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MICHAEL GELFAND, C.B.E., M.D., F.R.C.P.

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JOSEPH RITCHKEN, M.D.

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Table VII.

THE EFFECT OF THE DRUGS ON PERSONS WITH DOUBLE INFECTIONS OF S. HAEMATOBIUM AND S. MANSONI.

Group	INFECTIONS WITH *S. haematobium*								
	"CURED"			"IMPROVED"			FAILURES		
	Infections with *S. mansoni*			Infections with *S. mansoni*			Infections with *S. mansoni*		
	"Cured"	"Improved"	Failure	"Cured"	"Improved"	Failure	"Cured"	"Improved"	Failure
A		2	23			19	2	1	18
B		1	5			8		1	17
C	2	5	6	1	4	4	2	4	9
Intramuscular hycanthone	3	8	18		2				1

A Study of the Effects of Weekly Doses of Niridazole on Schistosome Egg Output and Miricidial Hatching in a Patient suffering from Bilharziasis

BY

D. M. BLAIR

AND

M. C. WEBER

Blair Research Laboratory, Salisbury, Rhodesia

INTRODUCTION.

The concept of "suppressive management" in the control of bilharziasis has long been an attractive idea. If it were possible to administer a dose of a schistosomicidal drug once a week, particularly to children attending school, a significant reduction in egg output and an improvement in health would make the method worthy of careful consideration in bilharziasis control programmes.

Children are undoubtedly the chief source of schistosome eggs for infection of waterbodies in endemic areas. If this could be substantially reduced by the administration of a single dose of a non-toxic drug, one day a week throughout a school term, the method, if economic, would be simple to apply.

Lees (1968) described a trial of a weekly dose of 500 mg Lucanthone hydrochloride, the tablets being coated with a cellulose acetate, Phthalate, at a school on the West Indian Island of St. Lucia. He found the *Schistosoma mansoni* prevalence to be 80 per cent. in the age group 10-14 years. Prior to the commencement of the trial for the 10 weeks of a school term the diagnosis was established by finding *S. mansoni* eggs in stools after sedimentation and concentration of eggs. The egg output level was thereafter established on a single whole stool using a filtration ninhydrin staining technique (Bell, 1963). Sixty infected children were chosen for the trial and the effect assessed by follow-up stool examinations 4 and 16 weeks after the completion of the 10 weeks of "suppressive management". It was possible to follow-up 49 of the children and it was estimated that an 89 per cent. reduction in egg output was achieved. The "cure" rate (the number of cases not passing any eggs) was, however, only 36,7 per cent. and all of these were in children who were passing less than 10 000 eggs, the group with the lightest egg loads and no complaints of side-effects were noted.

It had been decided to carry out a "suppressive management" trial at a school on the Mazoe Citrus Estate 30 miles from Salisbury, and groups of children were given uncoated Lucanthone hydrochloride, Niridazole and enteric-coated Hycanthone tablets to roughly comparable groups of children suffering from *S. haematobium, S. mansoni* and double infections with these parasites.

It was felt that it would be interesting to study, in more detail, in the Laboratory, a 10-week "suppressive management" course in a single patient. Niridazole was the drug selected.

A well-built young African, Town Mavida, aged about 19 years, volunteered for the trial. A general physical examination showed no signs of disease and his weight on 15th January, 1969, was 62,7 kg. Examination of urine showed him to have a light *S. haematobium* infection — 20 to 40 eggs being counted in deposits from mid-day terminal urine specimens. From them a good miracidial hatch was obtained. This was a light infection and seemed to cause him no inconvenience. He was also passing *S. mansoni* eggs and about 250 eggs were present in each sedimented and centrifuged stool deposit examined. Profuse miracidial hatching was obtained from the stool sediments.

The patient had come to Salisbury early in 1969, so it was most likely that he had contracted both infections in the same area as his elder brother, Foster Mavida (Blair *et al.* 1969).

Object of the Study.

The objective was to study the effect of a weekly dose of Niridazole on the egg output in urine and stool and the effect on hatchability of the eggs and any effect in his weight and general health.

Method.

The subject was given two 500 mg tablets of Niridazole (Ambilhar ® CIBA) at mid-day each Wednesday from 15th January to 19th March, 1969. Over this period he was weighed at the time of dosing and his weight ranged from 62,7 to 64,5 kg.

