Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-α-pyrone (coumarin)

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Abstract

***Objective*—To study efficacy of treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-α-pyrone.**

***Design*—Randomised, double blind, placebo controlled study with matching for grade and duration of disease, age, and sex. Treatment was given for 367 days, and subjects were followed up for another year.**

***Setting*—A town in Shandong Province, China.**

***Subjects*—104 men and women with chronic unilateral filarial lymphoedema or elephantiasis of the leg: 64 were randomised to benzopyrone and 40 to placebo. By the end of the study 19 patients had dropped out of the treatment group and two out of the placebo group.**

***Interventions*—Two 200 mg tablets of 5,6-benzo-α-pyrone or two placebo tablets given daily.**

***Main outcome measures*—Volumes of the affected and normal legs estimated every three months, and daily listing of any side effects.**

***Results*—Benzopyrone reduced oedema for all grades of lymphoedema during the year of treatment (pW0·001) and the follow up year (p=0·026). During treatment the mean monthly reductions in leg volume were 0·62% (95% confidence intervals 0·4% to 0·85%), 1·1% (0·71% to 1·6%), and 1·6% (0·89% to 2·3%) of the volume of the normal leg for grades 1, 2, and 3-5 (elephantiasis) of lymphoedema respectively. During follow up the mean monthly reductions were 0·18% (0·01% to 0·35%), 0·54% (0·27% to 0·82%), and 0·87% (0·51% to 1·2%). At the end of the trial the total reduction in oedema was 100%, 95%, and 45% for grades 1, 2, and 3-5. Symptoms and complications were considerably reduced, including attacks of secondary acute inflammation, while side effects were minor and disappeared after one month. In the placebo group there were no changes in the severity of lymphoedema.**

***Conclusions*—5,6 - benzo - α - pyrone reduces the oedema and many symptoms of filarial lymphoedema and elephantiasis. It has few side effects, and its relatively slow action makes it ideal for use without compression garments.**

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Introduction

Over 45 million people suffer from filarial lymphoedema and elephantiasis, including hydrocele.[1-3] An equal number are asymptomatic but are infested with filariae. Such patients often have damaged lymphatic systems and are likely to develop lymphoedema and elephantiasis.[4,5] Effective treatments for lymphoedema and elephantiasis are now available,[1,6-9] but patients in developing countries can seldom afford them. Of these, the first choice is adequate physical treatment.[6] This is non-invasive and gives large, rapid, and lasting reductions of swelling, but compression garments are essential. These are impractical in hot, wet, or dirty conditions such as paddy fields.

The benzopyrone group of drugs have many actions but all appear to reduce all forms of acute and chronic high protein oedema in animals and humans. Those drugs that have been studied do this by increasing both the numbers of macrophages and their normal proteolysis per cell.[1] These drugs thereby provide another path by which protein and its osmotically held water can be removed from the tissues. Removing the excess protein also reduces the chronic inflammation, which results from the simple chronic accumulation of excess plasma proteins and the consequent excess fibrosis.[1,10] All benzopyrones have similar effects on high protein oedemas, most can be taken orally, they are of low toxicity, and their actions persist for several days.[1] The cheapest and simplest is 5,6-benzo-α-pyrone (coumarin). This is available in large amounts of high purity, and has been tested in more clinical trials than any other.[1] While its chemical name is coumarin and it is the parent molecule of the dicoumerol anticoagulants, it has no anticoagulant activity itself.[1] The benzopyrones have no relation to the benzopyrenes and have a different chemical structure.

