PAPERS AND SHORT REPORTS

Single dose oral treatment in urinary schistosomiasis: a double blind trial

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Abstract

A double blind trial of three oral preparations given in single doses for the treatment of *Schistosoma haematobium* infection was carried out in schoolchildren; selection was biased towards those who excreted large quantities of eggs. Praziquantel 40 mg/kg was the most effective drug giving a >97% reduction in egg output six months after treatment; combined treatment with niridazole 25 mg/kg and metrifonate 10 mg/kg gave a reduction of >92% and metrifonate 10 mg/kg alone a reduction of >86%. Fewer children continued to have moderate to heavy infections (excretion >124 ova/10 ml urine) six months after treatment with praziquantel (5%) and the combined regimen (7%) than with metrifonate (16%).

Though our findings show that praziquantel appears to be the most effective and convenient drug available for individuals with *S haematobium* infection, the combined regimen is a cheaper alternative for treatment where cost is important and parasitological cure not an essential objective.

Introduction

The trial was conducted as a preliminary to studies of mass treatment in *Schistosoma haematobium* infections. Thus, good tolerance and efficacy with a single oral dose were important in selecting therapeutic agents for the trial.

Praziquantel (Biltricide) is highly effective and safe in single oral doses for treating all forms of schistosomiasis.¹⁻³ It

is an ideal drug for mass treatment in the control of the disease, except that it is expensive.⁴ In areas where the urinary form of the disease alone is endemic, however, two cheaper preparations may be used in single oral doses—namely, metrifonate (Bilarcil)⁵ and metrifonate and niridazole (Ambilhar) combined.^{6,7} Since cost effectiveness is important in mass treatment programmes eradication of the parasite is not usually aimed at. Control is achieved by selective treatment of the population most heavily infected⁸ or by targeting treatment to those subjects with a high incidence of infections associated with the disease.⁹ For this reason we included in the trial the two cheaper preparations, which have a lower efficacy than praziquantel.

In addition, two control groups were given either a placebo (ascorbic acid) or niridazole in a single dose, since the level of transmission could have influenced the chemotherapeutic response of the treated subjects who remained in contact with potentially contaminated water.¹⁰ Niridazole in a single dose was used as a control since it was a component of the combined regimen, and it is normally given alone for at least five days to be effective.

We report the results of a double blind trial in which the three treatment preparations (praziquantel, a combined regimen, and metrifonate) were given for up to six months to schoolchildren who were selected with a bias towards heavy *S haematobium* infection. To date most drug trials in schistosomiasis have studied a single agent whose performance is influenced by factors other than drug efficacy.¹⁰

Subjects and methods

The trial was conducted in the Pirimiti area, which is south-east of Zomba and within the Phalombe plain of southern Malawi and has a hot dry season from August to October. Transmission of *S haematobium* is heavy among the subsistence farming population, who frequent contaminated pools in the river beds. A total of 2516 children attending five primary schools in the area were screened for haematuria using Ecur-Test (Boehringer) reagent strips. Of these, 600 children (517 boys and 83 girls attending two local schools) aged 5-18 years with heavy haematuria were included in the study. Children with apparent malaise, with febrile illnesses, or who had received schistosomicidal drugs within six months were excluded from the trial.

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SELECTION AND STRATIFICATION

Two consecutive midday urine samples were collected from each child and labelled with an X number (1-600) indicating identity and age. At the field laboratory each number label was replaced with a corresponding Y number by an independent worker who had sole and confidential access to a randomised X-Y list. The urine samples were then filtered and the retained eggs stained and counted by a standardised quantitative technique.¹¹ The geometric mean egg count was determined on samples for both days and a list compiled indicating Y number, egg count before treatment, and age (from the Y-X list).

Subjects were included in the trial if they had a mean egg count $>19/10$ ml urine. They were stratified in chronological sequence by Y number according to mean egg count (a, 20-124; b, 125-499; c, 500-1999; and d, >2000 ova/10 ml urine), arranged within each stratum according to age (5-7, 8-11, 12-15, and 16-18 years), and randomised to one of five treatment groups: group 1, praziquantel 40 mg/kg; group 2, niridazole 25 mg/kg combined with metrifonate 10 mg/kg; group 3, metrifonate 10 mg/kg; group 4 (control), niridazole 25 mg/kg; and group 5, placebo (ascorbic acid 300 mg); all preparations were given as a single oral dose.

