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EFFICACY OF METRIFONATE IN A HIGHLY ENDEMIC AREA OF URINARY SCHISTOSOMIASIS IN KENYA

KATSUYUKI SATO,* MASAAKI SHIMADA,* SHINICHI NODA,†
NGETHE D. MUHOHO,‡ TATSUYA KATSUMATA,*
ATSUO SATO,† AND YOSHIKI AOKI*

**Department of Parasitology, Institute of Tropical Medicine, Nagasaki University, Japan,*
†Department of Medical Zoology, Faculty of Medicine, Kagoshima University, Japan, and
‡Centre for Microbiology Research, Kenya Medical Research Institute, Ministry of Health, Kenya

Abstract. In a community in Kwale district, Kenya, selective mass chemotherapy with metrifonate caused a marked reduction in the intensity of *Schistosoma haematobium* infection from 46.5 to 9.4 eggs/hr and a sharp fall in prevalence of gross hematuria from 18.3% to 5.1%, although overall prevalence was reduced only slightly from 67.4% to 54%. The effect of metrifonate on cure rate and reduction of infection intensity was limited by both age and pretreatment infection intensity. Rate of improvement from gross hematuria was similar in all ages and in all classes of intensity of infection. Two doses of metrifonate reduced the prevalence of gross hematuria as much as 3 doses did, while the effect of a single dose on morbidity remains to be clarified.

Chemotherapy is playing an increasing role in the control of schistosomiasis and also acts directly as a disease control agent.[1] Thus, the assessment of control programs should include the impact on morbidity.[2]

Metrifonate has been used in selective mass chemotherapy programs for urinary schistosomiasis because it is effective, inexpensive, and has few side effects.[1] This study was designed to assess its effectiveness against *Schistosoma haematobium* infection at the community level by using quantitative parasitological techniques and by assessing gross hematuria. We also describe the effectiveness of single and double doses of metrifonate on cure rate, reduction of infection intensity, and prevalence of gross hematuria.

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TABLE 1

Prevalence, intensity of infection, and frequency of gross hematuria of urinary schistosomiasis before and after selective mass chemotherapy

	Age group									
	0–4	5–9	10–14	15–19	20–29	30–39	40–49	50–59	≥60	Total
Pretreatment										
No. examined	103	136	103	49	77	65	46	51	47	677
No. (%) of egg positives	27 (26.2)	91 (66.9)	97 (94.2)	44 (89.8)	62 (80.5)	46 (70.8)	33 (71.7)	33 (64.7)	23 (48.9)	456 (67.4)
Eggs/hour (geometric mean)	3.1	51.1	925.5	215.0	90.1	22.6	35.5	12.7	9.4	46.5
No. (%) with hematuria	6 (5.8)	21 (15.4)	50 (48.5)	17 (34.7)	11 (14.3)	9 (13.8)	7 (15.2)	2 (3.9)	1 (2.1)	124 (18.3)
Post-treatment										
No. examined	64	158	128	89	80	61	46	51	49	726
No. (%) of egg positives	28 (43.8)	95 (60.1)	101 (78.9)	54 (60.7)	42 (52.5)	19 (31.1)	25 (54.3)	16 (31.4)	12 (24.5)	392 (54.0)
Eggs/hour (geometric mean)	1.7	20.3	61.6	30.2	6.1	1.8	3.4	2.1	1.2	9.4
No. (%) with hematuria	1 (1.6)	7 (4.4)	13 (10.2)	9 (10.1)	3 (3.8)	1 (1.6)	3 (6.5)	0	0	37 (5.1)

TABLE 2
Effect of dosage on parasitological cure rate and reduction in intensity of infection

Dosage (7.5 mg/kg)	Cure rate (%)		Geometric mean egg count	
	No. subjects	No. cured	Pretreatment	Post-treatment (% reduction)
Single dose	30	7 (23.3)	217.0	42.3 (80.5)
Two doses	69	21 (30.4)	508.8	23.5 (95.4)
Three doses	237	91 (38.4)	392.7	14.0 (96.4)

MATERIALS AND METHODS

Study area and population

The study was conducted in Kenya at Mwachinga village, Kwale district, an area known to be highly endemic for urinary schistosomiasis.[3] The number of residents registered at the 1982 census was 1,338 (617 males and 721 females). About half of the people were under 15 years of age.