Various benzopyrones have been shown to reduce human postmastectomy, primary, and other lymphoedemas[1,11-19] and to improve the results obtained with physical treatment.[20] They also decrease the incidence of secondary acute inflammation by removing the "incubation medium" for bacteria.[1,11-13,17-19] However, the effects of these drugs on the massive lymphoedema and elephantiasis caused by filariasis had not been studied. A trial was therefore conducted of 5,6-benzo-α-pyrone on filarial lymphoedema and elephantiasis in Ping-Yi County, Shandong, China. A similar trial was conducted simultaneously in India.[21] In India reinfestation with filariae is frequent,[21] but in Shandong, where bancroftian filariasis used to be endemic, a campaign of mass treatment with diethylcarbamazine and other measures have reduced the prevalence of microfilaraemia to 0·01%, compared with 20-30% 30 years ago.[22] While many patients still had elephantiasis, the lack of reinfestation permitted evaluation of the effectiveness of the drug after its administration ceased.

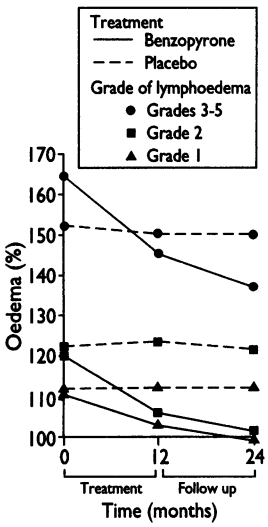
Patients and methods

Altogether 104 patients were chosen who had chronic lymphoedema or elephantiasis in one leg and one apparently normal leg. The patients were initially divided into eight groups of 13, each group being matched as closely as possible for grade of lymphoedema, duration of the disease, age, and sex (in decreasing order of importance). Random number tables were then used to assign the patients to treatment with benzopyrone or placebo. At the Chinese ethics committee's insistence, randomisation was weighted to assign more people to the treatment than to placebo: 64 patients received treatment and 40 received placebo. Blood specimens were taken from the patients, and, although blood films revealed no microfilariae, diethylcarbamazine 6 mg/kg/day was given to each patient for 12 days before the trial as a precaution. No other treatment was used (including no compressive bandaging) except that antibiotics were given for any bacterial infections. For the next 367 days the treatment group received 400 mg 5,6-benzo-α-

pyrone a day (as two 200 mg tablets) while the other group received placebo. Village doctors gave the tablets to the patients each day and ensured that they were swallowed so that patient compliance was 100%. When this was completed the patients were followed up for a further year.

While receiving tablets, the patients were asked daily about possible side effects of the drug. The patients were also examined every three months, during which the circumferences of both legs of each patient were measured at five points, at 10 cm intervals from the heel. The volume of each leg was estimated as the sum of four truncated cones,[23] which gives a value almost identical with that from water displacement.[24] The patients were also examined clinically and asked about possible symptoms and complications during the previous three months. Features such as the condition of the skin, hair growth, and ulcers were noted, as was the frequency and severity of secondary acute inflammation (because of confusion in terminology, the International Society for Lymphology recommends that this neutral term be used for any acute inflammation of the affected tissues[6]). Each clinical feature was catagorised as severe, moderate, mild, slight, or none. In addition, all the patients had chest radiographs and electrocardiograms taken and complete blood and urine examinations made. Ten patients in each group were tested for bleeding and coagulation times and for liver and kidney function.

Classification of lymphoedema and elephantiasis—The International Society for Lymphology classifies lymphoedema as grade 1 (pitting of skin and oedema reducible just by elevation) or grade 2 (evident fibrosis and oedema not reducible just by elevation) as well as noting if elephantiasis is present.[6] This classification is suitable only for Western communities, and a more complete scheme is necessary for filarial conditions. A modified version of Anderson's classification[25] has been proposed[26] and is used here. It consists of grade 1 (pitting of skin with little fibrosis), grade 2 (non-pitting lymphoedema with moderate to severe fibrosis), grade 3 (considerable hypertrophy of the skin and subcutaneous tissues with deep sulci and the skin being thick and coarse), grade 4 (grade 2 or 3 with frequent warts and papillomas), and grade 5 (grade 4 with a true elephantoid appearance, an enormously thickened and leathery skin and all the usual limb curvatures obliterated). Thus grades 2 to 5 are all included in the International Society for Lymphology grade 2, with grades 3 to 5 being elephantiasis.



