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Comparison of three regimens for malaria prophylaxis in travellers to east, central, and southern Africa

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Abstract

Objectives—Confirmation of breakthroughs in three different malaria chemoprophylactic regimens (chloroquine 300 mg weekly and proguanil 100 mg daily; chloroquine 300 mg weekly and proguanil 200 mg daily; proguanil 200 mg daily) and assessment of compliance.

Design—Prospective, randomised multicentre trial.

Setting—Five vaccination centres in the Netherlands.

Subjects—Dutch travellers to east, central, and southern Africa.

Main outcome measures—*Plasmodium falciparum* seen on blood film; concentrations of drugs measured in blood spots.

Results—*P. falciparum* infection was confirmed in 12 (21%) of 58 travellers with fever suspected to be due to malaria. No difference in prophylaxis failures between the regimens was found. Breakthroughs were difficult to confirm, as compliance could be determined in only 30% of the participants with fever and chloroquine in their regimen. One breakthrough was proved. The risk per 1000 people per month for travellers was 5.4 (95% confidence interval 2.4 to 12.6) for chloroquine 300 mg weekly and proguanil 100 mg daily, 2.8 (0.9 to 10.1) for chloroquine 300 mg weekly and proguanil 200 mg daily, and 6.0 (2.6 to 14.0) for proguanil 200 mg daily.

Conclusion—Prophylaxis failures occurred in less than 1% of the participants, and only 21% of those with a fever were suffering from *falciparum* malaria. Compliance was moderate. The chloroquine-proguanil combination can still be recommended for visitors to east, central, and southern Africa.

are both fairly non-toxic drugs, we conducted a prospective multicentre randomised trial among Dutch travellers to east, southern, and central Africa. The original study included travellers as well as expatriates; the preliminary data of the combined groups were reported at the second international conference on travel medicine, Atlanta, May 1992.

We compared three chemoprophylactic regimens: chloroquine 300 mg weekly and proguanil 100 mg daily (then the official Dutch recommendation); chloroquine 300 mg weekly combined with proguanil 200 mg daily (the advice in the United Kingdom and of the World Health Organisation⁶); and proguanil 200 mg daily. The proguanil only regimen was included because a retrospective study in Dar-es-Salaam suggested good prophylactic efficacy.⁸

The aim of the study was to assess the efficacy of the three regimens. The objective was to confirm a breakthrough by means of a blood film containing *P. falciparum* and by assessing compliance by measuring drug concentrations in whole blood.

Subjects and methods

RECRUITMENT OF SUBJECTS

From March 1987 until November 1989 participants were enrolled at one of the five vaccination centres in the Netherlands. The central supervision and coordination was performed by JW at the Academic Medical Centre, Amsterdam.

Subjects were defined as travellers if staying abroad less than 365 days. Those originating from endemic malarious areas and those with known allergy to one of the drugs were excluded. We calculated that about 400 participants in each regimen were required to permit inferences about prophylactic efficacy, assuming one breakthrough in every 100 participants with chloroquine 300 mg weekly and proguanil 100 mg daily, chloroquine 300 mg weekly and proguanil 200 mg daily, and four in every 100 with proguanil 200 mg daily.

ALLOCATION TO REGIMENS

Participants allocated themselves to a regimen by taking an envelope out of 99 (33 each of the three regimens). Members of one family were allocated to one regimen. The drugs had to be taken from the day before entering the malarious area until four weeks after leaving the area.

INSTRUCTIONS TO PARTICIPANTS

Each participant was provided with a booklet with information on how to deal with a possible break-

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Introduction

Since 1979 chloroquine resistant strains of *Plasmodium falciparum* have spread through tropical Africa. Most patients with imported malaria in industrialised countries acquire their infections in sub-Saharan countries.¹⁻³ Sound advice for chemoprophylaxis is increasingly difficult to give; a balance should be made between the risk of infection, the case fatality rate, the protection afforded by preventive measures, and the possible risks of these measures. The real incidence of malaria among travellers is not known and the estimates of the risk of infection have so far been based mainly on surveillance of imported malaria. The case fatality rate of imported *falciparum* malaria varies between 0.6% and 7%.^{4,5} To investigate the most appropriate use of chloroquine and proguanil, which

through, with microscope slides and sterile lancets to make thick blood films, and filter paper (Whatman chromatographic) with imprinted circles to be filled up with blood from the fingerprick (50 µl).

The participants received three sulfadoxine-pyrimethamine tablets as standby treatment. The booklet contained a request to local physicians to confirm the diagnosis of malaria by examining the film before giving treatment and to report their findings in the booklet. If a local doctor could not be reached in time the participants were instructed to take the sulfadoxine-pyrimethamine tablets after making the films and blood spots themselves. The slides and filter papers were to be taken home or to be sent to the laboratory for tropical medicine at the Royal Tropical Institute in Amsterdam.