Each morning, Monday to Friday, the subject passed a stool at 0800 hours into a plastic container 25 x 17 x 8 cm deep. From the specimen two samples were taken without selection; each was about one gram in weight and was placed in screw-topped glass jars each containing 40 ml of hypertonic saline. One sample was processed at once, the other being kept for 24 hours at room temperature and processed the following day. The processing followed the methods of Blair *et al* (*op. cit.*). From each stool deposit 0,05 ml was taken and examined microscopically and eggs counted, and the remainder of the deposit subjected to hatching of miracidia in an examination rack (Meeser *et al* 1948). Each specimen was examined for hatched miracidia at 1200 and 1500 hours on the day it was examined microscopically, and at 1000, 1200 and 1500 hours on the following two days. By this means each sample was examined at least eight times.

The extent of miracidial hatching was estimated on a rating of 1+ to 5+ at each observation time. These observations not only give an indication of the amount of miracidia hatched at the time of observation, but also by persistence of hatching in the second, third and occasionally subsequent days of observation give some indication of the number of eggs showing delayed hatching. It is difficult to decide on the best way to reduce the information to figures. It is conceded that miracidia hatched and seen at one observation may also be seen and again counted in the next observation. It is, however, highly unlikely that miracidia hatched and active on any one day will still be active on the next day. It was therefore decided to record the maximum hatching rate recorded on each of the three days and by adding together the totals for each of the three days and the two samples of stool of the day, a figure is obtained which reflects the extent of miracidial hatching.

During the period of the trial the subject produced at 1200 hours each day, Monday to Friday, a specimen of terminal urine and his urine egg output estimated. He had, in fact, a light *S. haematobium* infection, but nevertheless during the course of the trial, miracidia were observed even on those instances where no eggs had been seen in the 0,05 ml of the centrifuged deposit which was examined microscopically. On only one day, 7th February, 1969, no eggs were seen and no miracidia hatched.

Results.

The weekly dose of 1 g. of Niridazole represents only 15,7 mg/kg or 157 mg/kg spread over 10 weeks as compared with the standard course of treatment used here of 30 mg/kg daily for six days — a total of 180 mg/kg, so no curative dose at this level could really be expected. This is especially so as Faigle and Keberle (1965) have shown in experimental work on animals that it is necessary to maintain a concentration of the drug in the blood for 100 hours and in order to maintain the blood level doses have to be given every 12 hours. They show that a single dose of Niridazole persists in the blood for only 10 to 15 hours.

SUPPRESSION USING NIRIDAZOLE

Table I shows the daily egg output over the 10 week treatment period and the succeeding five weeks. It will be noted that the day with the lowest average egg output was Thursday, 24 hours after the administration of the drug; and the average daily eggs fell from 34 in week one to 12 in week five; rose to 75 in week seven and then settled back to its previous level of about 34. When the 10-week dose period was over, the average egg output on Thursdays and Fridays was much higher than the other three days, and the weekly egg output was higher than during the treatment period. It would appear that the drug did have an immediate depressant effect on egg output on the day following dosing, and did depress the weekly average over the first six weeks; thereafter and continuing throughout the five-week follow-up period, there was, if anything, an increased output of *S. haematobium* eggs with no evidence of any diminution in hatching potential.

The results of the examination of stool specimens is set out in Table II. This shows that in the 10-week period of the trial over one-third of the total eggs were seen in the Monday specimens. In the observations (Blair *et al, op. cit.*) on the stools of Foster Mavida, the subject's brother, a similar increase in eggs on Mondays was observed, but not to the extent observed in the present series of observations. It will be noted that in the stools, egg output was at its lowest in weeks two and three, but thereafter recovered to the former level; this was maintained during the five weeks of observation after the completion of the trial.

The last column of Table II sets out average daily miracidia hatch before the trial, during the trial and for five weeks after. The lowest average hatch was in the third week, but by the eleventh and twelfth week the active hatch was back to the level above the first week, but distinctly lower than the pre-trial hatch figures.

Table I.

MID-DAY TERMINAL URINE EGG COUNTS DURING 10 WEEKS WHEN SUBJECT WAS GIVEN ONE GRAM NIRIDAZOLE AT 1200 HOURS EACH WEDNESDAY.