Changes in oedema ((volume of affected leg/volume of normal leg) x 100) in subjects with unilateral filarial lymphoedema of the leg who were given 5,6-benzo-α-pyrone or placebo

Statistical analysis—The volumes of the patients' apparently normal legs did not change significantly during the trial and were used as controls. Although such legs often have abnormal lymphatic systems,[4,5] their use as controls still reduces SE/mean compared with the use of other subjects as controls.[11,17,19] A value for the oedema in each patient's affected leg was provided by calculating the volume of the patient's oedematous leg as a percentage of the volume of the normal leg. The results were analysed by means of an unbalanced repeated measures model with structured covariance matrices (BMDP version five), with grouping factors of treatment, grade of disease (three levels), and time, and individual linear regressions were calculated against time. Paired *t* tests were used to assess the significance of the differences between individuals' initial and final values from zero and between the treatment and placebo groups for the individual grades.

The results of the clinical examination were reported as remained bad (severe or moderate), remained good (mild to none), worsened (started as good and became bad), or improved (started as bad and became good). They were analysed with χ^2 tests of homogeneity, using Yates's correction if required. Often small numbers made it necessary to pool the categories remained bad and worsened and the categories remained good and improved.

Results

During the first year of the trial eight patients withdrew from the treatment group, six for reasons unconnected with the drug and two whose symptoms were so reduced that they felt that they were cured and refused any further treatment (one after one month and one after five months). No patients withdrew from the placebo group. During the follow up year 11 patients withdrew from the treatment group and two from the placebo group, all for reasons unrelated to the trial. These patients moved away from the region and could not be monitored.

Table I shows the initial characteristics of the patients in the two groups. Although the mean values for patients with different grades of lymphoedema differed significantly, there was no difference between the treatment and placebo groups in the values of each grade. Table II shows the mean volumes of the patients' oedematous legs at different times. There was no significant change in the volumes of the patients' normal legs so the results are combined, and there was no significant difference between results for men and women so these are combined. Results for patients with lymphoedema of grades 3-5 (all those with elephantiasis) were combined because of the small numbers of subjects. In the placebo group the volumes of legs did not change whereas in the treatment group volumes were reduced for all grades of lymphoedema throughout the trial.

The figure shows regression lines of the changes in oedema of affected legs ((volume of affected leg/volume of normal leg) x 100). The figure is based on the means of individual values of oedema, which differ slightly from the values calculated from the means shown in table II. During treatment, oedema for grades 1 and 2 of lymphoedema was reduced by over a half and for grades 3-5 by a third. By the end of follow up oedema was completely gone for grade 1 and was

TABLE I—*Initial characteristics of 96 subjects with chronic unilateral filarial lymphoedema of the leg who were randomised to treatment with 5,6-benzo-α-pyrone or placebo and who completed first year of trial. Values are means (standard deviations) unless stated otherwise*

Grade of lymphoedema	Benzopyrone			Placebo		
	No of subjects	Age (years)	Duration of disease (years)	No of subjects	Age (years)	Duration of disease (years)
Grade 1:						
Men	13	55 (14)	26 (13)	12	58 (10)	33 (7)
Women	16	50 (10)	29 (8)	9	53 (13)	30 (5)
Grade 2:						
Men	7	56 (13)	30 (14)	6	57 (8)	31 (14)
Women	4	52 (8)	23 (5)	5	62 (6)	33 (8)
Grades 3-5:						
Men	11	60 (7)	36 (8)	7	63 (9)	40 (12)
Women	5	57 (3)	32 (10)	1	53	30

TABLE II—*Mean (SD) volumes of legs (cm^3) of subjects with chronic unilateral filarial lymphoedema of the leg who were given 5,6-benzo-α-pyrone or placebo for one year and followed up for a second year*