Four weeks after returning home the participants had to send their booklet to the Academic Medical Centre in Amsterdam. Three to five reminders were sent to participants who did not mail their booklet spontaneously.

LABORATORY METHODS

The films were examined for malaria parasites immediately after arrival. Whole blood concentrations of chloroquine and desethylchloroquine were determined from the blood spots with high pressure liquid chromatography with fluorescence detection⁸; the lower limit of the required chloroquine concentration was set at 0.19 µmol/l.⁹ The determination of proguanil concentration was not feasible at the time of the study.

DEFINITIONS

Failure of prophylaxis was defined as *P falciparum* present in the thick blood film during the period of travel and the four weeks after returning home, irrespective of compliance. Compliance with the regimen was defined as a chloroquine concentration of >0.19 µmol/l determined from the blood spots prepared at the same time as the films were made.

A breakthrough was signalled by *P falciparum* present in the thick blood film during the travel period and the four weeks after returning home despite good compliance.

DATA ANALYSIS

The incidence of prophylaxis failures in the regimens was compared by using the χ^2 test. Significance was defined as $p < 0.05$.

Results

PARTICIPANTS

A total of 1625 subjects participated. Data on the 204 residents are not reported here. Of the 1421 travellers enrolled, 16 cancelled their trip or changed their destination and in 19 (1.3%) the data were incomplete. Thus, 1386 travellers remained for final analysis. Of these, 911 (60%) spent less than six weeks in the tropics.

RESPONSE

The booklet was returned by 1263 (91%) of all

travellers and by 830 (91%) of the 911 travellers who spent less than six weeks abroad. The proportion on each regimen was not different among the travellers who did and did not respond: 452/497 (91%) for chloroquine 300 mg weekly plus proguanil 100 mg daily; 390/423 (92%) for chloroquine 300 mg weekly plus proguanil 200 mg daily; and 421/466 (90%) for proguanil 200 mg daily.

FAILURE OF PROPHYLAXIS

Twelve (21%) of 58 travellers with a fever had falciparum malaria (nine of 54 blood films examined in Amsterdam and three of the four examined abroad contained *P falciparum*). Three of these attacks occurred within six weeks of starting prophylaxis. Eight (18%) of 46 travellers who became ill in the tropics and four (33%) of 12 who fell ill after returning home were suffering from falciparum malaria. Five had taken chloroquine 300 mg weekly and proguanil 100 mg daily, two had taken chloroquine 300 mg weekly and proguanil 200 mg daily, and five had taken proguanil 200 mg daily ($p > 0.05$).

Seventeen of the 830 travellers who stayed less than six weeks abroad had a fever. In three patients *P falciparum* was found; one had been taking chloroquine 300 mg weekly and proguanil 100 mg daily, and two had been taking proguanil 200 mg daily.

COMPLIANCE

Assessing compliance was possible for chloroquine users only; it was not possible to determine reliable proguanil concentrations from the blood spots on filter paper. Thirty nine of the 58 travellers with an assumed breakthrough were chloroquine users (25 used chloroquine 300 mg weekly and proguanil 100 mg daily, 14 chloroquine 300 mg with proguanil 200 mg). No filter paper was received from 13 and a test was not possible in a further 13 (the spots contained <50 µl blood, or blood could not be extracted from the filter paper). Six of the remainder were found to have ≥ 0.19 µmol/l of chloroquine and seven had <0.19 µmol/l.

BREAKTHROUGHS

Compliance could be determined in three of the seven travellers with falciparum malaria and chloroquine in their regimen. The chloroquine concentration in whole blood was ≥ 0.19 µmol/l in one patient and <0.19 µmol/l in two patients.

RISK OF PROPHYLAXIS FAILURE

The number of person-months of exposure for each regimen was calculated by counting the months of exposure of every traveller on that regimen known to have returned from Africa ($n = 1263$). The table gives the risks of a failure in travellers who spent less than a year abroad. For those who spent less than six weeks abroad the risk was 4.0/1000 person-months (95% confidence interval: 0.56 to 28) for chloroquine 300 mg weekly and proguanil 100 mg daily and 7.9/1000 person-months (2.0 to 31) for proguanil 200 mg daily. The risks were not significantly different between the regimens nor for length of travel (all travellers *v* those travelling <6 weeks).

Discussion

Because prophylaxis failures were analysed sequentially, after 2.5 years it was apparent that the original assumptions of expected failures were wrong. A much greater number of participants would be required to attain a significant difference between the regimens. Even more importantly, it seemed at this time that the slight differences between the regimens would not be sufficient to alter the national recommendations for chemoprophylaxis.