Week	Thurs.	Fri.	Sat.	Sun.	Mon.	Tues.	Wednes.	Total	Average daily eggs
0	—	30	—	—	40	20	20	100	28
1	50	60	—	—	30	20	10	170	34
2	0	20	—	—	50	40	40	150	30
3	10	0	—	—	60	20	40	130	26
4	40	0(a)	—	—	30	0	20	90	18
5	0	40	—	—	0	0	20	60	12
6	20	50	—	—	0	10	0	80	16
7	20	50	—	—	30	180	80	360	75
8	20	50	—	—	0	90	10	170	34
9	30	40	—	—	0	30	50	150	30
10	10	60	—	—	110	30	10	220	44
Total 1-10 weeks	200	370	—	—	310	420	280	1 580	32
Daily Average	20	37	—	—	31	42	28	32	—
11	20	40	—	—	20	0	60	140	28
12	140	—	Easter		—	0	20	160	53
13	60	160	—	—	80	80	100	480	96
14	100	40	—	—	10	0	60	210	42
15	40	110	—	—	30	0	60	240	48
Total 11-15 weeks	360	350	—	—	140	80	300	1 230	54
Daily Average	72	87	—	—	35	16	60	54	—

(a) No miracidia hatched, the only occasion this was observed.

Table II.

STOOL EGG COUNTS, SUM OF TWO SAMPLES FROM DAILY MORNING STOOL, ONE PROCESSED AT ONCE, THE OTHER AFTER 24 HOURS STORAGE, FOR A 10-WEEK PERIOD WHEN ONE GRAM OF NIRIDAZOLE WAS ADMINISTERED EACH WEDNESDAY AT 1200 HOURS.

Week	Thurs.	Fri.	Sat.	Sun.	Mon.	Tues.	Wed.	Total	Av. daily eggs	Average miracidia hatch each day
0	—	—			600	600	750	1 950	650	15
1	330	270			530	980	680	2 790	558	11
2	370	210			460	220	380	1 640	328	14
3	150	190			130	150	200	820	164	8
4	390	220			3 240	460	570	4 480	896	13
5	260	310			1 570	540	290	2 970	594	10
6	840	400			2 170	560	640	4 610	922	13
7	220	330			1 450	410	480	2 890	578	10
8	370	440			700	720	280	2 510	502	10
9	260	300			210	910	650	2 430	486	12
10	940	250			490	680	280	2 530	506	11
Total weeks 1-10	4 130	2 920			10 950	5 630	4 450	28 080	562	
Av. daily eggs weeks 1-10	413	292			1 104	563	435			
Av. miracidia hatch	10	8			13	12	12			
11	540	210			680	470	230	2 230	446	9
12	510	—	Easter		—	490	640	1 640	547	10
13	580	530			350	290	210	1 960	342	10
14	240	410			710	1 240	540	3 190	638	13
15	340	410			730	1 140	250	2 870	574	11
Total 11-15 weeks	2 260	1 660			2 470	3 630	1 870	11 890	517	
Av. daily eggs 11-15 weeks	452	415			617	726	374	517		
Av. miracidia hatch	9	9			12	13	10			

The hatch figures for the Monday, Tuesday and Wednesday, prior to taking the first dose of Niridazole, were 18, 16 and 12, respectively. In the ten weeks of the trial period it will be seen that average figures for miracidia hatching for each day of the week corresponds to the average number of eggs counted on that day. In general this agreement is evident also in the five-week post-treatment observations.

Discussion.

The concept of "suppressive management" in the control of bilharziasis is an attractive one and if by the administration on a weekly basis of a schistosomicidal drug, even if only a significant reduction in egg load was achieved, the method might merit more widespread use.

Town Mavida was a good deal heavier than an average African school child, and so, of course, the dose of Ambilhar of 1 gram per week resulted in a much lower concentration of drug in his case than would be the case when treating school children in the same way. However, despite the lack of any real reduction in *S. mansoni* output, there seemed to be a significant reduction in the miracidia hatching ratio. In the case of the subject's *S. haematobium* infection, the results were frankly very disappointing, and, in fact, the drug seems to have stimulated egg output to reach a higher level. Town Mavida's weight remained unaffected by the course of treatment, which would seem to indicate that worm destruction was not really being achieved.

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