Urine examination

Pretreatment urine examination was done in December 1983. Urine was collected 1 hr after the previous urination during mid-day. The intensity of infection was expressed as the number of eggs excreted per 1 hr assessed by the filtration method of Peters.[4] The rationale for this method has been published elsewhere.[5] The geometric mean was obtained by using the n + 1 transformation for a series of egg outputs including zeros. The appearance of urine was classified as yellow, brown (bloody), or red (very bloody). Bloody urine was used as a morbidity indicator, because it is a simple, specific, and sensitive indicator of infection.[6]

Selective mass chemotherapy

Treatment was given in February and March 1984 and effectiveness was evaluated 4 months later. Subjects passing eggs at least once in 4 previous examinations (June and December 1982, June and December 1983) and all children 5–15 years old were treated. Metrifonate was scheduled to be given 3 times at a dose of 7.5 mg/kg body weight at 2-week intervals.[7]

RESULTS

Post-treatment prevalence and intensity of infection, and frequency of gross hematuria

Urine specimens of 677 villagers were examined. Prevalence and intensity of infection and frequency of hematuria showed similar patterns of variance with age, all increasing rapidly to the 10–14 year group, followed by a steady decline in adults (Table 1). Overall prevalence of hematuria was 18.3%, with 5% (34/677) having very bloody urine.

Out of 813 subjects qualifying for treatment, 690 took metrifonate: in a single dose (n = 118), 2 doses (n = 159), and 3 doses (n = 413).

Four months later, 726 villagers were examined for eggs and urine color. The results are

TABLE 3
Effect of dosage on reduction in prevalence of gross hematuria

	No. examined	No. with hematuria (No. with red urine)		Presence or absence of hematuria pre- and post-treatment				
		Pre-treatment	Post-treatment	(Pre-) (Post-)	+ +	+ −	− −	− +
Single dose	30	6 (2)	4 (0)		3	3	23	1
Two doses	67	20 (8)	4 (0)		4	16	47	0
Three doses	232	73 (2)	10 (2)		9	64	158	1
Total	329	99 (12)	18 (2)		16	83	228	2

TABLE 4

Parasitological cure rate of patients given 3 doses of metrifonate at 7.5 mg/kg body weight by sex, age, and intensity of infection

Patients	No. examined	No. cured	Rate (%)
Male	108	36	33.3
Female	129	55	42.6
≤14 years	122	25	20.5
≥15 years	115	66	57.4
Intensity of infection			
<10	20	14	70.0
10–99	44	20	45.5
100–999	87	41	47.1
≥1,000	86	16	18.6

shown in Table 1. Mass chemotherapy caused a sharp fall in the intensity of infection, though the overall prevalence was only slightly reduced. Prevalence of hematuria was reduced to less than one third of the pretreatment level, and red urine was observed in only 0.8% of the specimens.

Cure rate, reduction in egg output, and gross hematuria in relation to dosage

Among those treated with metrifonate, 336 individuals underwent both pre- and post-treatment urine examinations (7 samples were not examined for color due to an oversight). Results are shown in Tables 2 and 3. The cure rate and percent reduction of mean egg output were significantly lower in the groups with fewer doses ($P < 0.01$). However, reduction of hematuria was not significantly different between the 2-dose and 3-dose groups (Yates' correction, $P > 0.5$). It was not possible to assess precisely the efficacy of a single dose on hematuria because the number of subjects with hematuria in this group was very small (Table 3).

TABLE 6

Reduction in intensity of infection of patients receiving 3 doses of metrifonate

	No. subjects	Geometric mean egg count: Pre-treatment	Geometric mean egg count: Post-treatment	% reduction
Male	108	487.6	18.5	96.2
Female	129	327.5	11.1	96.6
≤14 years	122	879.8	52.8	94.0
≥15 years	115	166.5	2.9	98.3

Cure rate in relation to sex, age, and intensity of infection

Table 4 shows the cure rate among subjects receiving 3 doses of metrifonate. Cure rate was not influenced by sex, but varied with age and intensity of infection, being significantly lower in children (<14 years) than in adults (>14 years) ($P < 0.001$). Those with lower egg counts had a higher cure rate than those with initially higher egg counts ($P < 0.001$).

Table 5 compares the cure rate of children and adults who had the same level of infection intensity. At higher levels of infection, metrifonate was still less effective in children than adults ($P < 0.05$, χ^2 statistic).

