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## ON A NEW TREATMENT REGIMEN WITH THIABENDAZOLE AGAINST *ANCYLOSTOMA DUODENALE*\*

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The anthelmintic activity of thiabendazole syrup against *Ancylostoma duodenale* was investigated. Hookworm carriers (192) from the inhabitants of a village in Yamanashi Prefecture were treated under three dosage schedules. Before and after the administration, for the purpose of assessment, fecal examinations were performed by the thick smear method, the brine floatation method and quantitative direct smear method. Side effects were checked by direct questioning as well as the questionnaire done for successive days. The negative conversion rates of eggs in feces were 52% with a single dose of 50 mg/kg, 63% with 25 mg/kg twice daily and 85% with 25 mg/kg twice daily for two days. The negative conversion rates were 72%, 77% and 96%, in the order mentioned above, in the group of the light infestation, 44%, 74% and 82% in the moderate infestation group, and 17%, 100% (3/3) and 68% in the heavy infestation group. Main side effects were dizziness and fatigue which appeared in 33% and 13% of the patients, respectively, with a single dose of 50 mg/kg. These side effects reduced markedly with 25 mg/kg twice daily. However, it increased with 25 mg/kg twice daily for two days.

### INTRODUCTION

There are many reports concerning the noticeable anthelmintic efficacy of Thiabendazole on human helminths (Franz, 1963; Huang and Brown, 1963; Papasarathorn, Chulareak and Tong-Koom, 1964; Salunkhe, Gaitonde and Vakil, 1964; Betero, 1965; Franz, Schneider and Pohlman, 1965; Most, et al., 1965; Shah, 1965). There are also similar reports in Japan (Yanagisawa et al., 1963; Iwata et al., 1963; Noda, 1964; Yamazaki, 1964). The authors have already reported on the anthelmintic effect of thiabendazole syrup on human helminths (Ishizaki, Iijima and Ito, 1963). Further study was performed on *Ancylostoma duodenale* with special emphasis on an efficient treatment with minor side effects.

### MATERIALS AND METHODS

One hundred and ninety-two hookworm carriers were chosen from inhabitants of a village in Yamanashi Prefecture. Ages of the carriers ranged from 6 to 80 years, the

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majority of whom were 20 to 60 years old; and male and female were almost equal in number. According to the larva culture method (Harada and Mori, 1951), the sole prevalence of *Ancylostoma duodenale* was observed in this area.

Thiabendazole syrup with the concentration of 0.2 g/ml was given at least two hours after meal. During the treatment, carriers were prohibited from taking alcoholic beverages and greasy foods, and instructed to take rest. Carriers were divided into the following three groups according to the dosage schedules.

Group I (67 carriers): 50 mg/kg with a single dose in the morning.

Group II (52 carriers): 25 mg/kg twice daily in the morning and evening (50 mg/kg in total).

Group III (73 carriers): 25 mg/kg twice daily for two days in the morning and evening (100 mg/kg in total)

Anthelmintic effects of a drug in a mass-treatment differs markedly according to the degree of infestation of the worm. The objects were divided into three groups in order that each group included objects with every different infestation at the same ratios, as shown in Table 1. For detection of eggs of the carriers, fecal examinations by the thick smear method with cellophane (Kato, 1958; Komiya et al., 1960), the brine floatation method, and a quantitative direct smear method (Ishizaki, 1953) instead of Stoll's egg-counting technique, were used before and 22nd days after administration. The negative conversion rates of eggs and the egg-reduction rates in feces were used for the assessment of anthelmintic effects in each group. The negative conversion rate of feces represents the rate of persons who showed the absence of eggs in their feces after the treatment in subjected group. Side effects were checked by direct questioning to the individuals at the first administration of the drug and by the questionnaire on the symptoms which appeared on the following day.

## RESULTS

### *Evaluation of Anthelmintic Effects in the Three Dosage Groups*

The results obtained are shown in Table 2. Both rates of the negative conversion and the egg-reduction were obtained on the 22nd day after administration. According to the negative conversion rates, anthelmintic effects in the three groups were 52%, 63% and 85% in Groups I, II and III, respectively. The difference of the rates between Group III and the other two was statistically significant ( $P < 0.05$ ). The egg-reduction rates were 68%, 76% and 98% in Groups I, II and III, respectively. The difference of the rates between Group III and the other two was also significant ( $P < 0.05$ ).

