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Tolerability of long-term prophylaxis with Fansidar: a randomized double-blind study in Nigeria

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Summary

A randomized double-blind study was performed to compare the side effects of long-term chemoprophylaxis of malaria with Fansidar (1 tablet a week) with those of a 300-mg weekly chloroquine regimen. This study was designed as a field trial with Austrian industrial workers in Nigeria and included 173 volunteers, 86 taking Fansidar and 87 taking chloroquine for 6 to 22 months. Only a few complaints were reported during that time, gastrointestinal disorders predominating in the Fansidar group and insomnia in the chloroquine group (3 cases each). The other complaints in both groups included one case each of skin rash and of visual disturbance, as well as one case of facial erythema after alcohol consumption in the Fansidar group and one case of hair loss in the chloroquine group. Laboratory checks were performed at 3-monthly intervals, and included white and red cell counts, platelet counts and determination of GOT, GPT and alkaline phosphatase. There were no signs of drug-associated liver damage. In the Fansidar group there occurred a slight and transient decrease in the red cell count and in the chloroquine group a slight and transient decrease in the white cell count. Although statistically significant, these changes were without clinical significance. It is noteworthy that there were no cases of leucopenia in the Fansidar group. With the exception of one volunteer, who had discontinued his prophylactic drug regimen, malaria did not occur. Antibodies against blood stage parasites as determined by the indirect immunofluorescence test (IIFT), however, could be found at different stages of the study, which indicates that these two antimalarials are not causal prophylactic agents.

Key words: malaria; Fansidar; chloroquine; tolerability.

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Introduction

Resistance to 4-aminoquinolines represents an increasing problem in prophylaxis and treatment of falciparum malaria over a large part of its geographical distribution. Thus the combination of the "antifols" pyrimethamine and sulfadoxine has become a valuable tool in prevention and management of malaria in *Plasmodium falciparum*-infested areas with known chemoresistance to chloroquine.

In several trials the efficacy of a 20:1 combination of sulfadoxine and pyrimethamine (Fansidar) has been confirmed with respect to prophylaxis as well as to therapy (Leimer, 1981). However, only a few reports are available concerning the long-term tolerability of Fansidar. Muto et al. (1971), studying 121 Japanese and 404 Laotian workers during an observation period of twelve to nineteen months, found some cases of mild asymptomatic leucopenia, which quickly regressed on cessation of medication. The dose regimen had been 1 tablet of Fansidar a week or 2 tablets fortnightly. Lucas et al. (1969) observed 3 cases of mild leucopenia in a group of 113 children who were taking 12.5 mg pyrimethamine together with 125 or 250 mg sulfadoxine once a week for more than one year. Additionally, in children with G-6-PD deficiency a reduction of the hematocrit value was observed. Pearlman et al. (1977), in a study including 311 volunteers taking Fansidar as a chemoprophylactic agent for 26 weeks, reported a slight decrease in leucocyte counts. Ekanem and Bonmarchand (1980) could not detect any side effects in West Africans taking Fansidar during a period of 1 to 2 years despite a high incidence of G-6-PD deficiency in this population. No skin reactions were observed in the long-term trials mentioned here.

Since there are no long-term studies available with Europeans we decided to compare Fansidar with chloroquine with respect to tolerability and side effects in Austrian industrial workers employed at construction sites in Nigeria.

Materials and Methods

Study design and dose regimen

This investigation was designed as a randomized double-blind study in Austrian industrial workers, one group being resident in Bauchi State, the second group living in Benue State of Nigeria. Our study included only subjects who appeared physically healthy. Persons with a history of allergy against sulfonamides, pregnant women, or persons under chronic medication were not accepted as volunteers. The participants were serially numbered and randomized into two groups. All volunteers were advised to regularly take one tablet of the antimalarial. This was according to the serial number either a combination of 25 mg pyrimethamine and 500 mg sulfadoxine (Fansidar) or 300 mg chloroquine base (corresponding to 500 mg chloroquine diphosphate). To meet the requirement of a double-blind study the tablets containing chloroquine or Fansidar, were indistinguishable with regard to shape, size and colour.

Volunteers

The study included 173 volunteers, their age ranging from 14 to 57 years. 86 received Fansidar as malaria prophylaxis (57 males and 29 females) and 87 (59 males and 28 females) took chloroquine (for details see Table 1).