Reduction of egg output in relation to sex, age, and intensity of infection

Table 6 shows the geometric mean of egg count among subjects who completed 3 doses of metrifonate. Sex did not affect reduction in egg count,

TABLE 5

Comparison of parasitological cure rate after 3 doses of metrifonate between children and adults showing the same level of intensity of infection

Age		Geometric mean egg count: <10	10–99	100–999	≥1,000	Total
≤14 years	No. subjects	6	12	42	62	122
	No. cured	3	2	12	8	25
	Cure rate (%)	50.0	16.7*	28.6*	12.9*	20.5
≥15 years	No. subjects	14	32	45	24	115
	No. cured	11	18	29	8	66
	Cure rate (%)	78.6	56.3	64.4	33.3	57.4

* Cure rates of children were significantly less than those of adults in each level of intensity of infection ($P < 0.05$, χ^2 statistic).

TABLE 7

Comparison of reduction in egg count between children and adults showing the same level of intensity of infection

Age		Geometric mean egg count				
		<10	10–99	100–999	≥1,000	Total
≤14 years	Pretreatment	4.6	40.1*	388.6*	4,521.9*	879.8
	Post-treatment	2.6 (6)	57.4 (12)	20.8 (42)	125.8 (62)	52.8 (122)
	% reduction	43.3		94.7	97.2	94.0
≥15 years	Pretreatment	3.7	35.9	301.5	3,329.5	166.5
	Post-treatment	0.7 (14)	2.0 (32)	1.9 (45)	14.3 (24)	2.9 (115)
	% reduction	81.5	94.4	99.4	99.6	98.3

Number of subjects in parentheses.
After the transformation of egg count by log(x + 1), differences between pre- and post-treatment were calculated and compared between adults and children.
* Differences were statistically significant. ($P < 0.05$, Student's t-test.)

but the rate of reduction was higher in adults than in children. When adults and children were compared on the basis of intensity of infection at higher levels (Table 7), more drastic reductions again were observed in adults than in children ($P < 0.05$, Student's t-test).

Reduction of prevalence of gross hematuria in relation to sex, age, and intensity of infection

A total of 232 urine samples were analyzed, with the results shown in Table 8. The rate of reduction in frequency of hematuria did not differ by sex, age, or intensity of infection.

DISCUSSION

The therapeutic efficacy of metrifonate has been reported by many researchers.[2, 8–12] However, most of the reports have dealt exclusively with children as subjects. This study was designed to determine the therapeutic effect of metrifonate at the community level. A marked reduction in infection intensity and prevalence of gross hematuria was observed. Although our study showed only a modest cure rate, the results confirm that selective mass chemotherapy with metrifonate is an effective control strategy for morbidity due to urinary schistosomiasis.

Infection in children was less responsive to metrifonate than in adults. Lower cure rate and smaller reduction in egg output of children could be due to the age of the subjects or to higher intensity of infection. It is recognized that cure rate is greatly affected by pretreatment egg count,[7, 8, 13] and also that age plays an important role in the effectiveness of many drugs.[14]

The rate of improvement from gross hematuria was similar in all ages and in all but the lowest class of infection intensity, in which prevalence of hematuria was too low to draw a conclusion. The results suggest that morbidity in an entire community decreases homogeneously after treatment while intensity of infection remains

TABLE 8

Reduction of prevalence of gross hematuria in patients receiving 3 doses of metrifonate by sex, age, and intensity of infection

	No. examined	No. with hematuria		Presence or absence of hematuria at pre- and post-treatment			
		Pre-treatment	Post-treatment	(Pre-) (Post-) + +	+ −	− −	− +
≤14 years	120	49	8	7	42	70	1
≥15 years	112	24	2	2	22	88	0
Male	107	33	5	4	29	73	1
Female	125	40	5	5	35	85	0
Intensity of infection							
<100	63	3	2	2	1	60	0
100–999	85	20	2	2	18	65	0
≥1,000	84	50	6	5	45	33	1

heterogeneous. The improvement of gross hematuria using the 3-dose regimen is comparable to results obtained using praziquantel in Lake Volta, Ghana.[15]

Efficacy of metrifonate has been reported to be dose-dependent.[7] This was confirmed by the cure rate and reduction in intensity of infection in our study. The cure rate by 3 doses in our study is lower than that reported from other endemic areas,[8,9] which might be due to either variances in infection intensity or to a difference in schistosome susceptibility to metrifonate, as has been suggested by Wilkins and Moore.[11]

A single dose of metrifonate showed comparatively marked reduction in urine egg count.[10,12] Three out of 6 subjects with hematuria at pretreatment were negative and without red urine at post-treatment examination after a single dose. This indicates a promising effect of single-dose metrifonate on morbidity due to *S. haematobium* infection. Two doses of metrifonate reduced prevalence of gross hematuria similarly to 3 doses; therefore a 2-dose regimen is recommended and expected to increase compliance, as it did in our study by 20%.

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