·89X-20·2 R^2:0·98
CPG : Y=5·79X-20·3 R^2:0·99
CQ+CPG: Y=4·34X-10·8 R^2:0·99

25-39 kg
CQ: Y=4·67X-20·4 R^2:0·96
CPG: Y=4·36X-18·1 R^2:0·95
CQ + CPG: Y=3·88X-12·1 R^2:0·98

For the children weighing less than 25 kg a higher incidence was observed in the group treated with chlorproguanil (test of parallelism, $p<0{\cdot}025$). On the contrary, no difference in efficacy of treatments was observed with the children weighing between 25 and 39 kg (test of parallelism, $p = 0{\cdot}28$; analysis of covariance, $p = 0{\cdot}81$).

The comparison between the two weight ranges for each group of treatment (Fig. 2) demonstrated an influence of the weight in the chlorproguanil group (test of parallelism, $p<0{\cdot}25$) and in the chloroquine + chlorproguanil group (analysis of covariance, $p<0{\cdot}025$), while the weight seemed to have no effect in those treated with chloroquine alone (analysis of covariance, $p = 0{\cdot}26$).

On week 17, the spleen indexes in the chloroquine, chlorproguanil and chloroquine + chlorproguanil groups were 51% (n = 98), 49% (n = 97) and 37% (n = 100) respectively and the average enlargement of the spleen 1·38, 1·67 and 1·38 respectively. The spleen index was higher in the chloroquine group but this was not significant (chi-square test, $p = 0{\cdot}09$).

Antibody titres and percentages of positive individuals at the dilution of 1/40 were comparable in all groups between weeks 5 and 15. Mean titres were higher in children of more than 24 kg (Table 2).

Discussion

The utilization of proguanil (200 mg base daily, adult dosage) or chlorproguanil (20 mg base weekly, adult dosage) is based on observations that the pre-erythrocytic stage of a drug-sensitive and a drug-resistant strain of *P. falciparum* were found to be more sensitive to proguanil than the blood stages of the corresponding strain (FAIRLEY, 1946; DAVEY & ROBERTSON, 1957). In a recent study carried out in the laboratory it has been confirmed that the pre-erythrocytic stages of a drug-sensitive and drug-resistant strain of *P. yoelii* were more sensitive to inhibition than were the erythrocytic stages (HOWELLS *et al.*, 1985).

In a retrospective study carried out among non-immune residents in Dar es Salaam, the value of this causal prophylactic action seemed to be confirmed since, among 647 expatriate children aged one to six years receiving different drugs or drug combinations for chemoprophylaxis, the best results were observed among those who were taking proguanil at the adult dosage of 200 mg base daily (MCLARTY *et al.*, 1984). In a trial carried out in Ghana in 1961, the relatively good efficacy of chlorproguanil, despite the presence of some cross-resistance with pyrimethamine, was confirmed: only 5% of the children were positive on weeks 10 and 16 as compared with a parasite rate of over 50% in the control group. Failures were attributed to irregular administration (CHARLES, 1961). The weekly use of chlorproguanil for its causal prophylactic action, or at a higher dosage monthly as a prophylactic and therapeutic agent, has been recently recommended following a study conducted in a hyperendemic village in Liberia, where chlorproguanil had been administered monthly to children under 15 years of age for seven consecutive years, without any resistance to the drug being detected (BJÖRKMAN *et al.*, 1985).

Some reservations, however, regarding the value of biguanides as prophylactic agents continued to be expressed in view of the widespread resistance and/or cross-resistance to dihydrofolate reductase (DHFR) inhibitors (WHO, 1983), the lack of well documented field studies to confirm the efficacy of this class of compounds (WHO, 1985), or the fact that the various prophylactic regimens being recommended were not always based on well-established scientific criteria (BRUCE-CHWATT, 1982).

The present double-blind trial attempts to answer some of the above questions. It was known that *P. falciparum* chloroquine resistance was widespread in the study area (80% of the isolates) and responses at the RII level of resistance were frequently found at the local dispensaries (COOSEMANS *et al.*, 1985). The *in vitro* 48-hour test, using a medium poor in para-aminobenzoic acid (PABA), revealed the presence of pyrimethamine resistance in 18 isolates out of 21, and the resistant isolates showed cross-resistance with cycloguanil (COOSEMANS & NGUYEN-DINH, 1985).

Table 2—Mean titre and prevalence of a positive indirect fluorescent antibody test (IFA) by weight group and by prophylactic treatment group

		No. of schoolchildren examined	Mean IFA titre	Percentage positive (at 1/40 dilution)
Total	Week 5	298	29	73
	Week 15	271	28	73
15-24 kg	Week 5	206	23	69
	Week 15	186	25	73
25-39 kg	Week 5	92	46	80
	Week 15	85	37	75
Chloroquine	Week 5	100	31	72
	Week 15	91	33	77
Chlorproguanil	Week 5	99	24	71
	Week 15	91	29	74
Chloroquine + Chlorproguanil	Week 5	99	31	76
	Week 15	89	24	70

The results clearly show that, at the doses used, the causal prophylactic action of chlorproguanil, given either alone or in combination with chloroquine, was not sufficient to confer the protection required; indeed, chlorproguanil alone, or in combination with chloroquine, was not more effective than chloroquine alone. Moreover, in children weighing less than 25 kg, breakthroughs were more frequent in those treated with chlorproguanil alone than in those treated with chloroquine alone or with these two drugs in combination. The difference in efficacy between the different treatments disappeared in the group of subjects weighing more than 25 kg, a possible result of the immunological protection appearing in older children. This hypothesis is supported by the observation that the fluorescent antibody titres detected in the latter group were about twice as high as in those weighing less than 25 kg (Table 2).

The parasite rate was higher in the light weight group (15 to 24 kg) receiving chlorproguanil but no difference could be demonstrated between the two weight groups receiving chloroquine alone (Fig. 2).

The addition of chlorproguanil did not increase the effect of chloroquine; on the contrary, during the first weeks the incidence rate was higher in this group than in that receiving chloroquine alone (Fig. 1).

In children under prophylaxis, *P. malariae* and *P. ovale* were not seen and only *P. falciparum* was not always suppressed.

No changes were observed in the mean IFA titres between weeks 5 and 15. A serological survey performed before the beginning of the study would probably have been more appropriate.

A longitudinal survey was undertaken in a control village, 7 km north from the trial locality. The average incidence rates (h = 0·0103) from October to December 1985 for children between five and eight years old give the theoretical infection rates of 42% on week 9 and 68% on week 17.

These theoretical infection rates in unprotected children compared with the cumulative prevalence in protected children suggest that, at the dosages used, chlorproguanil neither alone nor in association with chloroquine had a protective effect superior to that conferred by chloroquine alone.

In the double-blind trial carried out in the Ruzizi valley of Burundi, chlorproguanil, which most probably acts after conversion to a triazine metabolite as does its parent compound proguanil, was chosen for its half-life, longer than that of proguanil, thus allowing weekly instead of daily drug administration.

It was realized that the dose of chlorproguanil used in the trial might have been insufficient to exert its protective effect. Since it had been found necessary to double the amount of proguanil (200 mg base instead of 100 mg base, daily) for this compound to retain its prophylactic action (Ross Institute, 1981; Public Health Laboratory Service, 1983) even the dose of chlorproguanil might have had to be doubled. This, however, could not be done as preliminary toxicity studies with an increased dosage of the compound had never been done.

The present investigations suggest that there is a need to carry out further pharmacokinetic, pharmacodynamic and toxicological studies on chlorproguanil before the drug is written off as a prophylactic agent.

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