Table 1. Demographic data and duration of prophylaxis

	Fansidar (n = 86) (57 ♂, 29 ♀)	Chloroquine (n = 87) (59 ♂, 28 ♀)
Age (years)	14–57	16–57
$\bar{x} \pm SD$	34.4 ± 8.6	35.1 ± 9.3
Duration of prophylaxis:		
Not evaluable (only baseline)	9	14
6 months	17	23
12 months	29	20
18 months or more	31	30

Parameters for tolerability

Subjective parameters. At the beginning of the study, each volunteer received a questionnaire which was designed to provide information on side effects according to the personal assessment of the volunteer. They were advised to report the kind, intensity, time of onset and duration of side effects as well as to what extent any medical treatment was necessary. At the end of the study the questionnaires were collected and evaluated.

Laboratory investigations. At the beginning of the study (pre-study values) as well as at 3-monthly intervals the following parameters were evaluated: red and white cell count, platelet count, transaminases (GOT and GPT) and alkaline phosphatase. Although it was not the aim of our study to investigate the effectiveness of chloroquine and Fansidar we routinely checked the sera of randomly selected volunteers for the presence of antibodies against *P. falciparum* by immunofluorescence (Falciparum-Spot IF, Bio Mérieux, Marcy l'Etoile, 69260 Charbonnières, France). In accordance with our laboratory standard values we regarded titers of 1:64 as doubtful and titers of 1:256 and more as significant positive results. Additionally, in all cases of intercurrent fever blood smears were prepared and checked for the presence of malaria parasites.

Duration of the controlled medication. To meet the requirement of a long-term study we intended to obtain an observation period of 18 months or more. This was achieved in 31 volunteers receiving Fansidar and in 30 receiving chloroquine. In 89 participants the controlled chemosuppression extended over a period of 6–12 months. In 23 cases no laboratory follow-up could be done since, apart from the first blood sample (baseline values), no further specimens could be obtained (for details see Table 1). The main reason for premature termination of the chemoprophylaxis was the departure from Nigeria. Only in 3 cases did more serious side effects lead the volunteers to cease chemoprophylaxis.

Statistical analysis of data

The Wilcoxon matched pairs signed ranks test was used for within-group comparisons of the laboratory parameters. Baseline values were compared with the corresponding values at months 6, 12 and 18.

The comparison of the haematological and biochemical parameters at different times, between the Fansidar and the chloroquine group was performed with the Mann-Whitney U-Test.

Table 2. Antibodies against *P. falciparum*. Follow-up of volunteers exhibiting at least one positive immune fluorescence test at a dilution of 1:256

Serial number	Drug	Titres pre	Titres after					
			6 mo.	9 mo.	12 mo.	15 mo.	18 mo.	21 mo.
1	Chloroquine	neg	neg	256	n.t.	256	n.t.	n.t.
4	Fansidar	256	256	n.t.	n.t.	256	n.t.	n.t.
5	Chloroquine	64	n.t.	256	neg	64	64	64
14	Fansidar	64	n.t.	64	neg	n.t.	256	neg
25	Chloroquine	neg	neg	256	neg	neg	neg	256
31	Fansidar	neg	256	neg	n.t.	n.t.	n.t.	n.t.
32	Chloroquine	64	neg	n.t.	neg	n.t.	256	64
42	Chloroquine	neg	neg	256	neg	64	neg	neg
57	Fansidar	64	neg	256	n.t.	neg	256	64
63	Fansidar	256	neg	neg	64	n.t.	n.t.	n.t.
67	Chloroquine	64	64	n.t.	neg	64	256	neg
70	Fansidar	64	n.t.	neg	neg	256	neg	64
74	Chloroquine	neg	256	n.t.	neg	neg	64	64

n.t. = not tested

Table 3. Adverse reactions

Reaction	Fansidar (n = 86)	Chloroquine (n = 87)
Vomiting	1*	
Gastralgia	2	
Skin rash	1	1*
Facial erythema after alcohol consumption	1	
Loss of hair		1*
Visual disturbance	1	1
Insomnia		3
Total	6	6

* prophylaxis discontinued because of side effect

Results

Concomitant diseases occurring during controlled prophylaxis

In the Fansidar group 1 case of unspecific viral infection and one case of parotitis occurred. In the chloroquine group 2 volunteers had intercurrent episodes of fever and one participant developed a duodenal ulcer.