Grade of lymphoedema	Benzopyrone			Placebo		
	No of subjects	Affected leg	Normal leg*	No of subjects	Affected leg	Normal leg*
Grade 1:						
Initial value	29	2824 (474)	2495 (436)	21	3021 (399)	2720 (371)
After year 1	29	2631 (393)		21	3048 (449)	
After year 2	23	2491 (336)		19	3097 (384)	
Grade 2:						
Initial value	11	3189 (391)	2550 (245)	11	3033 (415)	2508 (371)
After year 1	11	2852 (345)		11	3109 (378)	
After year 2	7	2590 (164)		11	3111 (391)	
Grade 3-5:						
Initial value	16	4206 (1500)	2669 (308)	8	3920 (438)	2575 (257)
After year 1	16	3720 (1272)		8	3899 (472)	
After year 2	15	3548 (1197)		8	3970 (472)	

*Values did not change significantly with time and are combined.

TABLE III—*Slopes of linear regression lines of oedema ((volume of affected leg/volume of normal leg) x 100) per month in subjects with unilateral filarial lymphoedema of the leg who were given 5,6-benzo-α-pyrone or placebo for one year and followed up for a second year*

	Benzopyrone				Placebo				
		Slope of line				Slope of line			
Grade of lymphoedema	No of subjects	Mean (SE)	95% confidence interval	p Value*	No of subjects	Mean (SE)	95% confidence interval	p Value*	p Value†
During first year									
Grade 1	29	−0·621 (0·110)	−0·85 to −0·40	W0·001	21	0·004 (0·147)	−0·30 to 0·31	0·98	0·001 } χ^2=41
Grade 2	11	−1·14 (0·192)	−1·6 to −0·71	W0·001	11	0·112 (0·117)	−0·15 to 0·37	0·36	W0·001 } pW0·001
Grades 3-5	16	−1·61 (0·340)	−2·3 to −0·89	W0·001	8	−0·183 (0·249)	−0·77 to 0·41	0·49	0·011 }
During second year									
Grade 1	23	−0·179 (0·084)	−0·35 to −0·01	0·044	19	0·058 (0·190)	−0·34 to 0·46	0·76	0·23 } χ^2=5·0
Grade 2	7	−0·544 (0·122)	−0·82 to −0·27	0·004	11	−0·255 (0·350)	−1·0 to 0·52	0·48	0·53 } p=0·049
Grades 3-5	15	−0·868 (0·165)	−1·2 to −0·51	W0·001	8	0·067 (0·540)	−1·2 to 1·3	0·92	0·049 }

*Difference between mean and 0 from multiple separate paired *t* tests (thus a smaller than usual p value needed to show a level of significance).
†Differences between means for benzopyrone and placebo from multiple separate paired *t* tests; overall significances from analysis of variance.

TABLE IV—*Changes in symptoms and complications in subjects with unilateral filarial lymphoedema of the leg in the year when they were given 5,6-benzo-α-pyrone or placebo. Values are numbers of subjects unless stated otherwise*

	Benzopyrone				Placebo				χ^2 Test of homogeneity*	
	Remained bad	Worsened	Improved	Remained good	Remained bad	Worsened	Improved	Remained good	χ^2 Value	p Value
Feeling of swelling and bursting of leg	13	2	8	33	4	10	12	14	16	0·001
Feeling of swelling and bursting of foot	0	1	12	43	4	5	5	26	10·2	0·0014
Increased hardness of skin	4	0	23	29	7	7	5	21	10·1	0·0015
Increased thickness of skin	2	2	19	33	7	7	7	19	10·1	0·0015
Attacks of secondary acute inflammation:										
In patients prone to it	2	0	5	0	6	0	0	0	4·3	0·039
No of attacks	4	0	17	0	18	0	0	0	23	W0·001
In patients not prone to it	0	9	0	40	0	5	0	29	0·19	0·66
Fungal infection	2	1	7	46	4	2	2	32	1·5	0·21
Ulceration	0	2	16	38	8	0	0	32	5·1	0·024
Loss of hair	3	2	33	18	38	0	0	0	66	W0·001
Gross deformities†	4	0	4	48	6	0	0	34	0·82	0·37