The Y numbers were randomised to each group after each subject had been listed sequentially according to age-stratum, beginning with the Y numbers in stratum a age 5-7 years and ending with the numbers in stratum d age 16-18 years. The Y numbers in this entire sequence were then designated to each group as follows: first number, group 1; second number, group 2; third number, group 3; fourth number, group 4; fifth number, group 5; and so on until the end of the list. This procedure ensured that the groups were as comparable as possible for egg count and age, except for the placebo group (group 5), which contained strata a and b egg counts only. Thus, egg counts and randomisation by the coded system were blind to subject identity.

ASSESSMENT OF TREATMENT

Treatment was given after the onset of the rainy season in the middle of November. Tolerance to treatment was not evaluated in detail, but any episodes of vomiting during the two hours after treatment were noted. All children who had haematuria and were not included in the trial were treated with metrifonate 10 mg/kg. Mean egg counts were repeated on single midday urine specimens at one, three, and six months after treatment. We did not use a hatching test to determine the viability of excreted ova since percentage reduction in egg output rather than parasitological cure was our main criterion of efficacy.

In accordance with local ethical guidelines the placebo group consisted only of children with light (20-124 ova/10 ml) or moderate (125-499 ova/10 ml) infections before treatment. Furthermore, any children with heavy infections (500- >2000 ova/10 ml) detected three months after treatment were identified and retreated with metrifonate 10 mg/kg. Since children retreated after three months would represent treatment failures and therefore give an overestimation of treatment efficacy at six months, and absence after a recorded cure an underestimation, egg counts at six months were corrected for retreated subjects and absentees by scoring their previously recorded counts after treatment.

Percentage reduction in egg output was determined by comparing the arithmetic and geometric means of pooled egg counts before and after treatment. The geometric mean was obtained by recording the logarithm of egg counts and using the $n+1$ transformation for a series of counts after treatment that included zeros.

Results

The pattern of endemicity of *S. haematobium* infections before treatment as indicated in the children screened for haematuria is shown in fig 1. The correlation between haematuria and *S. haematobium* infection in childhood was significant.^{12,13}

Treatment was well tolerated in the 433 children who qualified for inclusion in the trial (>19 ova/10 ml urine). Table I shows the absentee rate for each group and includes children who required retreatment for counts >499 ova/10 ml at three months. The children treated with praziquantel and with the combined regimen did not require retreatment. The placebo group contained fewer retreated children than the niridazole group since it did not include those with heavy infections before treatment (strata c and d).

FIG 1—Incidence of haematuria in the screened child population before treatment (n=2516: 5-7 yr, 418; 8-11 yr, 1029; 12-15 yr, 875; 16-18 yr, 194).

TABLE I—Results of treatment at one, three, and six months in children infected with *Schistosoma haematobium*

	Treatment groups*			Control groups*	
	1	2	3	4	5
No of children	97	97	92	95	52
% Absentee rate after treatment (months):					
One	4.1	4.1	2.2	2.1	0
Three	8.2	8.2	10.9	12.6	23.1
Six	20.6	17.5	21.7	52.6	42.3
% Children requiring retreatment after three months for heavy infections	0	0	4.3	46.3	25.0
Arithmetic mean egg count:					
Before treatment	780.9	778.3	813.5	730.9	188.8
One month after treatment	1.8	38.7	105.5	972.7	437.2
Three months after treatment	1.9	26.7	95.0	554.3	270.3
Six months after treatment	20.1	56.0	107.9	568.5	261.8
% Egg count reduction at six months	97.4	92.8	86.7	22.2	38.7†
% Cure rate at (months):					
One	63.4	31.2	20.0	1.1	1.9
Three	31.5	11.2	8.5	0	0
Six	16.9	5.0	6.9	0	0
% Distribution of children at six months according to egg output (ova/10 ml urine):					
0-124	94.9	92.8	83.7	43.2	48.0
125-499	4.1	5.2	12.0	29.5	42.3
≥ 500	1.0	2.0	4.3	27.3	9.7

*Group 1, praziquantel 40 mg/kg; group 2, combined niridazole 25 mg/kg and metrifonate 10 mg/kg; group 3, metrifonate 10 mg/kg; group 4, niridazole 25 mg/kg; group 5, placebo (ascorbic acid 300 mg).