Blood smears taken during febrile episodes were consistently negative for malarial parasites in volunteers taking their suppressive medication regularly. One participant, however, a 34-year-old man who stopped his suppressive medication and left Nigeria, died from falciparum malaria 8 weeks thereafter.

Serological findings

As shown in Table 2, in 13 randomly selected volunteers a serological follow-up was performed in order to detect anti-blood-stage parasite-specific antibodies. Among the 206 serum samples analysed, 18 exhibited a significant titer of 1:256 which were associated with 13 volunteers (Table 2). In the Fansidar group these were 9% and in the chloroquine group 8.4%.

Tolerability of the chemosuppressive medication as reported in the questionnaires

As shown in Table 3, 6 of the 86 volunteers of the Fansidar group and 6 of the 87 participants of the chloroquine group reported on adverse reactions. In detail, the following complaints occurred during the period of observations:

Gastrointestinal symptoms. Gastrointestinal symptoms were reported only by volunteers in the Fansidar group. In one case gastric disturbance and vomiting led to the cessation of the suppressive medication on day 450. A further participant suffered from short-term gastric pain after each Fansidar intake. This side effect was observed throughout the whole period of observation of

Table 4. Follow-up of 4 volunteers with high levels of alkaline phosphatase

Serial number/ Sex/age/drug	Concentration of alkaline phosphatase (U/l)					
	pre-	3 mo.	6 mo.	9 mo.	12 mo.	18 mo.
72/♂/15 years Fansidar	385	414	427	302	195	233
115/♂/14 years Fansidar	516	467	380	297	277	n.d.
116/♂/15 years Fansidar	532	545	397	235	n.d.	n.d.
124/♂/16 years Chloroquine	256	349	210	n.d.	n.d.	n.d.

559 days. Another volunteer suffered only once from gastric pain (on day 47) shortly after taking Fansidar.

Skin eruptions. In one volunteer (male, 49 years) who was taking Fansidar severe exanthema occurred on day 18 of the trial. This man, however, did not report to the camp doctor and kept his skin condition under control by self-treatment with betamethasone ointment. His data were collected only after his departure from Nigeria. A further participant in the Fansidar group reported the occurrence of a patchy redness in his face after consuming alcoholic beverages. Two volunteers of the chloroquine group also complained of dermatological problems: one (male, 37 years) developed severe exanthema on day 83, consequently he stopped the chloroquine medication and left the study. Another participant (female, aged 27 years) suffered from hair loss shortly after beginning the trial. For this reason she stopped the chemosuppressive regimen on day 61.

Visual disturbance. Impaired vision was reported by one volunteer in the Fansidar group (male, 26 years) and by one participant taking chloroquine (male, 23 years). These complaints were not substantiated.

Insomnia. Three volunteers in the chloroquine group complained of inexplicable insomnia in the night following each tablet intake.

Tolerability of test medication according to the laboratory parameters

Individual findings. – a) *Haematological parameters.* Apart from one exception the haematological findings including white and red cell count, platelet count and differential cell count showed only minor deviations, not of clinical importance. Since these were found irregularly before as well as after beginning the test medication, the observed deviations were not considered to be a consequence of the drug intake.

In only one case in the chloroquine group (male, 51 years) a steady

Table 5. Follow-up of 2 volunteers with high levels of transaminases

Serial number/ sex/age/drug	GOT/GPT values (U/l)			
	pre-	3 mo.	6 mo.	9 mo.
126/♂/33 years				
Fansidar	213/86	98/45	169/61	269/61
134/♀/30 years				
Chloroquine	180/287	19/21	8/10	n.d.

decrease in the white cell count took place during the course of chemoprophylaxis: pre-study value: 5200/μl; 3 months: 3700/μl; 6 months: 3600/μl; 12 months: 4600/μl; 18 months: 4000/μl; 22 months: 2800/μl. – b) *Biochemical parameters.* Liver enzymes GOT, GPT, and alkaline phosphatase irregularly exhibited significant deviations from normal values in some volunteers. Since these deviations were also noted at the beginning of the trial they were not considered to be drug-mediated.