*For first row df=3; for all others df=1 since small numbers required pooling of results for remained bad and worsened, and improved and remained good.
†Including sulci, warts, and papillomas.

reduced by a further 80% for grade 2 and 20% for grades 3-5. The total reductions in oedema throughout the trial were 100%, 95%, and 45% for grades 1, 2, and 3-5.

Table III shows the values of the slopes of the regression lines of the figure, the mean monthly percentage change in oedema. Analysis of variance of the slopes showed that benzopyrone significantly reduced oedema for all grades of lymphoedema combined in the first year of the trial (χ^2=41, pW0·001) and during follow up (χ^2=5·0, p=0·026). Throughout the trial the slopes of the regression lines were significantly less than zero for the individual grades (1, 2, and 3-5). No such changes in leg volume occurred in the placebo group.

Table IV shows the changes in the symptoms, signs, and complications of the disease in the first year of the trial. Treatment with benzopyrone improved sensations in the legs and feet (these were considered separately because in China the lower leg is affected much more than the upper). The drug lessened the attacks of secondary acute inflammation in the patients prone to it, who had often had three or four each year: attacks which did occur were much less severe and less frequent than before. All the patients in the placebo group who were prone to secondary acute inflammation had attacks of their usual severity and frequency. The daily questioning of patients led to the reporting of minor attacks which had been ignored previously, accounting for the appearance of new cases in both groups (the difference between the groups was not significant). Ulceration was reduced in the treatment group, and new growth of hair indicated the improved condition of the skin.

Although no attempt was made to quantify these changes, the observers reported that in the treatment group the skin of most of the oedematous limbs became softer with obvious decreases in the size of the limbs even after only six months of treatment. All nodules were much reduced or disappeared, wart-like (morula-like) lumps became smaller, and flakes started to come off. These changes were much more evident by the end of the treatment period. In some cases warts had almost disappeared. Elasticity of the skin was greatly improved, as was the secretion of sweat. The knees, whose immobility had greatly distressed many patients, became much more mobile. Two patients who had needed special footwear and clothing were able to wear normal shoes, socks, and trousers. No such changes were reported in the placebo group. These changes, while of little weight as evidence in themselves, indicate the improved quality of life given by the drug.

Side effects were mild. Initially most (about 60%) of the patients taking benzopyrone felt slightly dizzy or sleepy, three reported slight nausea and diarrhoea, and two had a skin rash. All continued taking the drug and the side effects all ceased after the first month. The placebo group did not report any side effects. Apart from five patients who withdrew from the trial because of infective hepatitis, no abnormalities were observed before or after the trial in the clinical examinations, in the blood and urine tests, or in the tests of liver and kidney function.

Discussion

Filarial lymphoedema and elephantiasis are reduced by 5,6-benzo-α-pyrone, confirming reductions in other trials of benzopyrones from lymphoedema of other aetiologies in Western communities.[1 11-20] The simultaneous study in India also produced significant reductions in filarial lymphoedema and elephantiasis, although to a lesser extent than in China.[21] The changes were not rapid, but the natural course of lymphoedema is to worsen slowly, with intervals of more rapid

deterioration during periods of acute inflammation.[1 2 6 13 27] The drug changed this slowly worsening condition to a slowly improving one. The total reductions in oedema were considerable for the lower grades of lymphoedema: over half of the oedema was lost in one year for patients with grades 1 and 2, and most of the oedema was lost by the end of the next year. With higher grades (3-5) oedema was reduced by about a third in one year and to about a half by the end of the second year. In Australian trials of this drug and another benzopyrone for lymphoedemas of varying aetiologies slightly smaller reductions occurred over six months for grades 1 and 2.[11 17 19] For grade 2 lymphoedema there was no significant difference between the slopes of the regression lines for the Chinese and Australian groups ($p=0{\cdot}46$), but both were significantly greater than that for the Indian group ($p=0{\cdot}025$ and $0{\cdot}0036$, respectively).[21] For grades 3-5 combined the reduction in China was also significantly greater than that in India ($p=0{\cdot}014$). Reinfestation in India might account for this.