Failure of malaria prophylaxis in subjects who spent less than a year in east, central, or southern Africa

	Chloroquine 300 mg weekly plus proguanil 100 mg daily	Chloroquine 300 mg weekly plus proguanil 200 mg daily	Proguanil 200 mg daily	Total
Exposure (per 1000 person-months)	927	713	830	2470
No of subjects	452	390	421	1263
<i>P falciparum</i> present	5	2	5	12
Risk (per 1000 person-months) (95% confidence interval)	5.4 (2.4 to 12.6)	2.8 (0.9 to 10.1)	6.0 (2.6 to 14.0)	4.9 (2.7 to 8.5)

In our study falciparum malaria could be confirmed in only 12 of the 58 patients suffering from a fever assumed to be malaria—that is, less than 1% of all participants. No difference in prophylaxis failures between the regimens was found. The risk in our study is comparable to that found in studies among travellers who used chemoprophylaxis by Lobel *et al* for different parts of Kenya (0.7–10 per 1000 person-months)¹⁰ and by Steffen *et al*, who calculated a risk of 5.5 per 1000 person-months for travellers to east Africa.¹¹ In our study the risk in those who travelled for less than six weeks was not significantly different from the risk for all travellers. In the study of Fogh *et al* *P. falciparum* was found in the thick blood film of 4 (1%) of 384 participants taking chloroquine 300 mg weekly and proguanil 200 mg daily.¹² Their study population, consisting of 95% travellers (of whom 70% spent less than four weeks abroad) and 5% residents, is comparable with that in our study.

COMPLIANCE

For comparison with other studies the definition of compliance should be considered. Usually compliance means a history of regular, uninterrupted use of prophylactic drugs during travel and for four or more weeks after leaving the malarious area or until the onset of symptoms of malaria. Lobel *et al* found good compliance in 52% of 3469 travellers to Kenya staying less than three weeks but lower percentages for those staying more than three weeks.¹⁰ Steffen *et al* reported that 57% of the travellers (defined as being abroad for less than three months) were compliant, compared with 29 of those who spent 3–12 months abroad.¹¹ Behrens reported higher non-compliance in patients admitted with falciparum malaria.¹³

It was not possible to confirm compliance by measuring drug concentrations in blood: blood spots were received from only two thirds of the subjects; proguanil concentration could not be estimated; some blood spots contained less than 50 µl; and there were difficulties with extraction from filter paper. In 13 blood spots tested, chloroquine concentrations were adequate in six (46%), which is in accordance with the figures above.

Compliance was confirmed in only one of the seven patients with a prophylaxis failure and chloroquine in the regimen. Thus, one prophylaxis failure was proved to be a breakthrough. Confirming compliance by measuring chloroquine concentrations in whole blood (not used in previous studies and incomplete in our study) contributed little to the results. As far as we could measure, compliance seemed far less than might be expected from the participants, who had agreed to

take part in the study. It nevertheless indicates that the data on prophylaxis failures previously reported might be overestimated. On the other hand, not adjusting for compliance is probably a better reflection of the reality.

RECOMMENDATIONS

To our knowledge, our study is the first to compare chloroquine 300 mg weekly and proguanil 100 mg daily (the national Dutch recommendation at the time the study was started) with chloroquine combined with proguanil 200 mg daily. No difference in the risk of prophylaxis failure between these regimens was found. To attain uniformity with Europe, however, in 1992 the Dutch recommendation was changed to proguanil 200 mg for travellers to east, southern, and central Africa; chemoprophylaxis with mefloquine was recommended for visits to west Africa. In the recently published recommendations for travellers from the United Kingdom mefloquine is preferred for visits to east and central Africa, with the chloroquine-proguanil combination still considered second best.¹⁴

In view of the low risk of prophylaxis failures in travellers using the chloroquine-proguanil combination our results support the national recommendation for Dutch travellers to east, central, and southern Africa. Where chloroquine is contraindicated, prophylaxis with proguanil alone (200 mg/day) can be considered.

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Clinical implications

- Owing to the rise and spread of drug resistant *Plasmodium falciparum*, it is increasingly difficult to give recommendations on malaria chemoprophylaxis for areas with high transmission
- A balance has to be found between risk of infection and risk of adverse reactions
- In this study, which compared different regimens of well known, fairly non-toxic drugs, prophylaxis failures occurred in less than 1% of the participants
- Compliance with chemoprophylaxis is still quite poor
- Failure of compliance should be clearly distinguished from failure of chemoprophylaxis