†Increase in egg count.

FIG 2—Overall pattern of egg output in the three treatment and two control groups.

There was a significant difference ($p < 0.01$) in the reduction of arithmetic mean egg counts between each treatment group; praziquantel (97%) was the most effective drug followed by the combined regimen (93%) and then metrifonate (87%). Exactly the same percentage differences were obtained by calculating the reduction in pooled aggregate egg counts. When this is expressed as geometric mean counts, which are less influenced by clustering of high counts in a few subjects, these differences decreased (fig 2 and table II). The relative efficacy was, however, maintained—namely, praziquantel 99%, combined regimen 98%, and metrifonate 96%. Children treated with praziquantel had a significantly higher cure rate compared with those treated with the combined regimen or metrifonate (table I).

The distribution of children at six months according to egg output was an important indicator of efficacy (table I). Treatment with metrifonate left a significantly greater proportion (16%) of children with counts $> 124/10$ ml urine than did treatment with praziquantel (5%) or the combined regimen (7%) ($p < 0.05$, $\chi^2 = 4.69$, 1df). There was no significant difference between the groups treated with praziquantel or the combined regimen ($p > 0.05$).

The maintenance of drug efficacy up to six months after treatment may have been influenced by the level of transmission. Results in the two control groups suggested that egg output naturally decreased and the level of reinfection was low. Treatment was given after a seasonal peak period of intense transmission, after which an appreciable incidence of reinfection was not expected until over a year later. For this reason, the timing of treatment was important. In this area treatment should perhaps have been given a little later to allow maturation of recently acquired parasites. Since immature schistosomes are less susceptible to chemotherapy, the efficacy in children who had low egg counts at the beginning of the trial but presumably heavy infestation with maturing worms was lower than expected.

Since the trial was carried out as a preliminary to mass treatment the distribution of subjects according to egg output was an important indicator of efficacy. The fewer the subjects left with heavy (disease associated) and moderate (potential

TABLE II—Geometric mean egg counts and percentage reduction in egg output at six months in the three treatment and two control groups of children

Group	Before treatment			After treatment			
	Strata (ova/10 ml urine)	No of children	Geometric mean egg count	Geometric mean egg count at:			Percentage reduction
				1 m	3 m	6 m	
Treatment:							
(1) Praziquantel	20-124	21	51.7	2.1	1.9	2.3	94.8
	125-499	30	234.7	1.5	1.9	2.0	99.1
	500-1999	38	907.6	1.7	1.8	2.6	99.7
	≥ 2000	8	3433.3	2.8	2.2	2.8	99.9
	All	97	358.5	1.8	1.9	2.4	99.3
(2) Combined regimen	20-124	19	72.0	3.5	4.3	4.0	94.4
	125-499	30	261.2	3.9	5.1	7.6	97.1
	500-1999	40	840.6	13.4	13.7	17.0	98.0
	≥ 2000	8	3178.5	76.1	30.7	19.0	99.4
	All	97	403.8	8.2	8.6	10.1	97.5
(3) Metrifonate	20-124	17	48.0	5.6	3.8	5.1	89.4
	125-499	30	305.1	13.7	12.7	14.5	95.2
	500-1999	38	945.9	46.6	24.8	27.8	97.1
	≥ 2000	7	3536.3	32.1	28.3	11.8	99.7
	All	92	416.9	20.7	14.3	15.4	96.3
Control:							
(4) Niridazole	20-124	21	45.9	41.8	56.9	41.8	8.9
	125-499	31	314.2	182.2	118.9	135.8	56.8
	500-1999	37	932.5	656.9	337.7	301.4	67.7
	≥ 2000	6	3312.0	2308.1	957.1	951.1	71.3
	All	95	364.0	252.9	173.0	161.5	55.6
(5) Placebo	20-124	20	52.7	35.6	36.8	22.0	58.2
	125-499	32	248.0	256.2	145.7	143.3	42.2
	All	52	136.8	119.9	85.9	69.7	49.0

Discussion

This trial showed that praziquantel was the most effective agent ($> 97\%$ egg count reduction). The combined regimen ($> 92\%$) was the next most effective at six months after treatment whereas metrifonate ($> 86\%$) did not achieve the accepted 90% reduction in egg count. These results were based on the comparison of arithmetic mean counts, which give a greater weighting to the few subjects with disproportionately high counts after treatment than the geometric mean. Thus, overall figures based on the geometric mean calculation produced higher percentage reductions in egg count and smaller differences between the treatment groups.