Of even more importance to patients than the reduction of the excess volume was the reduction of the symptoms and complications. The patients particularly noticed reductions in attacks of secondary acute inflammation, feelings of swelling and bursting in the leg, ulceration, and inability to wear normal clothes. Treatment made a considerable contribution to the patients' comfort. This has been noted in other trials of the benzopyrones.[1 11 14 17 19] The reduction of the secondary acute inflammation by itself would undoubtedly help to limit the progress of the disease.

The relatively slow reductions in oedema produced by benzopyrone are probably beneficial. Strong compression garments are necessary if rapid reductions are to be maintained,[7-9] otherwise a rapid reduction in oedema leaves large potential cavities in the interstitium, which readily refill with high protein oedema fluid. These are ideal sites for the growth of bacteria, which may enter easily since the baggy skin is prone to injury. Compression garments, however, are impossible to wear in hot, wet, or dirty conditions. The slow reduction seen with benzopyrones allows the interstitial tissue continually to readjust to the new dimensions of the limb. The remodelling fibrous tissue, although its total amount lessens, is able to perform its normal role of keeping the tissues together and resisting any excessive inflow of fluid from the capillaries. External compression garments only attempt to imitate this.

In this study the side effects of treatment were minor and disappeared after a month in agreement with other trials.[1 11-19] There have been about 300 clinical trials of the benzopyrones, about 150 being of 5,6-benzo-α-pyrone, and many of these included hundreds of patients and some lasted decades.[1] The mild gastrointestinal side effects reported can almost always be prevented by an enteric coating (unpublished data), but this was not available in the present study. The slight dizziness and sleepiness reported here has not been found in other trials. The benzopyrones show low toxicity to animals even after long term administration at doses over 100 times the relative dose used here.[1] Hence long term treatment with this drug appears feasible.

The reduction in oedema continued after treatment with benzopyrone had stopped. Macrophages destroy both live and dead filariae[28] as well as removing detritus from the tissues. When these are removed the lymphatics may again function to some extent, especially if the excess fibrosis around them is also removed. Thus, by stimulating macrophage activity, 5,6-benzo-α-pyrone may reopen some of the lymphatics which were blocked by filariae and fibrosis. In regions of endemic filariasis reinfestation would make it unlikely that such a continuing reduction could be maintained without continued treatment. (Nor do such reductions usually continue after stopping the drug in non-filarial lymphoedemas (unpublished data).) It would be essential to prevent reinfestation—for example, by treatment with diethylcarbamazine. This should be given as short courses every few months rather than continuously because its continuous administration combined with 5,6-benzo-α-pyrone is significantly less effective than 5,6-benzo-α-pyrone alone, although the combination reduces oedema more than diethylcarbamazine alone.[21]

Clinical implications

- Over 45 million people suffer from filarial lymphoedema and elephantiasis, and, although effective treatments are available, people in developing countries can seldom afford the drugs
- Furthermore, adequate physical treatment requires compression garments, which are impractical in hot, wet, or dirty conditions
- In this study Chinese patients with filarial lymphoedema of the leg were treated with 5,6-benzo-α-pyrone, a cheap and readily available drug that seems to reduce all forms of high protein oedema
- Oedema and many symptoms were considerably reduced during the one year of treatment and during a further follow up year
- Benzopyrone is effective in treating filarial lymphoedema with few side effects, and its relatively slow action makes it ideal for use without compression garments

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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.**

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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 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 Organisation[6,7]); 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-