Alkaline phosphatase. 4 volunteers (male, 14–16 years) in keeping with their adolescence, had grossly elevated concentrations of alkaline phosphatase in the serum which decreased somewhat during the observation period (see Table 4).

Transaminases. Two volunteers showed significantly elevated levels of GOT and GPT at the beginning of the study. In one case receiving Fansidar these parameters remained more or less unchanged, whereas in the other case in the chloroquine group a dramatic return to normal levels took place within 6 months (for details see Table 5).

Follow-up of overall findings within groups. The comparison regarding the haematological parameters (white cell, red cell and platelet count) as well as the liver enzymes (GOT, GPT and alkaline phosphatase) revealed only a few statistically significant differences ($p < 0.05$) which were clinically irrelevant.

Erythrocytes. Of the male volunteers in the Fansidar group 36 exhibited a decrease in the red cell count within the first 6 months of the trial, whereas only 13 had an increase during this time. The difference in the mean values did, however, not exceed $0.2 \times 10^6/\mu$l and was therefore clinically negligible.

Leucocytes. A comparison of the pre-study values with the values at 6 months and at 12 months revealed in the chloroquine group significantly more decreases in white cell counts ($n = 44$ and 48, respectively) than increases ($n = 26$ and 17). Since the difference between the mean values did not exceed 500/μl, these findings were not regarded as being clinically relevant.

Alkaline phosphatase. Comparing baseline values with those at 12 months there were significantly more decreases than increases in both groups (Fansidar: 54 decreases, 4 increases; chloroquine: 39 decreases, 11 increases).

GOT. In the chloroquine group, comparing baseline with 12-month values revealed a significantly higher number of volunteers with decreases (35) than with increases (14). The decrease in the mean value (male and female), however, was 3.6 U/l and therefore clinically negligible.

GPT. There was also a slight decrease in GPT which was restricted to the female participants in the chloroquine group in the comparison of the pre-study and the 12-month values (pre: 15.3; 12 months: 7.8 U/l, mean values).

Comparison of Fansidar and chloroquine with respect to laboratory findings at different times

No statistically significant differences were found between the Fansidar and the chloroquine group ($p > 0.05$).

Discussion

It was the aim of this study to evaluate the tolerability of Fansidar when used as a chemoprophylactic agent for a prolonged period of time. Since 4-aminoquinolines are regarded as the standard medication in Western Africa for the suppressive management of malaria, chloroquine was chosen as the reference medication.

One volunteer, who had discontinued his prophylactic drug regimen, died from an acute attack of falciparum malaria. This case underlines once more the importance of the regular intake of a suitable antimalarial drug by non-immune individuals living in endemic areas. Apart from this case no further attacks of malaria occurred during the whole period of observation. Serological follow-up studies, however at different times revealed significant titers of antibodies against *P. falciparum* in the indirect immunofluorescence test.

Since the chemosuppressive medication against malaria cannot prevent infection, these findings suggest the presence of cross-reacting anti-sporozoite antibodies (Cohen, 1982) after a prolonged stay in malaria endemic areas. Another possibility is the induction of anti-blood-stage, parasite-specific antibodies by transient low level and thus subclinical parasitaemias.

The prolonged intake of the antimalarials was well tolerated. Only a few complaints were reported by volunteers taking Fansidar or chloroquine. Gastrointestinal disturbances prevailed in the Fansidar group and insomnia in the chloroquine group. Prophylaxis was discontinued because of side effects by 2 volunteers in the chloroquine group (1 case of hair loss and 1 case of skin rash), whereas vomiting in one participant in the Fansidar group was the reason for premature cessation of the chemoprophylaxis.

In neither group was evidence of drug-related liver damage found. Even in volunteers with initially elevated transaminase values no adverse effects with respect to liver cell function could be observed during the course of chemoprophylaxis.

In the Fansidar group no case of leucopenia occurred. This is remarkable since in a study with Laotians and Japanese (Muto et al., 1971) this side effect was observed in a one-year period of observation in 3% and 10% of volunteers following a chemoprophylactic Fansidar regimen. At a lesser frequency a decrease in leucocyte counts during long-term Fansidar intake was also observed in Africans (Lucas et al., 1969) and in Thais (Pearlman et al., 1977). Obviously, there are race-specific and thus genetically determined differences with respect to sulfonamide- and/or pyromethamine-induced bone marrow depression.

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