The highest percentage cure rates were achieved with praziquantel. True cure may have been underestimated since the quantitative technique used did not indicate viability of excreted ova. Of those children treated with praziquantel 92% were excreting < 20 ova/10 ml at six months. The addition of niridazole to metrifonate in a single dose produced a greater effect on egg output than metrifonate given alone. Increasing the single dosage of metrifonate may not have improved efficacy, but it would have produced dose related adverse reactions. Up to three doses at weekly intervals of metrifonate 7.5 mg/kg or 10 mg/kg are needed to increase efficacy at an acceptable level of tolerance.¹⁴

disease associated) infections, the more effective the drug. A significantly lower percentage of children were left with moderate to heavy infections (excretion > 124 ova/10 ml) six months after treatment with praziquantel (5%) and the combined regimen (7%) than with metrifonate (16%).

The cost of praziquantel was five and 18 times greater than that of the combined regimen and metrifonate respectively. The results of this trial suggest that the combined regimen may be suitable for cost effective disease control, praziquantel being too costly for large scale use in areas endemic for *S haematobium* alone. Such predictions cannot, however, be made with confidence since total operational costs minimise differences in drug costs, which may be 15-20% of the costs of the delivery system. Furthermore, since egg reduction may be adequately maintained with praziquantel, its frequency of delivery (and attendant costs) within an endemic area over a period may be less than that with the combined regimen or even metrifonate. On the other hand, the rate of reinfection may be so high after one year that any early differences in efficacy are minimised. At least in an area of seasonal *S haematobium* infections we can expect well timed chemotherapy to be effective in controlling disease up to a year; given adequate surveillance and instant diagnosis the control of heavily reinfected subjects may be for much longer.¹³

Though this trial compared the therapeutic efficacy of the

three preparations up to six months after treatment, only their potential value in mass treatment may be estimated as follow up for one year is a minimum requirement. For the individual subject infected with *S haematobium* praziquantel is the most effective and convenient drug available. If, however, cost is an important factor and parasitological cure not an essential objective the combined regimen in a single dose is a valid alternative in an endemic area.

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Dietary sodium restriction for mild hypertension in general practice

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Abstract

Eighteen patients with stable mild hypertension (mean blood pressure 144/93 mm Hg) restricted their sodium intake for eight weeks while taking part in a double blind randomised crossover trial of slow sodium and placebo tablets. Mean 24 hour urinary sodium excretion was 143 mmol(mEq) during the period on slow sodium and 87 mmol during the period on placebo. Five patients were unable to reduce their sodium intake below 120 mmol, but the others had a mean 24 hour urinary sodium excretion of 59 mmol during the period on placebo. There was no significant difference in blood pressure between the slow sodium and placebo treatment periods, although the study had a power of 99% to detect a

difference of 5 mm Hg in mean arterial pressure between the two periods.

Moderate dietary sodium restriction does not lower blood pressure in patients with this degree of hypertension.

Introduction

Recent studies suggest that moderate dietary sodium restriction is effective in lowering blood pressure in hypertensive patients.^{1 2} These studies were based on patients referred to hospital and managed subsequently as inpatients or outpatients. We set out to establish whether dietary sodium restriction is also feasible and effective in the treatment of mild hypertension in general practice.

Patients and methods

Glyncorrwg is a relatively isolated former mining village in the South Wales valleys. About 1500 residents are registered with one general practitioner, along with about 600 other patients in neighbouring villages. Case finding for high blood pressure began in 1968-9, when 98% of adults aged 20-64 had their blood pressure measured. Subsequently ascertainment, treatment, and follow up have been maintained more or less completely.³

Until mid-1981 the policy was to treat patients with hypotensive drugs when the mean of three consecutive readings exceeded 104 mm Hg diastolic (phase V: reduced to 99 mm Hg in 1981) or 179

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