The anthelmintic effects of thiabendazole was not decreased by the administration with 25 mg/kg twice daily (Group II) as compared with a single dose of 50 mg/kg (Group I). The effects with 25 mg/kg twice daily for two days (Group III) was the highest among the three dosage schedules.

### *Evaluation of Anthelmintic Effects in the Three EPG Groups*

Since the anthelmintic effects must be compared in the group of the same intensity of infestation, each of three groups was further divided into three sub-groups according to the EPG of the individuals. Sub-groups A, B and C consist of individuals with EPG of less than 200, from 201 to 1,000 and more than 1,001, respectively. The results are shown in Table 3.

Table 1. Results of pre-treatment examination of hookworm infections in three groups

EPG count	Group I		Group II		Group III	
	No. of cases	%	No. of cases	%	No. of cases	%
- 100	24	35.8	18	34.7	18	24.6
- 200	8	11.6	12	23.1	9	12.3
- 300	4	6.0	11	21.1	4	5.5
- 400	3	4.5	2	3.9	9	12.3
- 500	2	2.9	3	5.8	8	11.0
- 600	4	6.0	1	1.9	3	4.1
- 700	4	6.0	1	1.9	0	0
- 800	1	1.5	1	1.9	2	2.7
- 900	4	6.0	0	0	0	0
-1,000	1	1.5	0	0	1	1.4
-1,200	3	4.5	0	0	2	2.7
-1,400	3	4.5	1	1.9	3	4.1
-1,600	0	0	0	0	1	1.4
-1,800	1	1.5	0	0	1	1.4
-2,000	0	0	0	0	2	2.7
-2,500	1	1.5	0	0	2	2.7
-3,000	3	4.5	0	0	0	0
-4,000	0	0	0	0	1	1.4
-5,000	0	0	1	1.9	3	4.1
5,000-	1	1.5	1	1.9	4	5.5
Total	67	100	52	100	73	100

Table 2. The negative conversion rate of eggs and the egg-reduction rate in feces in three dosage schedules

Group	Dosage	Total number of examined	Negative conversion			Egg-reduction		
			No. of examined	No. of negative	%	No. of examined	No. of reduction	%
I	50 mg/kg (Single)	67	67	35	52.2	60	41	68.3
II	50 mg/kg (25 mg/kg × 2)	52	49	31	63.2	49	37	75.5
III	100 mg/kg (25 mg/kg × 4)	73	62	53	85.0	62	61	98.0

The negative conversion rates of eggs in Sub-group A were 72%, 77% and 96% in Groups I, II and III, respectively. In Sub-group B, the rates were 44%, 74% and 82% in Groups I, II and III, respectively, and in Sub-group C the rates were 16%, 100% (3/3) and 68%, respectively.

In these results, thiabendazole was most effective in the case of light infestation of

Table 3. The negative conversion rate under various grades of EPG

Sub-group	EPG	Group I (50 mg/kg × 1)			Group II (25 mg/kg × 2)			Group III (25 mg/kg × 4)		
		No. of examined	No. of negative	%	No. of examined	No. of negative	%	No. of examined	No. of negative	%
A	less than 200	32	23	71.8	30	23	77.0	27	26	96.0
B	201-1,000	23	10	43.5	19	14	73.7	27	22	82.0
C	more than 1,001	12	2	16.6	3	3	—	19	13	68.0

the worm (Sub-group A). A single dose of 50 mg/kg was sufficient for the mass-treatment with a single or divided use, and a dose of 25 mg/kg twice daily for two days was considered to expect a complete cure. In the case of moderate infestation (Sub-group B), this drug was not effective with a single dose of 50 mg/kg, but effective with both 25 mg/kg twice daily and 25 mg/kg twice daily for two days. In the case of heavy infestation (Sub-group C), the negative conversion rate was 68 % only with 25 mg/kg twice daily for two days and no effects were observed in others.

#### Side Effects

Side effects obtained from Groups I and II are presented in Table 4. Side effects appeared within a half or one hour after the first administration and disappeared mostly within the next one hour. Side effects lasted for more than three hours in some cases, but there was no one who complained of any disturbance on the following day. Side effects were observed in 41 % of the carriers in Group I, and 33 % of the carriers complained of dizziness, 13 % of fatigue, 7 % of nausea, 6 % of weakness, 3 % of vomiting, and 3 % of headache. Thirteen per cent of the carriers complained of side effects in Group II, and 9 % of dizziness, 4 % of headache and 2 % of nausea.

As shown in Table 5, side effects appeared markedly after the 4th administration in Group III. After the first administration, 9 % of the carriers complained of side effects

Table 4. Side effects observed in Group I and Group II

Side effect	Group I (50 mg/kg × 1)		Group II (25 mg/kg × 2)	
	No. of cases	%	No. of cases	%
Examined	70	100	55	100
Complained	29	41.4	7	12.7
Dizziness	23	32.8	5 (slight)	9.3
Nausea	5	7.1	1	1.8
Vomiting	2	2.8	0	0
Fatigue	9	12.8	0	0
Headache	2	2.8	2	3.5
Weakness	4	5.8	0	0

and 49 % complained at the end of the 4th administration, i. e. 24 % of the carriers complained of dizziness, 21 % of headache, 15 % of anorexia, 13 % of fatigue, 12 % of nausea, 7 % of weakness, 4 % of stomachache, 4 % of diarrhea, 4 % of constipation, and 3 % of urticaria. These side effects, however, disappeared on the following day.

Table 5. Side effects observed in Group III

Side effect	Number of the patients who complained on the				Total	
	1st day		2nd day	3rd day		
	After the first administration	After the second administration	After the fourth administration			
No. examined	89	67	62	67	67	100 %
Dizziness	3	1	15	4	16	24 %
Nausea	0	1	7	1	8	12 %
Vomiting	0	1	1	0	2	3 %
Fatigue	0	2	9	3	9	13 %
Headache	2	1	13	1	14	21 %
Weakness	0	0	5	0	5	7 %
Anorexia	0	1	10	3	10	15 %
Stomachache	1	3	2	0	3	4 %
Diarrhea	0	1	2	0	3	4 %
Constipation	0	0	1	2	3	4 %
Urticaria	0	1	0	1	2	3 %
Lumbago	0	0	1	0	1	1.5 %
Stiffness in the shoulder	0	0	1	0	1	1.5 %
Total	5	6	28	5	33	49 %

## DISCUSSION

The results obtained from Group II showed that the anthelmintic effects of thiabendazole seemed to be additive or cumulative against hookworms. These effects were seen also in Group III, in which the negative conversion rate of 85 % was obtained by a repeated usage of a small dose of 25 mg/kg. It was well known that tetrachlorethylene (Komiya, Nakayama and Tsukagoshi, 1959) and 1-bromo-2-naphthol (Komiya et al., 1964), each of which is commonly used at present for the removal of hookworms, showed a marked decrease of its efficacy when used in divided doses for the purpose of reduction of side effects. The anthelmintic effects of thiabendazole, however, was not reduced by the divided administrations (Group II), and the effects increased with further repeated administration of the small dose (Group III). These particular effects of thiabendazole were substantiated by the present paper.

Since this drug was found to be anthelmintic in the laboratory and domestic animals, side effects was observed carefully in this work. Side effects reduced markedly in a dose of 25 mg/kg twice daily as compared with those in a single dose of 50 mg/kg, but increased markedly in that of 25 mg/ks twice daily for two days. In general, a pharmacological action is closely related to the amount of a drug given at one time and it decrease with the lapse of time. The side effects mentioned above suggest that the action of thiabendazole on the human body continues to the 2nd administration performed 12 hours after the first one. Many side effects manifest up to the 4th administration.

From the results of this study, an adequate treatment regimen of thiabendazole, the most effective to the worms and the most harmless to the human body, is to be a multiple usage of a small dose with a sufficient interval to avoid major side effects. One example is an administration of 25 mg/kg twice daily with an interval of 12 hours.

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